Gestational Weight Gain and Modifiable Risk Factors of Severe Maternal Morbidity in a Hospital-Based, Retrospective Cohort

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Abstract

Severe maternal morbidity affects nearly 50,000 women every year and its incidence has risen over the past 3 decades. However, there remain several gaps in the epidemiologic literature. Our goal was to quantify the burden that modifiable risk factors place on severe maternal morbidity, with a focus on gestational weight gain because of its amenability to intervention during pregnancy.

We used two, retrospective cohorts of delivery hospitalizations at Magee-Womens Hospital in Pittsburgh, PA to address three specific aims: 1) determine the association between total gestational weight gain and the risk of severe maternal morbidity, 2) determine the association between early gestational weight gain and the risk of severe maternal morbidity, and 3) calculate the population attributable fraction of known, modifiable risk factors of severe maternal morbidity.

A total gestational weight gain z-score of +2 (31kg at 40 weeks gestation among normal weight women) was associated with 1.0 (0.46, 1.5)) excess cases of severe maternal morbidity per 100 delivery hospitalizations compared with a z-score of 0 (16kg at 40 weeks among normal weight). Very low weight gain was also associated with an increased risk, though the magnitude of association was smaller. The relationship between early gestational weight gain and risk of severe maternal morbidity followed an inverted-U distribution, though the divergent findings with Specific Aim #1 were likely due to differences in sample characteristics. For Specific Aim #3, we found that

optimizing eight, known risk factors concurrently could prevent 36% (626 cases) of the severe maternal morbidities in this sample. High gestational weight gain, high body mass index, advanced maternal age, preexisting hypertension, and lack of a college degree had population attributable fractions ranging from 4.5% to 13%.

Our results suggest that optimizing individual-level risk factors, including gestational weight gain, would have modest impacts on reducing risk of severe maternal morbidity and that the burden of severe maternal morbidity is likely due to a constellation of components. This is significant for future public health efforts because, while additional research should confirm and extend our findings, the greatest change will likely come through addressing larger, population-level factors and disparities.

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Preface

The work presented here would not have been possible without my family, friends, and colleagues in Pennsylvania and Arizona; I am forever grateful for your patience, sacrifice, and unyielding support over the years it has taken to accomplish this goal.

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1.0 Introduction

1.1 Background

Pregnancy-related maternal mortality occurs more frequently in the United States (U.S.) more than any other developed nation and its incidence has more than doubled over the past three decades.[1] Because maternal mortality is often used as a metric for the health of the broader population, professional medical societies have called for more research to better understand its risk factors and causes.[2] However, the cumulative incidence of pregnancy-related maternal mortality remains low,[3,4] making it a challenging target for epidemiologic studies. Severe maternal morbidity shares etiologies and risk factors with pregnancy-related maternal mortality and occurs nearly 70-times more frequently. Therefore, severe maternal morbidity can be viewed as a reasonable proxy outcome for maternal mortality, allowing us to study and better understand the larger problem of increasing incidence of life-threatening pregnancy complications.

Though several risk factors of severe maternal morbidity are cited in the available literature, many of those that are potentially modifiable are only amenable to intervention before conception. Given many women do not have access or do not seek healthcare before pregnancy[5] and half of pregnancies are unplanned,[6] identifying risk factors that can be targeted during pregnancy, such as gestational weight gain, should be of high importance. Unfortunately, most administrative datasets that are powered to adequately study this rare outcome are limited in the depth and breadth of factors that can be studied.

Furthermore, while there are known modifiable risk factors of severe maternal morbidity, the extent to which they contribute to the overall burden of severe maternal morbidity is not. For

example, observational studies have reported on the association between prepregnancy BMI and severe maternal morbidity, but traditional measures of association (e.g. odds or risk ratios) cannot be readily translated to real-world implications of intervention. Methods such as calculating the population attributable fraction allow us to quantify the burden of severe maternal morbidity due to specific risk factors and estimate the number of cases that could be prevented by optimizing or reducing the prevalence of those risk factors.

1.2 Specific Aims

The overarching purpose of this dissertation is to address critical gaps in the literature regarding the contribution of individual modifiable risk factors of severe maternal morbidity, with a specific focus on gestational weight gain. Specifically, we will add to the current epidemiologic literature by 1) exploring the association between severe maternal morbidity and both, total and early gestational weight gain and 2) quantifying the proportion of severe maternal morbidity that is attributable to known, modifiable risk factors. We will accomplish the following aims using two separate datasets. For specific aim one, we will use a retrospective cohort of singleton pregnancies from Magee-Womens Hospital in Pittsburgh, Pennsylvania from 2003-2012 (n=84,241). Specific aim two will be accomplished using a retrospective cohort of 4,774 delivery hospitalizations from the same institution, augmented with data on serial weight measurements that were abstracted via medical chart review (2003-2011). For specific aim three, we will use a retrospective cohort of 86,260 of singleton and twin delivery hospitalizations from Magee (2003-2012).

Specific Aim 1. Determine the association between total gestational weight gain and severe maternal morbidity.

Hypothesis: Higher gestational weight gain will be associated with increased risk of severe maternal morbidity.

Specific Aim 2. Determine the association between early gestational weight gain and severe maternal morbidity.

Hypothesis: Higher gestational weight gain at 16-19 weeks gestation will be associated with increased risk of severe maternal morbidity, but the magnitude of the association will be smaller compared with that of Specific Aim 2.

Specific Aim 3. Determine the population attributable fraction of modifiable risk factors of severe maternal morbidity (maternal education, marital status, prepregnancy BMI, preexisting hypertension or diabetes, advanced maternal age at delivery, smoking during pregnancy, and gestational weight gain).

Hypothesis: Chronic medical conditions and high prepregnancy BMI will account for the highest frequency of preventable cases of severe maternal morbidity.

Overall impact: At the patient level, these results will provide clinicians with additional information on the association between risk factors and important, adverse health outcomes among women who are or thinking about becoming pregnant. For healthcare systems, quantifying the expected number of cases of severe maternal morbidity that could be prevented by optimizing individual risk factors may help identify priority surveillance areas. Filling gaps in the epidemiologic literature may also have broader, policy implications by demonstrating the

need to reduce the prevalence of known risk factors through improved education efforts and access to affordable healthcare.

2.0 Literature Review

2.1 Introduction

2.1.1 Pregnancy-related maternal health in the United States

Historically, maternal health during pregnancy has fallen secondary to fetal health, following the traditional paradigm of "what is good for the child is good for the mother".[7] In 1985, Rosenfield and Maine brought attention to the disparity in an important article in the Lancet, intending to motivate the public health community to better understand and address maternal mortality and improve maternal health".[8] But sadly, the rate of maternal mortality and morbidity continued to rise worldwide and over 30 years later, has more than doubled in the United States (U.S.), which by many measures, has the worst incidence of maternal death among all high-income countries.

Maternal health is an important indicator of the overall health and healthcare system of a nation.[9] So, together with rising obesity rates, chronic disease, and its related conditions, these trends signal a challenging future for healthcare in the U.S. In contrast, Scandinavian countries and the United Kingdom (U.K.) have both seen declines in maternal mortality so significant that in the U.K., "a [similar age] man is more likely to die while his partner is pregnant than she is".[10]

Though the problem surrounding declining pregnancy-related maternal health has been known to the scientific and medical communities for decades, the issue remained mostly unknown to the general U.S. public until recently. In 2017, ProPublica and National Public Radio (NPR) reported on Lauren Bloomstein, a neonatal nurse who died during childbirth in the

hospital where she worked. The first of an eight-article series, this report chronicled the events surrounding her death and the lapses in her care that contributed to the outcome. Since the series began, there has been a surge in public awareness and advocacy. And while increased attention is beneficial, much work is still needed to better understand why these events occur.

Maternal mortality is the final endpoint in the continuum of adverse maternal outcomes during pregnancy, delivery, or postpartum, but its cumulative incidence remains low. However, severe maternal morbidity, which shared the risk factors and etiologies with maternal mortality and has short-and long-term ramifications of its own, occurs 70-times more frequently. Its incidence has increased nearly 200% from 1993 to 2014 (0.50% to 1.4% of delivery hospitalizations, respectively).[1] By better understanding this outcome, the goal is to not only better understand potential modifiable risk factors of severe maternal morbidity, but along with additional research, gain insight into how better to identify, monitor, and treat women on the path to pregnancy-related mortality.

2.2 Severe Maternal Morbidity

2.2.1 Defining severe maternal morbidity

Severe maternal morbidity is broadly defined as a life-threatening complication experienced during pregnancy, delivery, or postpartum.[2,11] While professional medical societies have not endorsed a single definition, organ system failure, postpartum hemorrhage, and life-saving medical intervention are commonly used indicators for severe maternal morbidity. Criteria in the available literature vary by the scope and underlying objective of the research as

well as the type of dataset used. For example, population-based, epidemiologic research using administrative data typically use broader criteria than chart-review efforts aimed at identifying preventable cases. For the former category, the Centers for Disease Control and Prevention (CDC) published a list of ICD-9 and ICD-10 codes, corresponding to 21 unique indicators of severe maternal morbidity that has been widely used.[12] For the latter, where cases are screened and reviewed, the American College of Obstetricians and Gynecologists (ACOG) recommends screening criteria of blood transfusion of 4+ units or intensive care unit (ICU) admission, followed by detailed review of each screen-positive case.[13] Hybrid definitions are also common because the available data vary between healthcare institutions and highlighting additional cases is warranted.

Early definitions

The definition of what constitutes a severe maternal morbidity has evolved since the mid-1990s. Prior to this time, standard practice was to use hospital admissions as a proxy for near-miss morbidity.[14] Once recognized that these criteria could not distinguish between life-threatening and non-life threatening events, some researchers moved to count ICU admissions instead.[15,16] Though a much better indicator of serious events, using a single indicator is problematic because it cannot capture patients who deliver in facilities that do not have an ICU and may still not account for some critically ill women.[14] So, from 2002-2004, Stacie Geller, et al. developed a conceptual framework and scoring system aimed at including additional factors that would 1) capture serious events better than current definitions and 2) further distinguish between serious events and true, life-threatening complications.[14,17,18] Using a multi-stage review process whereby potential cases were identified, medical charts abstracted, narrative summaries compiled, and qualitative review conducted, the authors identified 5 factors– surgical intervention, extended intubation, >3 units of

blood transfusion, ICU admission, and organ system failure– as indicators of severe maternal morbidity. The two principal limitations of this work were the failure to review screen-negative cases and using qualitative review processes as their gold standard, the implications of which include failing to identify false negative cases and limited generalizability of results outside the study sample. Their approach, though not without shortcomings, helped foster new ways of thinking about how to study near miss events. Also, since these early efforts, myriad definitions have been proposed, but few have been the subject of internal and/ or external validation studies.

Validation studies

Available validation studies can be categorized into one of two, main groups based on the type of definition of severe maternal morbidity they aim to validate. The first group focuses on scoring systems (like the one developed by Geller, et al.) and the second, on multi-factor identification systems such as the CDC and ACOG criteria listed above.

The Geller criteria have been the focus of two validation studies, one internal and the other external. An internal validation study by Geller, et al. found that compared with qualitative chart review, individual factors had sensitivities and specificities of 73%-96% and 82-99%, respectively. A single, external validation study by You, et al. reported lower sensitivities (42%-79%) and similar specificities (90%-99%) in a sample of 816 deliveries.[19] However, neither group reviewed screen negative cases, so we cannot rely on these reported validation estimates. The authors should have reported the positive predictive value, as this is the only validation metric that can be reliably calculated using the review of screen-positive cases.

Another notable validation study by Christine Roberts, et al., focused on developing a new set of criteria for identifying maternal morbidity using ICD-10 codes in a nested case-control control study of 400 possible cases and 800 controls in Australia.[20] After applying sampling

weights, they determined the positive- and negative-predictive values as well as the sensitivity and specificity of each indicator compared with a gold standard of chart review. This is the only validation study where both, screen-positive and screen-negative cases were reviewed. Unfortunately, while some of the examined indicators align with those more commonly used in the U.S., many were unique to this sample. Indicators that align with common U.S. indicators include: eclampsia, disseminated intravascular coagulation, shock, cardiac failure, acute liver/ renal failure, sepsis, blood transfusion, hysterectomy, and ICU admission. Compared with the gold standard, these indicators had >83% positive predictive value, though their sensitivities ranged from 28% for hysterectomy to 100% for eclampsia. Negative predictive value and specificity was over 99% for all indicators. These results illustrate two points: 1) there are several reasonable definitions for severe maternal morbidity (some more justifiable than others), but that any conclusion of the validity of each definition is highly dependent upon the clinical judgement of those developing the gold standard to which a definition is compared and 2) there are likely more indications of severe maternal morbidity than any one study has examined to date. For example, in this study, "trauma to abdominal organs" was associated with a 93% positive predictive value, 65% sensitivity, and 99.8% specificity, but this indicator is not included in recent indications in U.S. studies. While many other indicators in this sample were less valid, there may be merit to the notion that a universal definition for severe maternal morbidity is not tenable or appropriate.

In the U.S., the 2016, seminal article by Elliot Main et al. tested the validity of defining severe maternal morbidity using common individual and hybrid definitions against a gold standard of chart review. This study included over 67,000 delivery hospitalizations in 16 California hospitals. ICU admission and massive blood transfusions fared the best among individual indicators; hybrid definitions that included any of the CDC criteria, prolonged postpartum length

of stay, and ICU admission all performed reasonably well. Strengths of the study include the large sample size (>67,000 delivery hospitalizations across 16 hospitals) and their reviewing of several individual and hybrid definitions of severe maternal morbidity. The primary limitations, as with other validation studies, was that negative screens were not reviewed to obtain accurate sensitivities and specificities. Nevertheless, they reported positive predictive values, which were highest when blood transfusions were considered indicators of severe maternal morbidity only when at least 4 units of blood product was transfused (i.e. a transfusion of <4 units of blood product was not considered a near miss event). These positive predictive values ranged from 56% to 88%. Other definitions fared reasonably well, though with a rare outcome such as severe maternal morbidity, high positive predictive values are difficult to achieve, even with accurate definitions.

Overall, several definitions of severe maternal morbidity are reasonable and appropriate depending on the specific aims of a research endeavor and the inherent limitations of datasets and available resources. As recommended, in the absence of consensus of a single definition, it is the responsibility of the researcher to create, adopt, or adapt an existing criteria.[21]

2.2.2 Causes and indicators of severe maternal morbidity

Severe maternal morbidity is a heterogeneous outcome with several distinct etiologies and phenotypes. Historically, there have been 3 approaches for categorizing the causes of near miss cases (based on disease-specific, management, and organ-system dysfunction criteria).[22] However, the current paradigm focuses on vital organ dysfunction/ failure and related, severe complications as the principle drivers.

Organ dysfunction or failure. Regulatory and research groups have recognized organ dysfunction or failure as an important, overarching cause of severe maternal morbidity.[1,11] Though

definitions of severe maternal morbidity have evolved over the past two decades, cardiovascular, respiratory, cerebrovascular, renal, and hepatic dysfunction/ failure remain recognized contributors. Conditions noted with the highest frequency in the literature include: blood transfusion, organ system failure (e.g. cardiovascular or renal failure), as well as eclampsia. Appendix B includes the full list of conditions that the CDC include as indicators and causes of severe maternal morbidity.

Severe complications. Separately, complications that occur during the peripartum period, such as hemorrhage, hypertensive disorders, obstructed labor, embolism, infection, sepsis, shock, and eclampsia may cause severe maternal morbidity.[23-25]

Historically, infection was the leading cause of maternal morbidity and mortality. In the 19th century, sepsis was responsible for up to 50% of all maternal mortality.[26] Recently, particularly in high-income settings, improved peripartum medical care and the introduction of new pharmacologic interventions has substantially reduced the burden; however, in some study populations, upwards of 1 in 4 cases are due to infection.[25] Cited risk factors for infection and sepsis include: Cesarean delivery, multiple pregnancy, artificial reproduction techniques, and hysterectomy.[25-27]

Consistently, postpartum hemorrhage accounts for the plurality of cases of severe maternal morbidity, but many reports lack consistent quality of data.[23,24,28,29] For example, some datasets do not include the volume of blood products administered, but rather include a binary variable indicating whether a blood transfusion occurred. Some argue that transfusion of <4 units of red blood cells alone might not constitute severe maternal morbidity because the mother's life was unlikely to be at risk. However, as discussed above, Main, *et al.* found that blood transfusion as an indicator was found to have high precision in identifying severe maternal morbidity when used as

part of a multi-factorial criteria system, though the positive predictive value increased if the definition was restricted to only including >4 units transfused.[30]

2.2.3 Known risk factors of severe maternal morbidity

2.2.3.1 Non-modifiable risk factors

Several nonmodifiable risk factors of severe maternal morbidity have been identified. First, those with *placental anomalies* are as much as 36-91 times greater for those with placenta accreta (placenta attaching too deep in the uterine wall) and 1-3 times greater for those with placental abruption compared with women without these characteristics.[31] **Second,** *shorter gestation* has been associated with increased risk of severe maternal morbidity. In a cohort of over 115,000 women, those delivering earlier than 37 weeks gestation exhibited higher risk than those who delivered at 39+ weeks' gestation (12.3/1,000 vs. 1.4/1,000, respectively). Women who delivered between 23-27 weeks were at the greatest risk (OR=9.1 [5.5, 15.0])[31] with other research groups finding similar effects.[32,33] **Third**, incidence of *gestational diabetes* is nearly 3-times higher in women with gestational diabetes compared with women free of diabetes (6.9/ 1,000 vs. 2.5/1,000, respectively).[31] Gestational diabetes might be viewed as a modifiable risk factor due to weight maintenance, etc., but within the context of a stand-alone risk factor, we choose to include it in this section. **Fourth**, *racial and ethnic minorities* exhibit some of the most elevated rates of severe maternal morbidity. Black women are at the highest risk compared with non-Hispanic Whites (28.4/ 1,000 deliveries vs. 11.4/ 1,000 deliveries, respectively).[32,34-39] Hispanic women have also been shown to be at increased risk (14.5/ 1,000) and Asian/ Pacific Islanders/ American Indians/ Alaskan Natives all exhibit approximately 1-1.5 times the risk compared with White women.[39] **Fifth**, women who have undergone a *previous Cesarean delivery* are approximately 2 times as

likely to experience severe maternal morbidity after adjusting for education, payer source, age, race, smoking status, parity, preexisting conditions, multiple births, and BMI (OR=2.0 [1.4, 3.0]).[36] **Sixth**, *multiparous and nulliparous women* are at increased risk of severe maternal morbidity compared with primiparous women, though the magnitude of effect is relatively small (8% higher among cases).[36,40] **Lastly**, compared with singleton births, *delivering multiples* has been associated with 2-4 times the risk of severe maternal morbidity, which is consistent across studies.[32,36,41] While there are many non-modifiable risk factors for the causes of severe maternal morbidity, there are others that might be effective targets of clinical intervention.

2.2.3.2 Modifiable risk factors

Preexisting, chronic disease increases the risk of severe maternal morbidity. In particular, hypertension, diabetes, asthma, cardiac disease, sickle cell disease, and cerebrovascular disease are all positively associated. In a large case-control study (9,500 cases and 41,000 random controls), women with a preexisting condition were at 2 times the risk compared with those without (OR=2.1 [1.9, 2.3]).[36] Similar findings have been reported in other populations, including in chart review and cohort studies.[29,39]

Cesarean delivery is positively associated with severe maternal morbidity, with 3 to 8-fold increased magnitude of risk. [33,42-44] While there is consensus regarding the association between Cesarean delivery and severe maternal morbidity, there may be merit in the notion of distinguishing between primary or repeat procedures (since 30-40% of Cesarean deliveries in the U.S. are repeat procedures) and timing of delivery, though the epidemiologic literature in this area is sparse.[42,45,46]

Obesity is a commonly studied risk factor for severe maternal morbidity,[29,33,42] yet there is some disagreement in the literature regarding the direction and magnitude of the association. For

example, in a large cohort study, obesity was found to be associated with mild, increased risk of severe maternal morbidity (OR: 1.2, [1.1, 1.3]).[36] Similar effects have been reported throughout the literature with the exception of a recent population-based retrospective cohort study, which found no association with BMI (measured as a continuous variable).[47] These disparate results might be a function of methodologic differences regarding study design, confounder selection, as well as exposure and outcome definition. A crucial component of our proposal is using theory-based causal graphs to select appropriate confounders.[48]

Maternal age, while not modifiable at the individual level, has been shown to be associated with increased risk of severe maternal morbidity.[36] The mean age of mothers in the U.S. has increased over the past 15 years, with women's age at their first birth having the largest increase (24.9 years to 26.3 years).[49] In a cohort of more than 3 million women, the risk of severe maternal morbidity increased with age,[39] a finding supported by a separate study that found mothers ≥35 years of age are at a modest increased risk compared with women <35 years of age (241.9/1,000 vs. 178.0/1,000).[36]

Smoking during pregnancy has a mild effect on severe maternal morbidity risk. It has been associated with 1-1.5 times the risk, however few studies have examined the association.[31,36] In the two studies we are aware of on this topic, the effect estimates indicated only mild increased risk above non-smokers. Furthermore, there was no distinction regarding smoking amount, which has been shown to impact pregnancy outcomes.[50]

2.3 Total Gestational Weight Gain

Inadequate or excessive gestational weight gain is associated with several adverse maternal, fetal, and child health outcomes.[51-55] However, to our knowledge, only one study has formally examined the association between gestational weight gain and severe maternal morbidity.

In 2019, Marissa Platner, et al. reported that weight gain above the 2009 IOM recommendations was associated with increased risk of severe maternal morbidity. In a retrospective sample of over 500,000 term, singleton deliveries, this group defined their outcome as the presence of any 1 of the 21 CDC indicators (excluding those with implausibly short length of stay, which was not specified), maternal death, or maternal transfer to another facility. Gestational weight gain was defined as within, below, 1-19 lbs above, or 20+ lbs above the IOM recommendations by prepregnancy BMI category. Adjusted logistic regression was performed and odds ratios calculated. The authors found that weight gain 1-19lbs above the IOM guidelines was associated with an 8% (2%-13%) increased odds of severe maternal morbidity compared with those who gained within the guidelines. Even higher weight gain (20+ lbs above the guidelines) was associated with 20% (12%-31%) increased odds, compared with the same referent. Overall, this was a well-designed and executed study; however, the principal limitation was this groups' exclusion of preterm deliveries, of which upwards of 40% of all severe maternal morbidity cases are a part.[32] Additional research is needed to fill this gap in the literature.

Though only Platner, et al. has reported on the direct association between gestational weight gain and severe maternal morbidity, previous efforts have shown that many of the adverse health outcomes for which suboptimal gestational weight gain is a risk factor are themselves risk factors for or causes of severe maternal morbidity, discussed below.

2.3.1 Vital organ dysfunction

Hypertensive disorders. It is well-established that preeclampsia and other hypertensive disorders are risk factors or causes of severe maternal morbidity.[56] Hypertensive disorders themselves are often the result of arterial stiffness and endothelial dysfunction, which may lead to renal and liver impairment, pulmonary edema, as well as other adverse, vascular anomalies. The epidemiologic literature on gestational weight gain and pregnancy-related hypertensive disorders is varied in quality. However, in a cohort of nearly 12,000 women, for every 200 grams per week gains up to 18 weeks gestation, there was approximately a 1.3 times increased risk of gestational hypertension and preeclampsia.[57]

Several plausible physiologic mechanisms may explain how excessive gestational weight gain may increase the risk of severe maternal morbidity by way of hypertensive disorders during pregnancy. First, women who gain excessive weight during pregnancy may express similar physiologic characteristics as overweight or obese individuals. Excess weight may lead to impairments in vasodilation properties, increased sympathetic activity, insulin resistance, and over activation of the renin-angiotensin system, and as a result, hypertension.[58] It has also been proposed that obesity leads to high activation of the nuclear factor kB pathway and increased superoxide (O_2^-) generation in the vascular wall may contribute to decreased bioavailability of nitric oxide, which plays a major role in endothelial behavior.[58] Dysfunction in these systems may lead to loss of vascular homeostasis. Second, increased visceral adiposity (such as that caused by excessive weight gain) may to physical compression of the kidneys, activation of the renin-angiotensin-aldosterone system, and increased sympathetic nervous system activity, which act as mediators of abnormal kidney function and hypertension.[59] To summarize, 1) increased adiposity may lead to endothelial dysfunction directly, which may cause one to develop hypertension, or 2)

physical compression of the kidneys due to excessive adipose tissue in the same compartment initiates a cascading reaction that may lead to hypertension.

Acute renal failure/ dysfunction. No known epidemiologic evidence exists on the association between gestational weight gain and renal dysfunction in pregnancy; however, as above, there are several pathways that may explain the relationship. In general, acute kidney injury is usually caused by ischemia, hypoxia, inflammation, and nephrotoxicity.[60] Adipose tissue and adipose-derived stem cells, which are associated with low-grade inflammation and hypoxia, exert influence on the microenvironment of surrounding tissues via paracrine and endocrine action.[61,62] Therefore, with the unique pattern of fat accretion during pregnancy (depositing preferentially over the hips, back, and upper thighs up to ~30 weeks' gestation),[63] it is plausible that physical compression of the kidneys can lead to their dysfunction and more indirectly, endothelial dysfunction caused by increased adiposity may lead to renal impairment.[58,59]

Acute liver failure. Pregravid central obesity increases the risk of nonalcoholic fatty liver disease.[64] The liver plays a key metabolic role in lipid metabolism, which proves exceedingly important with high calorie and fat consumption.[65] Through increased activation of transcription factors and a cascade involving fatty acid transport, translocase, and binding proteins, lipid droplets can begin to form within the hepatocytes. This accumulation is the hallmark of a variety of liver disorders including acute fatty liver in pregnancy. Though difficult to establish without rigorous dietary monitoring during pregnancy, it is possible that excessive weight gain during pregnancy, particularly if due to an imbalanced diet that is high in fat, places a woman at increased risk for fatty liver development, liver dysfunction and potentially, severe maternal morbidity.

Gestational diabetes. Pregnancy is a period characterized by increased insulin sensitivity. A recent systematic review found that, among 8 studies and 13,748 total participants, excessive gestational weight gain before glucose screening was positively associated with the odds of gestational diabetes compared with those without excessive gestational weight gain (OR=1.4 [1.2, 1.6]).[66] Diabetes, while not a primary cause of severe maternal morbidity, may increase the risk of experiencing a near miss.[42] Furthermore, if left untreated, these elevated blood glucose levels may damage vital organ systems such as the cardiovascular and renal systems, the dysfunction of which are known causes of severe maternal morbidity.[67]

Respiratory anomalies. Elevated pregravid BMI and excess weight gain during pregnancy may act amplify already diminished respiratory function, a characteristic common in overweight and obese individuals outside of pregnancy. [68,69] Some evidence suggests that prepregnancy obesity and excessive gestational weight gain are associated with increased risk of maternal respiratory complications.[70]

2.3.2 Severe complications

Hemorrhage. Evidence suggests an association between excessive gestational weight gain and postpartum hemorrhage.[71,72] Possible mechanistic links for this association include the susceptibility of prolonged labor with increased risk of uterine atony, increased pelvic soft tissue narrowing the birth canal, and hemostatic changes due to increased adiposity. Epidemiologic evidence suggests that in some populations, postpartum hemorrhage is responsible of up to 50% of all cases of severe maternal morbidity, but the lack of standardization in research settings, clinical disagreement regarding what volume of blood loss constitutes severe maternal morbidity, and the availability of robust data have made the study of this risk factor difficult.

Sepsis/ Shock. Finally, while gestational weight gain is not likely to increase the risk of infection or sepsis directly, excessive weight gain during pregnancy has been linked to higher rates of Cesarean delivery, which is a risk factor for both, sepsis and severe maternal morbidity.

2.4 Early Gestational Weight Gain

Gestational weight gain early in pregnancy is associated with maternal health outcomes. Weight gain early in pregnancy is a risk factor for many other pregnancy outcomes for both, mother and child, including delivering small or large for gestational age infants, maternal development of comorbidities such as gestational diabetes, asthma, or hypertensive disorders of pregnancy.[73,74] However, to this point, no one has endeavored to examine this exposure within the context of severe maternal morbidity. Our concurrent work *(Specific Aim 2)* supports an association between elevated, total gestational weight gain and severe maternal morbidity, but there is evidence that early weight gain might also be associated with risk of several, known risk factors or causes of severe maternal morbidity.

The available literature suggest that excess weight gain early in pregnancy has a negative effect on pregnancy outcomes and for certain outcomes, may be more critical than total gestational weight gain. **First**, it has been shown excessive weight gain in the first trimester is associated with an ~20% increased odds 95% confidence interval: 0.2%, 51%) of gestational diabetes compared with those who do not experience excessive weight gain,[75] a trend that was supported by a separate chart review study of 413 women that found an association between first trimester weight gain and risk of hyperglycemia.[76] Furthermore, these associations did not persist with gestational weight gain in the second trimester or beyond. **Second**, compared with women who remain within the

recommended weight gain during the first half of pregnancy, women who gain more weight during the same period are at increased risk of developing hypertensive disorders during pregnancy (125/1,000 versus 86/1,000, respectively),[57,77] a precursor for several causes of severe maternal morbidity. **Third**, excessive gestational weight gain in the first trimester might be associated with increased asthma exacerbation during pregnancy.[78] Incident asthma places one at higher risk of several causes of severe maternal morbidity, including placental anomalies, hemorrhage, pulmonary embolism, and intensive care unit admission,[79] all of which are causes of severe maternal morbidity. A common theme for the 3 examples above is that the magnitude of association with early weight gain is comparable or stronger than available evidence supporting their association with total weight gain.

Exploring gestational weight gain early in pregnancy because we can isolate weight gain before the development of any of the conditions above that might alter woman's weight gain trajectory (through clinical intervention or the natural course of disease). For example, at Magee-Womens Hospital, women are screened for gestational diabetes from 24-28 weeks gestation; any subsequent clinical intervention to treat the condition might lead to lower, total weight loss than if no intervention had been given. Also, women who develop hypertensive disorders during pregnancy are more likely to experience edema compared with women who remain normotensive, which might result in greater, total weight gain; however, weight gain in the first half of pregnancy is less likely a function of clinical edema caused by hypertensive disorders[57] There is sufficient evidence, both epidemiological and physiological, to support an association between early gestational weight gain and severe maternal morbidity, but no one has formally examined the relationship. This is an important gap in the literature that this project will fill.

2.5 Population Attributable Fraction in Pregnancy Research

An overarching gap in the epidemiologic literature on severe maternal morbidity is that, while many risk factors have been identified, none have endeavored to quantify the burden that these risk factors contribute to severe maternal morbidity. As demonstrated above, epidemiologic studies thus far have reported associations for various exposures and the risk of severe maternal morbidity to various degrees (e.g. preexisting medical conditions, elevated body mass index, and so on), but we do not know how those associations translate could translate to real-world reductions in severe maternal morbidity.

Calculating the population attributable fraction allows us to calculate the percent of severe maternal morbidity attributable to the risk factor of interest. Said another way, this method provides a way to calculate the percent of cases of a given outcome that could be prevented if the prevalence of a known risk factor was modified. [80] Given the output generated using this method, it has practical implications for informing interventions.

Population attributable fractions have been used across research fields, including those studying adverse pregnancy outcomes. One of the largest studies to incorporate this methodology was a systematic review and meta-analysis by Flenady, et al., which was published in the Lancet in 2011.[81] Here, the authors calculated the burden of risk factors of stillbirth in high income countries and found population attributable fractions ranging from 4-23%, depending on the risk factor. Similar methods have been used in other high-profile research and is recognized as a valuable tool in providing practical information for public health intervention efforts.[82,83]

Severe maternal morbidity as an outcome is a well-suited candidate for the use of this method. First, one of the assumptions of calculating population attributable fractions is that the risk factors that are being calculated are modifiable, of which severe maternal morbidity has

several. Second, for population attributable fractions to be reliable, the analysis must be performed in a well-defined population. Since much severe maternal morbidity research is done at individual institutions, there is less heterogeneity in sample demographics. Third, severe maternal morbidity, like nearly all pregnancy-related adverse outcomes, can be measured in a short time frame (compared with say, development of cardiovascular disease). Finally, given severe maternal morbidity and mortality are the worst endpoints of pregnancy among mothers, there is heightened interest in developing interventions to decrease its incidence. Taken together, new research in this field should use practical approaches like population attributable fraction to present results that are geared towards translation to clinical practice.

3.0 Manuscript 1: Total Gestational Weight Gain and Severe Maternal Morbidity

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3.1 Abstract

Objective

High pregnancy weight gain has been associated with severe maternal morbidity among term deliveries. We tested this association and extended it to preterm deliveries, which make up half of all cases.

Methods

We used a retrospective cohort of 84,241 delivery hospitalizations from Magee-Womens Hospital, Pittsburgh, PA (2003−2012). Total gestational weight gain was assessed using gestational age- and body mass index (BMI)-specific z-scores. We defined severe maternal morbidity as the presence of any 1 of the 21 Centers for Disease Control and Prevention diagnosis or procedure codes, admission to the intensive care unit, or extended postpartum length of stay. We used multivariable logistic regression stratified by term/preterm birth to determine the association between total gestational weight gain and risk of severe maternal morbidity after adjusting for confounders.

Results

Severe maternal morbidity occurred in 4.7% and 1.2% of delivery hospitalizations among preterm and term deliveries, respectively (1.9% overall). Among term deliveries, the risk of severe maternal morbidity was flat from a weight gain z-score of -2 SD to +0.5 SD, after which it increased. A z-score of +2 and +3 (equivalent to 31kg and 41kg at 40 weeks gestation for a normal weight woman) were associated with 0.53 (95% confidence interval 0.09, 0.96) and 0.86 (0.09, 1.6) excess cases of severe maternal morbidity per 100 delivery hospitalizations compared with a z-score of 0 (16kg at 40 weeks). Low weight gain was not associated with risk of severe maternal morbidity in this group. Among preterm deliveries, the adjusted risk of severe maternal morbidity

decreased from a z-score of -3 (6.6/100), reaching its nadir at a z-score of approximately +0.5 SD (5.71/00), after which it increased until a z-score of +3 (9.1/100). In this group, low weight gain was mildly associated with increased risk of severe maternal morbidity, with a z-score of -3SD associated with 0.44(-1.4, 2.2) excess cases per 100 delivery hospitalizations. High weight gain was associated with the highest number of excess cases among preterm deliveries, with a z-score of +0.3 SD associated with 3.0 (-0.54, 6.6) excess cases.

Conclusions

Excessive gestational weight gain is associated with increased risk of severe maternal morbidity during delivery hospitalizations in both, term and preterm deliveries and low weight gain is associated with increased risk among preterm deliveries. Interventions aimed at avoiding very high weight gain during pregnancy might reduce the risk of severe maternal morbidity.

3.2 Introduction

Severe maternal morbidity affects over 50,000 women every year in the U.S, more than double that than women in the U.K.[84] Its incidence in the US has doubled since 1993,[1,22] paralleling the increase in pregnancy-related maternal mortality.[1,13,85] Examples of severe maternal morbidity include eclampsia, myocardial infarction, pulmonary embolism, renal failure requiring dialysis, or hemorrhage requiring an unplanned hysterectomy.[1] Severe maternal morbidity often leads to extended hospital stays, long-term rehabilitation, prolonged morbidity, and decreased quality of life.[23,86-88] To reduce risk, professional medical associations stress improvements in the quality of healthcare and identification of high risk women during pregnancy and delivery.[21] However, major

gaps remain in our understanding of modifiable risk factors for severe maternal morbidity that could be targets for prevention.

The obesity epidemic is thought to be a major contributor to the rise in severe maternal morbidity.[85,89] Modifying weight before conception, however, is challenging because most women do not seek preconception care[5] and half of pregnancies are unplanned.[6] Alternatively, weight gain during pregnancy can be effectively managed using antenatal lifestyle interventions .[90,91] A recent study examined the relation between gestational weight gain and severe maternal morbidity among term deliveries in New York City.[92] The authors reported that pregnancy weight gain in excess of the 2009 Institute of Medicine weight gain recommendations had a positive association with severe maternal morbidity. Nevertheless, around 40% of severe maternal morbidity cases deliver preterm[31,32] and whether these findings are generalizable to all cases is not known.

We sought to determine the association between total gestational weight gain and the risk of severe maternal morbidity separately among preterm and term deliveries.

3.3 Methods

Data source

We used a retrospective cohort of delivery hospitalizations at Magee-Womens Hospital of the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania. Data came from the Magee Obstetrics, Medical, and Infant (MOMI) database, an electronic data repository, which populates information from admitting services, medical records coding (procedure & diagnosis codes), medical record abstraction, the birth record, ultrasound and other ancillary systems. Administrators routinely examine the database to ensure accuracy and verify the information with

medical records. An inter-rater reliability study showed excellent agreement for self-reported prepregnancy weight, self-reported height, and gestational age at delivery.[93] This analysis was approved by the University of Pittsburgh Institutional Review Board.

There were 88,713 delivery hospitalizations in the MOMI database from 1-January-2003 to 31-May-2012, when all key variables for this analysis were routinely available. We excluded 4 records that were missing data on infant sex, parity, and dates of admission and discharge as well as 242 records with a gestational age at delivery <20 or >42 weeks. We excluded 4,226 multiple gestations because their gestational weight gain and mean gestational age at delivery differ from singleton pregnancies.[94,95] The final analytic sample was 84,241.

Exposure definition

Prepregnancy weight was self-reported at the first prenatal visit. Body mass index (BMI) was calculated using prepregnancy weight (kg) divided by prepregnancy height (m^2) and categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese (≥30.0 kg/m^2).[96] Weight at delivery was based on last measured antenatal weight or a self-reported weight at delivery. Total gestational weight gain (kg) was calculated by subtracting prepregnancy weight from delivery weight. To remove the correlation between gestational weight gain and length of pregnancy,[97-99] we converted total weight gain to gestational age-standardized z-scores based on prepregnancy BMI category-specific charts. These charts were created using serial weight gain measurements from a sample of women with healthy, term pregnancies at Magee-Womens Hospital.[97,98]

Outcome definition

We defined severe maternal morbidity as having any of the following criteria: the presence of any one of the twenty-one Centers for Disease Control and Prevention International

Classification of Diseases (9th revision) diagnosis or procedure codes used for the identification of severe maternal morbidity (See appendix A for specific ICD-9 codes),[12,23] maternal admission to the intensive care unit (ICU), or extended postpartum length of stay (>3 standard deviations beyond the mean length of stay according to mode of delivery).[30] We chose this definition because these criteria are commonly used in studies relying on administrative data.[30] We determined the sensitivity of our results to removing each of the 3 criterion or eclampsia, severe anesthesia complications, and puerperal cerebrovascular disorders if they were they only indicator of severe maternal morbidity. Others have shown that misclassification may be common in these ICD codes.[100]

Covariates

Gestational age was determined using the best obstetric estimate based on a comparison of menstrual dating and ultrasound dating[101] ascertained from the medical record. Preterm birth was defined as delivery of a live-born infant at <37 weeks' gestation. Self-reported data were available on maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, and Other), education (less than high school, high school graduate, some college, and college graduate), smoking during pregnancy (yes/no), marital status (married, unmarried), and maternal age (5-knot restricted cubic spline). Insurance type (private/ other) and parity (none or ≥1) came from newborn records. Preexisting hypertension (yes/no) and preexisting diabetes (yes/no) were based on ICD-9 codes.

Statistical analysis

In our final analytic sample, records were missing data on prepregnancy weight or height (24%), delivery weight (8.6%), length of hospital stay (3.6%), maternal education (0.5%), or race/ethnicity (0.05%). We addressed the missing data using multiple imputation by chained equations (MICE), which allows for the specification of independent distributions for each

imputed variable.[102,103] We jointly imputed mother's height, prepregnancy weight, delivery weight, length of stay, education, and race/ethnicity using data on preexisting conditions, year, route of delivery, maternal age, smoking, parity, gestational diabetes, insurance, marital status, fetal death, gestational age at delivery, maternal ID, and census tract of residence). All continuous variables were log-transformed before the imputation. We created 25 imputed datasets to stabilize our variance estimates.[104] Counts of subjects in each BMI group were averaged over the imputed datasets. We also performed a sensitivity analysis using the sample with complete data (n=57,922).

We estimated the association between gestational weight gain and severe maternal morbidity using multivariable logistic regression. Models use generalized estimating equations and an exchangeable correlation structure to account for 11,224 repeated pregnancies in the cohort. A priori, in addition to performing nonstratified analyses, we stratified models by term and preterm birth. Denominators were based on all delivery hospitalizations. To accommodate flexible, nonlinear relations, we specified total gestational weight gain z-score as a restricted cubic spline with 3 knots determined by Akaike information criterion and placed at 10%, 50%, and 90% on the distribution.[105] We used theory-based causal graphs[106] to identify potential confounders, which were set to the population means and included in the final model. After model estimation, we used the 'margins' command in STATA to calculate adjusted predicted probabilities, risk differences and corresponding 95% confidence intervals for selected z-score values ranging from -3 SD to +3 SD. We multiplied the adjusted risk differences and 95% confidence intervals by 100 to estimate the number of excess cases of severe maternal morbidity per 100 delivery hospitalizations. Associations between pregnancy weight gain and other health outcomes tend to vary by prepregnancy BMI,[107] so we reran models separately for normal weight, overweight, and obese women (counts of cases among underweight women were prohibitively small). Further, we reran

models using the sample with complete data as well as with modifications to the definition of the outcome.

3.4 Results

Women tended to be non-Hispanic White, multiparous, married, college-educated, normal weight, and had private health insurance (Table 1). The mean (standard deviation) age of mothers was 29 (6.1) years and the mean gestational age at delivery was 38 (2.5) weeks in the overall population. The incidence of preterm birth was 11%. Compared with women who delivered at term, those who delivered preterm were more likely to be unmarried, less educated, and smokers, and have preexisting hypertension or diabetes and use non-private health insurance.

In the overall sample, the mean gestational weight gain was 15(7.0) kg (z-score (SD) -0.10(1.1), and 16 (5.7), 16 (5.9), 15 (7.2), and 12 (8.8) kg among underweight, normal weight, overweight, and obese women, respectively. Total pregnancy weight gain was higher in term (15 (6.9) kg) compared with preterm deliveries (12 (7.3) kg), but weight gain z-scores did not differ (-0.09(1.0) and -0.12(1.3), respectively). Women who were younger, non-Hispanic White, unmarried, had preexisting hypertension or diabetes, had completed some college, did not smoke during pregnancy, or were nulliparous tended to have higher gestational weight gain z-scores (Table 2). There were negligible differences in weight gain by insurance status. There were similar patterns in term and preterm deliveries with one exception: women who delivered preterm and were married tended to have higher weight gain.

Overall, severe maternal morbidity occurred in 1.9 per 1000 delivery hospitalizations (n=1,598) and was over five times as common in preterm (6.4%) versus term (1.3%) deliveries

(Table 3). Among both term and preterm deliveries, women who were obese, non-Hispanic Black, unmarried, lacking private health insurance and started pregnancy with hypertension or diabetes were more likely than their counterparts to have severe maternal morbidity (Table 3). Overall and in term deliveries, women who were younger and less educated were more likely to have severe maternal morbidity, but preterm deliveries among older women were more likely to face a severe event. There were no differences in the incidence of the outcome by parity in preterm deliveries or smoking in term deliveries. However, term nulliparas had a higher incidence than term multiparas, and non-smokers had a higher incidence than smokers in preterm births. Compared with term cases of severe maternal morbidity, cases occurring preterm were more likely to be admitted to the ICU, have a long postpartum stay, or have acute renal failure, adult respiratory distress syndrome, eclampsia, pulmonary edema, shock, sickle cell anemia with crisis, hysterectomy, or require ventilation, and less likely to have heart failure, puerperal cerebrovascular disorders, or severe anesthesia complications (Appendix I).

Overall, the unadjusted incidence of severe maternal morbidity followed a J-shaped distribution (Table 4), with a weight gain z-score of ≥+2 SD associated with the highest risk (3.9/100 delivery hospitalizations), a z-score from -1 to <0 the lowest (1.7/100), and a z-score<-2 similar to z-scores +1 to <+2 (2.5 and 2.4/100, respectively). Term and preterm births followed a similar pattern (Tables 5 and 6), but the highest unadjusted risk among term deliveries with z-scores≥+2 SD was 2.7/100 and among preterm deliveries with the same z-scores, 9.3/100.

After adjusting for maternal age, prepregnancy BMI, race/ ethnicity, parity, education, preexisting hypertension/ diabetes, method of payment, marital status, and smoking during pregnancy, there was a non-linear association between gestational weight gain z-score and risk of severe maternal morbidity in our overall analysis as well as among term and preterm deliveries

(Figures 1 and 2). Risk decreased gradually from a z-score of -3 to approximately +0.5, after which it increased. Compared with a weight gain z-score of 0 (16kg among normal weight woman at 40 weeks), pregnancy weight gain z-scores of +1 and +2 (equivalent to 23 kg and 31 kg at 40 weeks)) were associated with 0.38(0.20, 0.56) and 1.0(0.46, 1.5) excess cases of severe maternal morbidity per 100 delivery hospitalizations, respectively (Table 7). Furthermore, in the extremes of weight gain, compared with the same referent, a z-score of +3 (41kg at 40 weeks among normal weight women) was associated with 1.6(0.68, 2.6) excess cases. There was more variability in the point estimates among low weight gain groups when we stratified analyses by prepregnancy BMI category, but the relationships were not meaningfully different to warrant alternative conclusions; point estimates were not meaningfully different in high weight gain groups, though compatibility intervals were wider in stratified analyses, as expected (Appendix E). In analyses limited to complete cases or after modifying the definition of the outcome, there was no meaningful differences in associations (data available upon request).

3.5 Discussion

Our data suggest that gestational weight gain outside normal ranges is associated with increased risk of severe maternal morbidity. In terms of absolute risk, preterm deliveries were at higher risk of severe maternal morbidity across all z-scores had roughly a 4-fold higher risk of severe maternal morbidity from weight gain z-scores from -3 to +3 SD. Importantly, our estimates were of the strongest magnitude in the highest strata of weight gain (i.e. >50 lbs for normal weight women at 40 weeks gestation). This is relevant because we found only 13% of women gained within these ranges (13% among term and 16% among preterm deliveries. Our results suggest that

high gestational weight gain is a moderately potent risk factor for severe maternal morbidity. Taken together, our findings help add support to the importance of avoiding very high weight gain during pregnancy.[54]

This is an important contribution to the literature because we confirm and extend the findings of previous reports. Others have shown that high gestational weight gain is associated with severe maternal morbidity[92] and other adverse perinatal outcomes,[54,108] but we are the first to examine the former among both, preterm and term deliveries. This is a valuable addition because nearly half of all severe maternal morbidities occur in deliveries before 37 weeks gestation.[32] In the only other known, published study of the association between gestational weight gain and severe maternal morbidity, Platner, et al. reported that among term deliveries, the odds of severe maternal morbidity was elevated among those who gained 1-19 pounds above the 2009 Institute of Medicine recommendations (OR (95% CI): 1.08 (1.02, 1.13)) and even higher among those who gained 20 or more pounds above the recommendations (1.21 (1.12, 1.31)) compared with those who gained within the recommendations.[92] Our findings support their conclusions among term deliveries, including the threshold of gestational weight gain at which a substantial increase in risk is observed (approximately >20 pounds above the IOM recommendations for normal weight women).[94] Among preterm deliveries, however, we found that the risk of severe maternal morbidity was over 3-times higher than term deliveries across all z-scores ≥0.5 SD (~19kg among normal weight women at 40 weeks gestation). Furthermore, we found that very low weight gain was associated with slightly increased risk of severe maternal morbidity, but only among preterm deliveries. Our finding that low weight gain was not associated with increased risk among term deliveries follows Platner, et al, who found no effect among those who gained less than the IOM recommendations. Though we found no evidence of effect measure modification by gestational

age at delivery of the association between gestational weight gain and severe maternal morbidity, knowing that women who deliver preterm are at increased risk of severe events should give clinicians pause when determining risk status. This would be of added importance for multiparous mothers with a history of preterm birth. Though we do not recommend departing from the current guidelines,[94] we urge clinicians to educate their patients about the potential risks of gaining too little or too much weight during pregnancy.

Our findings must be considered within the context of the study limitations. The first broad group of limitations is commonly encountered when studying severe maternal morbidity. Professional obstetrical societies have not endorsed a single comprehensive definition of severe maternal morbidity and we use criteria used widely in studies employing administrative databases.[12,32,34,36,39] However, compared with current gold standard criteria, it is likely that we overestimated the incidence of severe maternal morbidity (more specifically, some cases may not have been sentinel events). Conversely, there are two ways in which we could have underestimated the true incidence; 1) there is potential for false negatives when identifying morbidity from administrative databases and 2) our outcome window was limited to delivery hospitalizations.[30] Though it is common to identify severe maternal morbidity during delivery hospitalization, it is well known that severe events can occur before or after this timeframe.[23] Without data from a validation study on the positive predictive value of our definition, stratified by gestational weight gain categories, it is difficult to know if this introduced bias into our associations. Finally, because severe maternal morbidity is a heterogeneous outcome with multiple etiologies and phenotypes, it is likely that excessive gestational weight gain does not increase the risk of all types of severe maternal morbidity equally. For example, though excessive weight gain plausibly increases the risk of delivery complications (Cesarean section, heart failure, and so on), it probably does not lie

on the causal pathway to sickle cell anemia with crisis or amniotic fluid embolism. Future studies with adequate samples might consider performing analyses using specific indicators rather than a composite measure of severe maternal morbidity.

Regarding limitations specific to our study, the first is related to our exposure definition. Misreporting of weight before pregnancy (which varies across prepregnancy BMI categories[109]) or at delivery may have led to misclassification of gestational weight gain. Though a 2017 systematic review of 62 studies suggested that average reporting error did not largely bias associations between pregnancy-related weight and pregnancy outcomes,[110] if in our sample there was differential misclassification of our exposure, our results may be biased. Second, if the missing data in this analysis varied by key covariates (missing not at random), our estimated association may be spurious. However, we explored the pattern of missing data and found that, while the data was not missing completely at random, there were no concerning patterns among key variables. Finally, others should exercise caution in applying these results to the general obstetric population in the U.S., especially community hospitals or facilities serving a population significantly different from this sample because the incidence of severe maternal morbidity varies by facility type and ethnic/ racial composition of the patient population.[30,34]

Because pregnancy is a time when women have access to regular healthcare and are motivated to optimize their health,[111] gestational weight gain is a potential target to decrease the risk of severe maternal morbidity. Clinicians can pair these specific findings alongside other literature on gestational weight gain and adverse perinatal outcomes to educate their patients on the importance of healthy weight gain and inform their decision-making for when intervention is warranted. These findings could also be incorporated as part of risk assessment tools at the time of delivery hospitalization. Gestational weight gain is likely just part of a constellation of factors

that increases one's risk. To significantly reduce the burden that severe maternal morbidity places on healthcare systems, patients, and their families, we must continue to advocate for more holistic research on this topic, promote access to affordable healthcare, and strive for system-wide, collaborative approaches to better understand how high risk women can be identified and treated.

3.6 Tables and Figures

Table 1 Characteristics of women delivering singleton infants at Magee-Womens Hospital in Pittsburgh, PA, 2003-2012 (N=84,241)

Maternal characteristic	n(% of cohort)
Overall	
Prepregnancy body mass index (BMI cutpoints)	
Underweight (<18.5kg/m^2)	4,096 (4.8)
Normal weight (18.5-24.9kg/m^2)	43,709 (52)
Overweight (25.0-29.9kg/m^2)	20,099 (24)
Obese (≥30.0kg/m^2)	16,337 (19)
Age (years)	
<20	5,930 (7.0)
20-30	38,086 (45)
>30	40,225 (48)
Race/ ethnicity	
Non-Hispanic White	63,062 (75)
Non-Hispanic Black	16,540 (20)
Other	4,639 (5.5)
Parity at conception	
0	38,598 (46)
1 or more	45,643 (54)
Marital status	
Unmarried	33,450 (40)
Married	50,791 (60)
Education	
High school or less	25,694 (30)
Some college	19,477 (23)
College graduate	39,070 (46)
Preexisting hypertension or diabetes	
Yes	3,743 (4.4)
No	80,498 (96)
Smoking during pregnancy	
Yes	12,323 (15)
No	40,630 (85)
Insurance	
Private	43,611 (52)
Public/ Other	40,630 (48)

Table 2 Mean z-score among singleton pregnancies at delivery by maternal characteristic and gestational age at delivery. Magee-Womens Hospital in Pittsburgh, PA, 2003-2012 (N=84,241)

Maternal characteristic	Mean (SD) z-score at delivery
Prepregnancy body mass index (BMI cutpoints)	
Underweight (<18.5kg/m^2)	0.10 (1.0)
Normal weight (18.5-24.9kg/m^2)	-0.14(1.0)
Overweight (25.0-29.9kg/m^2)	-0.14 (1.0)
Obese (≥30.0kg/m^2)	0.03 (1.2)
Maternal age (years)	
<20	-0.05 (1.1)
20-30	-0.06 (1.1)
>30	-0.14 (1.0)
Maternal race/ ethnicity	
Non-Hispanic White	-0.06 (1.0)
Non-Hispanic Black	-0.15 (1.2)
Other	-0.37 (1.0)
Parity at conception	
0	0.02 (1.1)
1 or more	-0.19 (1.1)
Marital status	
Unmarried	-0.07 (1.2)
Married	-0.11 (1.0)
Maternal education	
High school or less	-0.11 (1.2)
Some college	-0.05 (1.1)
College graduate	-0.11 (0.99)
Preexisting hypertension or diabetes	
Yes	0.09 (1.2)
No	-0.11 (1.1)
Smoking during pregnancy	
Yes	-0.18 (1.2)
No	-0.08 (1.0)
Insurance	
Private	-0.08 (1.0)
Public/ Other	-0.11 (1.1)

[a] <11kg among normal weight, 9.5kg among overweight, and 3.3kg among obese women at 40 weeks' gestation.
[b] 11-23kg among normal weight, 9.5-25kg among overweight, and 3.3-19kg among obese
[c] >23kg among normal weight, >25kg among overweight, and >19kg among obese women.

Table 3 Incidence of severe maternal morbidity by maternal characteristic. Magee Women's Hospital Pittsburgh, PA, 2003-2012 (N=84,241)

Maternal characteristic	Cases of severe maternal morbidity (unadjusted incidence)
Overall	
Prepregnancy body mass index (BMI cutpoints)	
Underweight (<18.5kg/m^2)	69 (1.7)
Normal weight (18.5-24.9kg/m^2)	700 (1.6)
Overweight (25.0-29.9kg/m^2)	400 (2.0)
Obese (≥30.0kg/m^2)	427 (2.6)
Maternal age (years)	
<20	145 (2.5)
20-30	670 (1.8)
>30	782 (1.9)
Maternal race/ ethnicity	
Non-Hispanic White	1034 (1.6)
Non-Hispanic Black	468 (2.8)
Other	95 (2.1)
Parity at conception	
0	794 (2.1)
1 or more	804 (1.8)
Marital status	
Unmarried	797 (2.4)
Married	800 (1.6)
Maternal education	
High school or less	637 (2.5)
Some college	391 (2.0)
College graduate	570 (1.5)
Preexisting hypertension or diabetes	
Yes	221 (5.9)
No	1377 (1.7)
Smoking during pregnancy	
Yes	259 (2.1)
No	1339 (1.9)
Insurance	
Private	698 (1.6)
Public/ Other	899 (2.2)

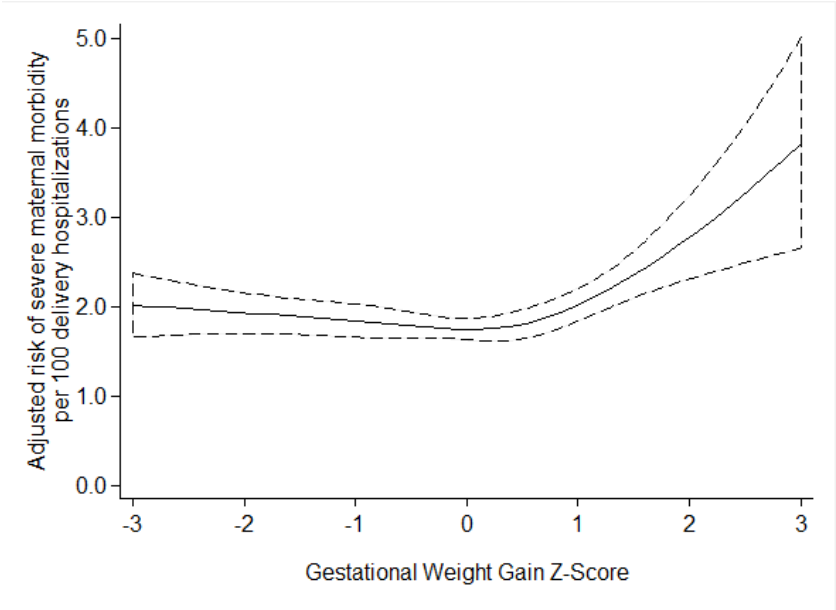

Figure 1 Adjusted, predicted risk of severe maternal morbidity by gestational weight gain z-score.

Solid line represents point estimates, dashed lines represent 95% confidence intervals

Table 4 Cumulative incidence of severe maternal morbidity by gestational weight gain z-score category. Magee-Women's Hospital. Pittsburgh, PA, 2003-2012 (N=84,241)

Gestational weight gain z-score category	n at risk	Unadjusted risk (cases)	Unadjusted RD (95% CI)	Adjusted RD (95% CI)
<-2	3,356	2.5 (86)	0.83 (0.21, 1.5)	0.60 (0.01, 1.2)
-2 to <-1	10,161	1.8 (185)	0.13 (-0.22, 0.48)	0.07 (-0.29, 0.42)
-1 to <0	30,298	1.7 (500)	Reference	Reference
0 to <+1	29,783	1.9 (542)	0.21 (-0.04, 0.45)	0.12 (-0.14, 0.37)
+1 to <+2	9,363	2.4 (234)	0.74 (0.33, 1.2)	0.49 (0.09, 0.89)
≥+2	1,280	3.9 (50)	2.3 (1.0, 2.5)	1.8 (0.67, 2.9)

40-week gestation equivalent weight gain for normal weight women: -2SD(7.0kg); -1SD(11kg); 0SD(16kg); 1SD(23kg); 2SD(31kg)

Table 5 Estimated number of excess cases of severe maternal morbidity per 100 delivery hospitalizations by select gestational weight gain z-scores. Overall delivery hospitalizations at Magee-Womens Hospital, Pittsburgh, PA, 2003-2012 (N=84,241)

Gestational weight gain z-score category	Adjusted risk per 100 delivery hospitalizations (95% confidence interval)	Adjusted RD per 100 delivery hospitalizations (95% confidence interval)
-3 SD	2.1 (1.7, 2.4)	0.30 (-0.07, 0.67)
-2.5 SD	2.0 (1.7, 2.3)	0.22 (-0.07, 0.51)
-2 SD	1.9 (1.7, 2.1)	0.14 (-0.07, 0.35)
-1.5 SD	1.8 (1.7, 2.0)	0.06 (-0.08, 0.21)
-1 SD	1.8 (1.6, 1.9)	-0.01 (-0.10, 0.08)
-0.5 SD	1.7 (1.6, 1.8)	-0.04 (-0.08, -0.002)
0	1.8 (1.6, 1.9)	Reference
+0.5 SD	1.6 (1.4, 1.7)	0.14 (0.08, 0.21)
+1 SD	2.1 (1.9, 2.3)	0.38 (0.20, 0.56)
+1.5 SD	2.4 (2.1, 2.7)	0.67 (0.33, 1.0)
+2 SD	2.5 (2.1, 2.8)	1.0 (0.46, 1.5)
+2.5 SD	3.1 (2.4, 3.8)	1.3 (0.58, 2.0)
+3 SD	2.4 (2.5, 4.3)	1.6 (0.68, 2.6)

40-week gestation equivalent weight gain for normal weight women: -2SD(7.0kg); -1SD(11kg); 0SD(16kg); 1SD(23kg); 2SD(31kg)

4.0 Manuscript 2: Early Gestational Weight Gain and Risk of Severe Maternal Morbidity

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4.1 Abstract

Background

Gestational weight gain is a potentially modifiable risk factor for severe maternal morbidity, but there is no literature on the relationship between weight gain in the first half of pregnancy and severe maternal morbidity.

Methods

We used a retrospective cohort of 4,774 delivery hospitalizations that was sampled from a large cohort and augmented with data on serial weight gain measurements and severe maternal morbidity indicators at Magee-Womens Hospital in Pittsburgh, PA (2003-2011). Absolute risk measures were calculated by weighting the sample by inverse probability weights based on sampling by prepregnancy BMI category. We defined gestational weight gain at 16-19 weeks using prepregnancy BMI- and gestational-age adjusted z-scores to remove potential confounding by gestational age at delivery. We used multivariable logistic regression models, adjusted for prepregnancy BMI race/ ethnicity, maternal education, maternal age at delivery, preexisting hypertension or diabetes, and parity. We calculated predicted probabilities of adjusted risk differences of severe maternal morbidity for select z-scores and present results as the number of excess cases per 100 delivery hospitalizations.

Results

The cumulative incidence of severe maternal morbidity in this sample was 2.1% and was highest among those with z-scores near the mean and lowest in the tails of the distribution of weight gain (2.4/100 among those with a z-score of 0 and 1.6 and 1.2/ 100 among those with z-scores of -2 and +2, respectively). After adjusting for known confounders, we found a similar trend; compared with a z-score of 0 (5.2kg at 19 weeks gestation among normal weight women),

z-scores of -2 and +2 were associated with -0.80(-2.7, 0.76) and -1.1(-2.4, 0.18) fewer cases of severe maternal morbidity, respectively.

Conclusions

We found that weight gain at 16-19 weeks and risk of severe maternal morbidity followed a much different distribution than our previous results on total weight gain, likely due to differences in sample characteristics. These results should be applied with caution across the broader population of those at risk of severe maternal morbidity and should not overshadow our results on the association between total weight gain and severe maternal morbidity. The strongest evidence suggests that weight gain outside normal ranges is associated with moderate risk of severe maternal morbidity and should continue to be monitored throughout pregnancy given its association with other adverse, pregnancy-related outcomes.

4.2 Introduction

Pregnancy-related maternal mortality and morbidity have risen significantly in the U.S. over the past 2 decades[1] and despite renewed focus on improving maternal outcomes,[8,13,112] there has been little abatement in their incidence. Meaningful reduction in severe maternal morbidity will require multidisciplinary approaches, but identifying patient-level risk factors should remain part of any risk reduction strategy. Of the commonly cited, potent risk factors of severe maternal morbidity, most are modifiable only prior to conception (e.g. higher prepregnancy body mass index or preexisting medical conditions)[29,36,89] or would require large-scale, population-level intervention (e.g. improving education and access to healthcare). Gestational weight gain, however, is one risk factor amenable to intervention during pregnancy.[90,91]

Previous work by our group and others suggest that suboptimal or excessive, total weight gain during pregnancy is associated with increased risk of severe maternal morbidity at delivery hospitalization.[92] While understanding this relationship might prove valuable as part of risk assessment protocols during delivery hospitalization or as a tool to help educate pregnant women on the importance of healthy weight gain during pregnancy, using total weight gain as a primary exposure is not without limitations, even when rigorous methods are used.

Total weight gain as an exposure does not account for the timing or trajectory of weight gain and, in the case of outcomes that are associated with hypertensive disorder during pregnancy (e.g. preeclampsia) or gestational diabetes mellitus, an association with total weight gain might be subject to reverse causation.[113] Specifically, hypertension-related edema can result in rapid weight gain in the second half of pregnancy[77,114,115] and gestational diabetes screening with subsequent clinical intervention may alter the trajectory of weight gain.[75] New research is needed to address this gap in the literature by measuring weight gain before clinical manifestations of hypertensive disorders and gestational diabetes screening. Doing so would provide context to existing literature and better inform when and if intervention on weight gain is warranted.

Our objective was to determine the association between weight gain at 16-19 weeks gestation and severe maternal morbidity.

4.3 Methods

Data source and sampling

The data for this retrospective cohort were collected as part of a larger case-cohort study on gestational weight gain at Magee-Womens Hospital of the University of Pittsburgh Medical

Center in Pittsburgh, Pennsylvania. There were 114,736 singleton deliveries at Magee from 1998-2010. In the original study, women were excluded if they were delivering multiple fetuses, had a gestational age <16 or >42 weeks, or did not have a prepregnancy weight measurement (n=80,812 remaining). From these eligible records, 1,411 pregnancies were randomly sampled from each prepregnancy BMI category to form a subcohort for statistical comparisons.

We augmented this dataset with information on serial weight gain measurements gathered via medical record abstraction. Standardized chart abstraction was performed by data collectors with uniform training, who entered data into a computer-assisted data entry system.[116] A reliability study showed high inter-rater agreement, including for important variables such as maternal weight and gestational age. We dropped those observations with missing antenatal weight measurements.

Finally, we merged with this dataset with diagnosis and procedure codes indicating the presence of severe maternal morbidity from the Magee Obstetric, Medical, and Infant (MOMI) database. MOMI is an electronic data repository comprised of information from admitting services, medical and birth records, as well as ultrasound and other ancillary systems. Administrators routinely code and clean the data as well as validate the stored data against medical records.

Of the 8,466 pregnancies in the original subcohort, women were eligible for the present analysis if they delivered from 2003-2011 at 20-42 weeks gestation and had complete data on parity, infant sex, admission and discharge date, and administrative codes indicating severe maternal morbidity (n=6,160). Women were excluded if they no prenatal weight measurements (n=184) or no weight measurement in the gestational age window of interest (16+0 weeks to 19+6 weeks, n=308). If women had more than 1 weight measurement in this window, the one closest to 19 weeks was used. Finally, women who had missing data in key variables were excluded from

the analysis (n=849). Appendix F presents the sampling fractions by prepregnancy BMI category. The final analytic sample consisted of 4,774 delivery hospitalizations. The University of Pittsburgh Institutional Review Board approved this study as exempt because no identifiable information was used.

Exposure definition

The exposure window of interest was 16+0 to 19+6 because it precedes the clinical onset of hypertensive disorders of pregnancy and gestational diabetes screening. Maternal weight at 16-19 weeks was collected by hospital staff at the corresponding prenatal visit. Maternal prepregnancy weight and height were ascertained via self-report at the first prenatal visit. Prepregnancy BMI was calculated and categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese ((≥30 kg/m^2).[96] Weight gain was defined as maternal weight at 16-19 weeks minus prepregnancy weight. If there were more than one weight measurement from 16-19 weeks, we chose the most recent. We converted each gestational weight gain to gestational age-specific z-scores for each prepregnancy body mass index (BMI) category using gestational-age and BMI specific charts, which produces a weight gain measure that is independent of gestational age.[98,99,117] We also modeled gestational weight gain z-scores as a categorical variable using -2 through +2 SD as cutpoints. Weight gain z-scores <-4 or >+4 were considered outliers and excluded. For ease of interpretation, we provide absolute weight gain (kg) at 19 weeks for a range of z-scores.

Outcome definition

We defined severe maternal morbidity as the presence of the 21 Centers for Disease Control and Prevention diagnosis or procedure ICD-9 codes (Appendix B), maternal intensive care unit admission, or maternal prolonged postpartum length of stay (>3 days for vaginal deliveries

and >5 days for Cesarean deliveries, corresponding to >3 standard deviations beyond the mean length of stay). These criteria have been used in a variety of administrative data research on severe maternal morbidity and have been shown to perform reasonably well against a gold standard of chart review.[30]

Confounders

We selected confounders based on theory-based causal graphs and because of the limited sample size, created a parsimonious model to stabilize our statistical models by removing confounders that changed our effect estimates by <7%. The full list of confounders included: mother's prepregnancy BMI, race/ ethnicity, maternal age at delivery, education, marital status, primary method of payment, preexisting hypertension or diabetes, parity, and smoking during pregnancy. The parsimonious model consisted of prepregnancy BMI (4-knot restricted cubic spline), race/ ethnicity (non-Hispanic White, non-Hispanic Black, and other), maternal education (less than high school, some college, or college graduate), maternal age at delivery (3-knot restricted cubic spline), preexisting hypertension or diabetes (yes/ no), and parity (nulliparous or 1+ previous birth). Confounders were set to population means and included in the final model.

Statistical analysis

Unadjusted risk measures were calculated after weighting the cohort by the inverse of the sampling fractions. To estimate the association between gestational weight gain at 16-19 weeks and severe maternal morbidity, we used multivariable logistic regression models with generalized estimating equations and an exchangeable correlation structure to account for 99 repeated pregnancies in the dataset. Denominators were based on all delivery hospitalizations. Following model estimation, we calculated the predicted probabilities, risk differences, and corresponding 95% confidence intervals of severe maternal morbidity by selected weight gain z-scores from -3

standard deviations to +3 standard deviations. We presented these results as the number of excess cases of severe maternal morbidity per 100 delivery hospitalizations. We also performed a series of sensitivity analyses where we modified our exposure window (10-13 weeks, 24-28 weeks, and 16-19 weeks to delivery) to test whether the association with severe maternal morbidity differed. We also tested the association between total gestational weight gain and severe maternal morbidity among women who had both, weight measurements at delivery hospitalization and serial weight gain measurements.

4.4 Results

Most of the women in this sample were normal weight, >30 years of age, non-Hispanic White, multiparous, married, holders of college degrees, and used private insurance as their primary method of payment (Table 6). The incidence of preterm birth was 9.5%. Less than 5% has preexisting hypertension or diabetes and 13% reported smoking during pregnancy.

There were no meaningful differences in the incidence of severe maternal morbidity or the prevalence of key maternal variables between this cohort with that of the larger cohort from which it was sampled (Appendix I). Appendix F presents the sample size and sampling probabilities of the eligible cohort and this sample.

The median (interquartile range) gestational weight gain at 16-19 weeks was 4.5 (3.2, 6.8) kg for underweight women, 4.5(2.3, 6.8) for normal weight women, 4.5 (2.3, 8.0) for overweight women, and 2.8 (0.0, 6.4) for obese women. Of the weight measurements used, 27% were from 19 weeks, 27% from 18 weeks, 24% from 17 weeks, and 22% from 16 weeks. Women tended to gain more weight at 16-19 weeks if they were greater than 30 years of age at conception, delivered

preterm, were non-Hispanic White, had preexisting hypertension or diabetes, or used private insurance. There were smaller differences in terms of marital status, education, and smoking during pregnancy (Table 7). Normal weight women tended to gain the least amount of weight at 16-19 weeks with women in the other groups having similar, mean weight.

The cumulative incidence of severe maternal morbidity in this sample was 2.1% (n=96). Roughly 72% of the severe maternal morbidity cases in this sample had at least 1 of the 21 CDC indicators of maternal morbidity, 32% were admitted to the ICU, and 25% had a prolonged postpartum length of stay. Women were more likely to have a severe maternal morbidity if they had a higher BMI before pregnancy, were older, delivered preterm, were non-Hispanic Black, had preexisting hypertension or diabetes, or reported smoking during pregnancy (Table 8). There were smaller differences in terms of parity, education, and insurance. The unadjusted risk followed an inverted-U distribution, with those with z-score <-1 and >=1 having the lowest risk (1.4/100 and 1.2/100, respectively). Those with z-scores -1 to <0 were at the highest risk (2.3/100 delivery hospitalizations, Table 9).

After adjusting for confounders, we found a similar relationship between weight gain z-score at 16-19 weeks and risk of severe maternal morbidity at delivery hospitalization (Figure 2). Compared with a z-score of 0, z-scores of -3 and +3 were associated with 1.2 (-0.74, 3.1) and 1.6 (-0.07, 3.0) fewer cases of severe maternal morbidity (Table 10). Sensitivity analyses are shown in Appendix J. Overall, we found that when weight was measured before 20 weeks gestation, the relationship with severe maternal morbidity followed the same, inverted-U distribution. For weight gain after 20 weeks (i.e. 24-28 weeks, weight gain the second half of pregnancy, and total weight gain), the relationship followed an a gradual, decreasing linear patter, with those with low weight gain being at the highest risk and those with high weight gain being at the lowest risk.

4.5 Discussion

In this analysis of 4,774 delivery hospitalizations augmented with data on serial weight gain measurements, we found that the association between weight gain at 16-19 weeks gestation and severe maternal morbidity followed an inverted U pattern, with risk decreasing above and below the mean weight gain z-score.

Our results are unexpected considering our other work on the association between total gestational weight gain and risk of severe maternal morbidity. Although there are no known studies on the association between early weight gain in pregnancy and risk of severe maternal morbidity, there are several possible explanations for these discordant results. There were no meaningful differences in key, maternal variables between the eligible cohort, the randomly sampled cohort, and our final analytic sample. We also compared the current cohort with the cohort from our previous analysis on total gestational weight gain. We found no significant differences between these variables among women in this sample who did not have a severe maternal morbidity, but we found notable differences in maternal characteristics among those with the presence of a severe maternal morbidity; however, because this was a cohort study, these differences are less informative than if it were a case-control study. Furthermore, there were no substantial differences in the type of severe maternal morbidity experienced between the cohorts. Conversely, the women for whom serial weight gain measurements are available might not be representative of the population at Magee or the broader statewide or U.S. population. These data are not regularly or consistently entered across facilities. The facilities who regularly use and upload serial weight measurements are likely different than those who do not. This would substantively impact our results, though without further analysis, we cannot predict the direction and magnitude that it

would change the association between early weight gain and risk of severe maternal morbidity. These limitations also impair our ability to compare our total weight gain results with these results.

We performed a series of sensitivity analyses, varying the exposure window, including the rate of weight gained in the second half of pregnancy, 10-13 weeks gestation, 24-28 weeks gestation, as well as replicated the analyses from our total weight gain manuscript among women who had both, serial weight measurements and weight measurements at delivery, shown in Appendix P. There was an inverse association between the rate of weight gain in the second half of pregnancy and risk of severe maternal morbidity at delivery hospitalization, with the highest risk among those with lower weight gain and the lowest risk among those with higher (3.5/100 delivery hospitalizations in the lowest quartile and 1.5/100 in the highest). The association between weight gain at 24-28 weeks as well as total weight gain in this cohort and severe maternal morbidity followed a similar pattern. Weight gain at 10-13 weeks gestational followed a similar pattern as our primary analysis (an inverted U risk distribution). If there were no underlying differences in the characteristics of the cohorts, we would expect the association between total weight gain and risk of severe maternal morbidity to be similar.

Even though in this sample we observed the lowest risk among those who gained the most weight, we cannot recommend gaining higher weight because of the strong evidence from our previous research and other efforts that high weight gain is associated with myriad adverse pregnancy outcomes for mother and child. However, as supported by the Institute of Medicine, clinicians must determine optimal weight for patients within the broader context of a woman's health profile, the consistency of her and the fetus's growth during pregnancy, and the development of any adverse health markers during gestation. In addition to confirming these findings in large, diverse samples, future research with these data should explore differences

between the facilities from which serial weight gain measurements are provided because they are not uniformly or consistently included across facilities. Along with this exploration, we should determine if any differences in the phenotype of severe maternal morbidity exists between low and high-risk pregnancies. This might help with not only reconciling the different results between the total and early weight gain findings, but also to inform planning efforts regarding delivery location and resource allocation.

Our findings must be interpreted within the context of the study's limitations. The principal limitation of this study is potential selection bias. As mentioned, it is plausible and likely that the women in this sample are not representative of the larger population of women who delivery at Magee nor the general population. The facilities from which these data are drawn do not report data with uniformity and consistency, often due to different usages of electronic medical record systems. In addition to facility-level bias, women with data on serial weight measurements might be 1) more compliant and more motivated to maintain a healthy weight throughout pregnancy or 2) have these data available because they were identified as high risk and required more frequent prenatal visits.[118] Though our data do not suggest any concerning differences in key variables, we showed that maternal characteristics among those who faced severe maternal morbidity are different than other, large, population-based studies.[32,119] As such, we must interpret these findings cautiously and without further exploration of the specific patient characteristics of the clinics from which these data are drawn, cannot determine the extent to which our data is biased. Future research should attempt to remedy this limitation by collecting these data and performing a formal bias analysis, if possible. Secondly, as with many other studies that used administrative data to study severe maternal morbidity, an overarching limitation of this research is that our outcome definition was not based on a gold standard of chart review. However, external validation studies

have found that a multi-factor definition used here performed reasonably well against the gold standard mentioned above. If we follow current screening guidelines, which recommend that severe maternal morbidity be defined using either >4 units of blood product of ICU admission as the principal screening tool,[21] it is likely that we overestimated the incidence in this sample because we did not have data on the specific volume of blood administered. It is also possible that we failed to identify some cases of severe maternal morbidity due to false negatives in this administrative database. We expect the misclassification is minimal, but without a formal bias analysis, we cannot determine whether potential misclassification was differential. Another limitation that is pervasive in the literature is our window of outcome ascertainment was limited to delivery hospitalization. Severe maternal morbidity can occur during pregnancy, delivery, or postpartum. Not including these cases would lead to underestimation of the incidence and depending on the underlying characteristics of the cases, bias our associations towards or away from the null. We also used a relatively small sample (n=96 cases of severe maternal morbidity), which prevented us from performing more robust sensitivity analyses of our outcome definition and exploring the associations between individual indicators of severe maternal morbidity, as we did in our analysis of total weight gain. However, in our previous work, we found no meaningful differences in our effect estimates when we excluded blood transfusion, ICU admission, or extended postpartum length of stay, though we recognize that given the differences in samples, there might be differences according to outcome definition. Though less likely than the mechanisms discussed above, it is possible that these associations are due to other factors, such as underlying physiologic mechanisms by the type of weight gained throughout pregnancy, potential mediating effects that could have obscured the direct association, or unmeasured factors such as the quality of prenatal care.[107] Finally, because we performed analyses on complete cases only, it is possible that our

associations could be biased if data was missing not at random. While we confirmed that missing data was not missing completely at random, we did not observe any patterns in key variables that we believe would lead to bias. Additionally, we decided that the benefit of imputing so few variables did not outweigh the complexity and risk of possible misspecification of the imputation model.

Gestational weight gain is an attractive intervention target for reducing the incidence severe maternal morbidity because it is one of the only known risk factors that is modifiable during pregnancy. In this sample, because the potential of selection bias, we should adopt these results cautiously. Future research efforts must confirm our findings, ideally in populations that are similar to the general population at risk of severe maternal morbidity, but clinicians should continue to use current recommendations alongside sound clinical judgement to balance risk factors with optimal weight gain during pregnancy.[107] Since severe maternal morbidity is a heterogeneous outcome with many different phenotypes, in addition to confirming our results, future research should examine specific indicators of severe maternal morbidity and determine if opportunities exist for improvement in care or for early risk identification. Given not all women access healthcare before pregnancy, understanding the risk factors that are amenable to intervention during pregnancy should be a top research priority in reducing the incidence of severe maternal morbidity.

4.6 Tables and Figures

Table 6 Characteristics of women with serial antenatal weight measurements delivering singleton infants.

Magee-Womens Hospital, Pittsburgh, PA, 2003-2011

Characteristic	Frequency of sample (%)	
	Unweighted (N=4,774)	Weighted (N=80,236)
Prepregnancy body mass index (BMI cutpoints)		
Underweight (<18.5kg/m^2)	800 (17)	2,000 (2.5)
Normal weight (18.5-24.9kg/m^2)	811 (17)	38,618 (48)
Overweight (25.0-29.9kg/m^2)	787 (16)	22,485 (28)
Obese (≥30.0kg/m^2)	2,376 (50)	17,133 (21)
Maternal age (years)		
<20	280 (5.9)	4,965 (6.2)
20-30	2,177 (46)	34,301 (43)
>30	2,317 (49)	40,970 (51)
Gestational age at delivery		
Term (≥37 weeks)	4,280 (90)	72,612 (91)
Preterm (<37 weeks)	494 (10)	7,626 (9.4)
Maternal race/ ethnicity		
Non-Hispanic White	3,602 (75)	62,758 (78)
Non-Hispanic Black	971 (20)	13,534 (17)
Other	201 (4.2)	3,944 (4.9)
Parity		
No births	2,103 (44)	35,889 (45)
Previous birth	2,671 (56)	44,347 (55)
Marital status		
Unmarried	1,898 (39)	28,402 (35)
Married	2,921 (61)	52,196 (65)
Maternal education		
Less than high school	1,438 (30)	20,700 (26)
High school or some college	1,283 (27)	19,531 (24)
College graduate	2,053 (43)	40,004 (50)
Preexisting hypertension or diabetes		
Yes	410 (8.6)	3,974 (5.0)
No	4,364 (91)	76,264 (95)
Smoking during pregnancy		
Yes	715 (15)	10,239 (13)
No	4,059 (85)	69,997 (87)
Insurance		
Private	2,549 (53)	44,647 (56)
Public/ Other	2,225 (47)	35,589 (44)

Table 7 Mean z-score by characteristics of women with serial antenatal weight measurements delivering singleton infants. Magee-Womens Hospital, Pittsburgh, PA, 2003 2011 (N=4,774)

Characteristic	Mean (SD) z-score at 16-19 weeks gestation
Prepregnancy body mass index (BMI cutpoints)	
Underweight (<18.5kg/m^2)	0.15 (1.1)
Normal weight (18.5-24.9kg/m^2)	-0.07 (1.1)
Overweight (25.0-29.9kg/m^2)	0.15 (0.98)
Obese (≥30.0kg/m^2)	0.21 (0.91)
Maternal age (years)	
<20	-0.15 (1.1)
20-30	0.01 (1.1)
>30	0.12 (0.94)
Gestational age at delivery	
Term (≥37 weeks)	0.04 (1.0)
Preterm (<37 weeks)	0.22 (1.2)
Maternal race/ ethnicity	
Non-Hispanic White	0.08 (0.98)
Non-Hispanic Black	0.04 (1.2)
Other	-0.22 (1.1)
Parity	
No births	0.04 (1.0)
Previous birth	0.07 (1.0)
Marital status	
Unmarried	0.07 (1.2)
Married	0.05 (0.96)
Maternal education	
Less than high school	0.05 (1.1)
High school or some college	0.07 (1.1)
College graduate	0.05 (0.93)
Preexisting hypertension or diabetes	
Yes	0.55 (1.0)
No	0.03 (1.0)
Smoking during pregnancy	
Yes	0.06 (1.1)
No	0.06 (1.0)
Insurance	
Private	0.08 (0.96)
Public/ Other	0.02 (1.1)

Table 8 Cumulative incidence of severe maternal morbidity among women with serial antenatal weight measurements delivering singleton infants. Magee-Womens Hospital, Pittsburgh, PA, 2003-2011 (N=4,774)

Characteristic	Cases of severe maternal morbidity (unadjusted risk)
Prepregnancy body mass index (BMI cutpoints)	
Underweight (<18.5kg/m^2)	4 (0.50)
Normal weight (18.5-24.9kg/m^2)	16 (2.0)
Overweight (25.0-29.9kg/m^2)	16 (2.0)
Obese (≥30.0kg/m^2)	60 (2.4)
Maternal age (years)	
<20	7 (2.2)
20-30	35 (1.2)
>30	54 (2.7)
Gestational age at delivery	
Term (≥37 weeks)	69 (1.7)
Preterm (<37 weeks)	27 (5.8)
Maternal race/ ethnicity	
Non-Hispanic White	64 (2.0)
Non-Hispanic Black	29 (2.6)
Other	3 (1.6)
Parity	
No births	51 (2.3)
Previous birth	45 (1.9)
Marital status	
Unmarried	43 (2.3)
Married	53 (1.9)
Maternal education	
Less than high school	35 (2.2)
High school or some college	18 (1.7)
College graduate	43 (2.1)
Preexisting hypertension or diabetes	
Yes	13 (4.2)
No	83 (1.9)
Smoking during pregnancy	
Yes	13 (1.0)
No	83 (2.2)
Insurance	
Private	51 (2.2)
Public/ Other	45 (1.9)

Table 9 Association between gestational weight gain z-score category at 16-19 weeks and severe maternal morbidity at delivery hospitalization. Magee-Women's Hospital, Pittsburgh, PA, 2003-2011 (N=4,774)

Gestational weight gain z-score category	n at risk	Cases	Unadjusted risk (95% CI)	Adjusted risk (95% CI)	Adjusted RD (95% CI)
<-1	485	9	1.4 (0.04, 2.7)	1.6 (0.05, 3.1)	-0.72 (-2.6, 1.2)
-1 to <0	1,480	28	2.3 (1.2, 3.4)	2.3 (1.2, 3.4)	Reference
0 to <+1	2,027	45	2.4 (1.5, 3.4)	2.4 (1.4, 3.3)	0.07 (-1.4, 1.6)
≥+1	782	14	1.2 (0.38, 1.9)	1.1 (0.36, 1.8)	-1.2 (-2.6, 0.14)

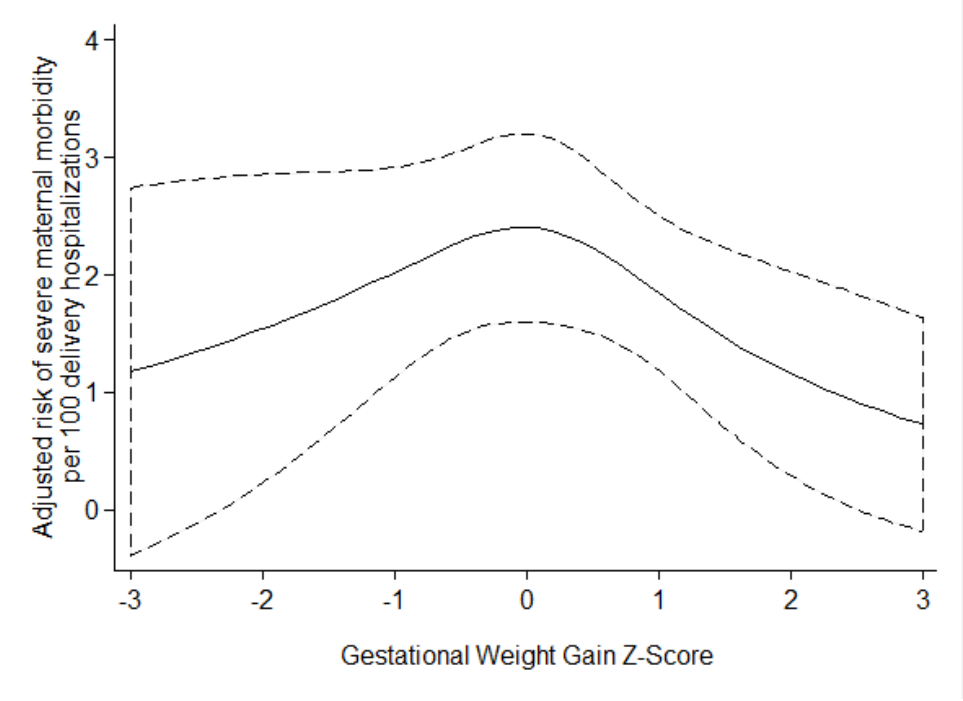

Figure 2 Adjusted, predicted risk of severe maternal morbidity by gestational weight gain z-score.

Solid lines indicate point estimates and dashed lines, 95% confidence intervals. Pittsburgh, PA. N=4,774

Table 10 Adjusted risk difference of severe maternal morbidity by gestational weight gain z-score at 16-19 weeks gestation. Magee-Womens Hospital, Pittsburgh, PA, 2003-2011 (N=4,774)

Gestational weight gain z-score at 16-19 weeks	Adjusted risk per 100 delivery hospitalizations (95% confidence interval)	Number of excess cases per 100 delivery hospitalizations (95% confidence interval)
-3 SD	1.2 9-0.42, 2.8)	-1.2 (-3.1, 0.74)
-2.5 SD	1.4 (-0.12, 2.9)	-1.0 (-2.7, 0.76)
-2 SD	1.6 (0.22, 2.9)	-0.80 (-2.3, 0.74)
-1.5 SD	1.8 (0.66, 2.9)	-0.58 (-1.8, 0.66)
-1 SD	2.0 (1.1, 2.9)	-0.35 (-1.2, 0.52)
-0.5 SD	2.2 (1.5, 3.0)	-0.11 (-0.53, 0.30)
0	2.4 (1.6, 3.1)	Reference
0.5 SD	2.2 (1.5, 2.9)	-0.16 (-0.51, 0.19)
1 SD	1.9 (1.2, 2.5)	-0.50 (-1.3, 0.26)
1.5 SD	1.5 (0.73, 2.3)	-0.84 (-1.9, 0.25)
2 SD	1.2 (0.31, 2.2)	-1.1 (-2.4, 0.18)
2.5 SD	1.0 (-0.0006, 2.0)	-1.4 (-2.8, 0.07)
3 SD	0.80 (-0.21, 1.8)	-1.6 (-3.0, -0.07)

5.0 Manuscript 3: Population Attributable Fraction of Modifiable Risk Factors of Severe Maternal Morbidity

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5.1 Abstract

Objective

To determine the population-attributable fraction (PAF) of potentially modifiable risk factors for severe maternal morbidity.

Methods

We used a retrospective cohort of 86,260 delivery hospitalizations from Magee-Womens Hospital, Pittsburgh, PA for this analysis (2003-2012). Severe maternal morbidity was defined as any of the following: Centers for Disease Control and Prevention International Classification of Diseases 9th Revision diagnosis and procedure codes for the identification of maternal morbidity; prolonged postpartum length of stay; or maternal intensive care unit admission. We used multivariable logistic regression with generalized estimating equations to estimate the association of prepregnancy overweight or obesity, maternal age ≥35 years, preexisting hypertension, preexisting diabetes, excessive gestational weight gain, smoking, education, and marital status with severe maternal morbidity. We calculated the PAF for each risk factor.

Results

The overall rate of severe maternal morbidity was 2.0 per 100 delivery hospitalizations. Overweight and obesity, maternal age ≥35 years, preexisting hypertension, and lack of a college degree had PAF ranging from 6% to 13%. If all risk factors were eliminated, 36% of cases could have been prevented. Modest reductions in the prevalence of excessive BMI, high gestational weight gain, and advanced maternal age, and prepregnancy diabetes had minimal impact on preventing severe maternal morbidity. Smoking during pregnancy and marital status were not associated with severe maternal morbidity.

Conclusions

Our data suggest maternal morbidity can be reduced somewhat by modifying common, individual-level risk factors. Nevertheless, most cases were not attributable to the risk factors we examined. These data support the need for large studies of patient-, provider-, system- and population-level factors to identify high-impact interventions to reduce maternal morbidity.

5.2 Introduction

Maternal mortality has more than doubled in the United States (U.S.) over the past 30 years and occurs more frequently in the U.S. than in any other high-income nation.[12,23,120] While an important public health problem, maternal mortality remains rare—roughly 0.017 deaths per 100 live births in the U.S. annually– making it a difficult subject for epidemiologic studies. Severe maternal morbidity is more common (approximately 1.4 cases per 100 delivery hospitalizations), and shares risk factors and etiologies with maternal mortality.[1] Thus, severe maternal morbidity can serve as a reasonable proxy for maternal mortality in epidemiologic studies. Severe maternal morbidity also leads to prolonged hospital stays, increased need for rehabilitation, and increased health care costs.[23,119]

Public health interventions that target modifiable risk factors may reduce severe maternal morbidity. Prepregnancy overweight and obesity, advanced maternal age, preexisting hypertension and diabetes, and smoking have all been associated with severe maternal morbidity.[29,31,33,36,39,42-44,47,121] Preliminary evidence by our group suggests that high, total gestational weight gain might also increase the risk of severe maternal morbidity. Social determinants of health such as maternal education and marital status may also be important leverage points for improving maternity

care.[122,123] The extent to which these risk factors contribute to the overall burden of severe maternal morbidity is not known, but quantifying this burden would help to identify priority areas for maternal morbidity prevention efforts in the U.S. Our objective was to determine the population-attributable fraction of potentially modifiable, individual-level risk factors and estimate the proportion of severe maternal morbidity that could be prevented if these risk factors were eliminated or reduced to a level that may be achievable.

5.3 Methods

Data source

We used an administrative database to identify all deliveries including 20 to 42 weeks gestation from January 1, 2003 to May 31, 2012 at Magee-Womens Hospital, Pittsburgh, Pennsylvania (N=86,429). The database includes information on maternal, fetal and neonatal outcomes from electronic and medical record data. Administrators code, clean, and store the data as well as validate it against medical records. We excluded 166 higher order pregnancies (triplets or higher) and 3 records that were missing data on infant sex, parity, or admission or discharge date. A total of 86,260 delivery hospitalizations were included in the final analytic sample. The University of Pittsburgh Institutional Review Board approved this study.

Exposure definitions

Maternal prepregnancy weight and height were ascertained via self-report at the first prenatal visit. Prepregnancy body mass index (BMI) was calculated and categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30.0 kg/m^2).[124] Maternal weight at delivery was collected by hospital staff using either the

last measured weight in the prenatal records or the weight recorded upon admission to labor and delivery.[125] Total gestational weight gain (kg) was standardized into gestational-age-specific z-scores and then classified as 'below', 'within', or 'above' the Institute of Medicine recommendations based on pregravid BMI category.[107,126] Preexisting hypertension and diabetes were based on ICD-9 codes. Maternal age, smoking status, maternal education and marital status were based on self-report. We defined advanced maternal age as either ≥35 years or ≥40 years of age depending on the population attributable fraction calculation. We categorized maternal education as less than high school, some college, or college graduate and marital status as married or unmarried.

Outcome definition

We defined severe maternal morbidity as the presence of the following: any of the 21 CDC disease and procedure codes for identification of severe maternal morbidity (Appendix B), intensive care unit admission, prolonged postpartum length of stay (defined as >3 standard deviations beyond the mean length of stay: >3 days for vaginal deliveries and >5 days for Cesarean deliveries). The CDC criteria have been widely used in administrative data research, and this multipronged definition was found to perform well against a gold standard of chart review.[30]

Missing data

Of 86,260 delivery hospitalizations, 24% of the sample was missing prepregnancy weight or height; 8.5% delivery weight; 3.6% length of stay; and less than 1% maternal education, ICU admission status, and race/ethnicity. We use multiple imputation with chained equations to address these missing data. This method allowed us to specify unique, conditional distributions for each imputed variable. This approach is effective in addressing data that are missing up to 50% of values.[102] After we log transformed all continuous variables, we jointly imputed maternal height,

prepregnancy weight, delivery weight, length of stay, education, and race using data on maternal identifier, census tract of residence, preexisting hypertension, preexisting diabetes, year of delivery, route of delivery, maternal status at discharge, fetal malformation, use of assistive devices during delivery, maternal age, smoking during pregnancy, parity, plurality, gestational diabetes, method of payment, marital status, fetal death, and gestational age at delivery.

*Statistical analysis*We used multivariable logistic regression with generalized estimating equations to estimate the association between each risk factor and severe maternal morbidity. We specified an exchangeable correlation structure to account for the correlation among pregnancies from the same woman (n=12,140 women with more than one pregnancy during the study period). Denominators were based on all delivery hospitalizations during the specified time period. Since we were simultaneously evaluating eight risk factors of interest, the final regression models included all risk factors as well as potential confounders: race (non-Hispanic White, non-Hispanic Black, and other), insurance (private, public), parity (nulliparous/ multiparous), and plurality (singleton or twin), which were selected using theory-based causal graphs.[127]

We calculated the population-attributable fraction and 95% confidence intervals for each risk factor of interest using the "punaf" postestimation user-written command in STATA version 14. We approximated the proportion of severe maternal morbidity in this sample that may be attributed to prepregnancy overweight or obesity, advanced maternal age (≥35 years or ≥40 years of age), preexisting hypertension, preexisting diabetes, excessive gestational weight gain, and smoking during pregnancy using the following formula:

$$Population\ attributable\ fraction = \frac{P(D) - \sum_c \mathrm{P(D|C,\ E)P(C)}}{P(D)}$$

where ‘P(D)’ is the mean probability of disease in the population over a specified time interval and ‘P(D|C, E)P(C)’ is the marginal conditional probability of disease given an alternate exposure, averaged over strata of other risk factors or confounders.[80] To calculate the population-attributable fraction, we assume that the relationship between each exposure and severe maternal morbidity was causal, that any lack of independence between risk factors is accounted for in our statistical models, and that the risk factors of interest are amenable to intervention. All other variables were set to their respective means.[128]

We first calculated the population-attributable fraction associated with each individual risk factor. This indicates the proportion of cases that could be prevented if the individual risk factor were eliminated-- all overweight and obese women were normal weight, all women were less than 35 years of age at delivery, there were no preexisting hypertension, diabetes or tobacco use, and all women gained an amount of weight that was within the 2009 Institute of Medicine guidelines. We were also interested in the number of cases of maternal morbidity that could be prevented by more realistic reductions in risk factors, particularly in prepregnancy BMI. Thus, we estimated the proportion of cases that could be prevented by reducing prepregnancy BMI by 3.5 kg/m^2 among overweight and obese women, a reduction that reflects the change in BMI among women enrolled in diet and exercise interventions.[129] We also tested the effect of all women being less than 40 years of age at the time of delivery. Finally, we estimated the PAF due to all of the examined risk factors which corresponds to the estimated proportion of cases prevented by eliminating all risk factors simultaneously.

5.4 Results

Most women in this sample were non-Hispanic White, married, multiparous, and used private insurance as their primary method of payment (Table 11). Twin pregnancies accounted for 2.2% of the sample. Approximately 44% of women were either overweight or obese before pregnancy. The mean maternal age at delivery (standard deviation[SD]) was 29 (6.1) years. The overall mean (SD) gestational weight gain among singletons and twins was 15 (7.0) kg and 17 (8.0) kg, respectively, with 17% of women gaining below the Institute of Medicine recommendations for total weight gain and 57% gaining above the guidelines.

The unadjusted risk of severe maternal morbidity was 2.0 per 100 delivery hospitalizations. Of the 1,739 cases of severe maternal morbidity, 905 were defined based on the Centers for Disease Control and Prevention Criteria alone, 200 on ICU admission alone, and 250 on having an extended postpartum length of stay alone (Appendix B). Women were more likely to experience a severe maternal morbidity if they were overweight or obese, Non-Hispanic black, or ≤20 or ≥35 years old, or had less than college education, gestational weight gain outside the Institute of Medicine guidelines, public insurance, a twin gestation, or preexisting hypertension or diabetes (Table 11).

Overweight and obesity, maternal age ≥35 years, and preexisting hypertension had similar PAF, ranging from 6.0% to 7.1%, although precision around these estimates varied (Table 12). Gestational weight gain had a PAF of 5.8%, but our estimate was only marginally precise (95% CI: -0.42, 12). Preexisting diabetes had a low PAF of 2.4% (95% CI: 1.4, 3.4%). Lack of a college education had the highest PAF of all risk factors in our study—13% (95% CI: 5.7%, 19%), although the estimate was imprecise. Tobacco use and marital status were not associated with

severe maternal morbidity. All the studied risk factors combined had a total PAF of 36% (95% CI: 14%, 53%) for severe maternal morbidity (Table 12). Thus, eliminating all the risk factors simultaneously would prevent an estimated 626 cases of severe maternal morbidity during the ten-year study period.

We also evaluated alternative risk reduction scenarios for maternal overweight and obese and advanced maternal age. A 3.5 kg/m^2 reduction in BMI for overweight and obese women would prevent 3.9% (1.4%, 6.4%) of severe maternal morbidity cases in this group. If all women were less than age 40 at delivery we estimate we could prevent 1.8% (0.74%, 2.9%) of cases.

5.5 Discussion

The changing demographics of pregnant women is frequently cited as contributing to the rise in severe maternal morbidity —pregnant women are older, have higher prepregnancy BMI, and often begin pregnancy with more complex medical conditions.[22,121] Our data suggest that prepregnancy overweight and obesity, advanced maternal age, preexisting hypertension, and excessive gestational weight gain each contribute to approximately 6% of the cases of severe maternal morbidity. Overall, this suggests that focusing public health efforts on a single risk factor will have a modest impact on maternal morbidity. Importantly, the PAF is similar between these disparate risk factors because factors that are common, such as prepregnancy overweight and obesity (44% of cohort), have modest risk ratios [1.1(1.0,1.3)] while risk factors with more robust risk ratios such as chronic hypertension [2.4 (2.0,2.8)] are uncommon (3.5% of cohort).

We also examined two important social determinants of health. Interestingly, while marital status was not associated with severe maternal morbidity, lack of a college education had the

highest attributable fraction of all risk factors examined. Examining social determinants of health is a particularly important for this outcome given the profound racial disparities in maternal morbidity and mortality.[130] The relatively large PAF associated with maternal education is not surprising. A 2013 report from the Institutes of Medicine cited the combination of societal factors such as education and unhealthy behavior as the leading explanations for health disadvantage.[131]

If all the risk factors we examined were eliminated from the population, approximately one in three cases of severe maternal morbidity could have been prevented. This level of risk reduction is unrealistic, however, and our data support a more somber conclusion with regards to realistic risk reduction. When we estimated the PAFs associated with achievable risk reduction—a decrease of BMI by 3.5 units or shifting the age at delivery to less than 40 years of age —the PAFs were small and the number of cases of severe maternal morbidity prevented was low. This suggests that public health efforts that focus on modifying common risk factors will need to address multiple risk factors simultaneously to have a substantial impact and that efforts to address key social determinants of health must be part of the solution to be maximally effective.

We are unaware of other studies that have reported the PAF of patient level risk factors for severe maternal morbidity, but the risk ratios we reported are comparable to other studies.[31,36] Recently, investigators performed a state-level analysis of factors that contributed to the temporal changes in U.S. maternal mortality from 1997-2012.[122] Similar to our findings, they reported that obesity and low education were important contributors to maternal mortality.

The findings of our work have important limitations—the first are limitations inherent to estimates of PAF and the second are limitations specific to our work. Estimations of PAF assume both causal relationships and exposures with well-defined interventions. Nevertheless, for most of these risk factors, we have not defined the intervention that would, for instance, reduce BMI by

3.5 units. Lowering BMI could be a result of dietary restriction, exercise, or bariatric surgery (or some combination of treatment options), and each may have a different impact on severe maternal morbidity risk.[132] PAF also assumes that the disease risk is independent across risk factors. Altering obesity prevalence, however, likely impacts the prevalence of diabetes and hypertension, thereby leading to synergistic effects we have not captured. PAF also does not consider the consequences of altering risk factors on the underlying population at risk of severe maternal morbidity. For instance, reducing BMI may improve fertility rates, which would increase the number of pregnancies and thus increase the number of pregnant women at risk for severe maternal morbidity. Finally, our estimates of PAF also assumes all biases are absent.

Regarding limitations unique to our work, we used a commonly used screening definition of severe maternal morbidity, rather than the gold standard of medical chart review.[30] If we had used the gold standard definition for maternal morbidity recently outlined in a ACOG Obstetric Care Consensus, we would expect fewer cases of severe maternal morbidity. However, it is difficult to predict the direction and magnitude of potential misclassification without a formal quantitative bias analysis.[133] Additionally, because we did not perform a medical record review, we do not have information about cause-specific morbidity. The PAF of the different risk factors we examined may vary by type of morbidity, and this information would be important for health systems and public health officials.

Our work highlights the need to extend research beyond the commonly measured individual-level risk factors we examined to include anemia, substance use, pre-pregnancy control of pre-existing medical problems and additional social determinants of health. Furthermore, risk factors should be expanded to include provider, system, and structural factors, such as state Medicaid coverage of pregnancy termination, that contribute to severe maternal morbidity and its

subtypes.[134] Only with this more holistic understanding of the drivers of severe maternal morbidity can we inform care pathways that will powerfully reduce severe maternal morbidity and improve maternal health.

5.6 Tables and Figures

Table 11 Characteristics of women delivering newborns at Magee-Womens Hospital in Pittsburgh, PA, 2003-2012 (N=86,260)

Characteristic	Population at risk n (%) N=86,260)	Cases of severe maternal morbidity (unadjusted incidence per 100 delivery hospitalizations)
Overall	86,260 (100)	1,739 (2.0)
Maternal prepregnancy BMI		
Underweight (<18.5kg/m^2)	4,102 (4.8)	76 (1.8)
Normal weight (18.5-24.9kg/m^2)	44,797 (52)	778 (1.7)
Overweight (25-29kg/m^2)	20,599 (24)	435 (2.1)
Obese (≥30kg/m^2)	16,772 (20)	450 (2.7)
Gestational weight gain		
Below IOM guidelines	14,374 (17)	320 (2.2)
Within IOM guidelines	22,282 (26)	383 (1.7)
Above IOM guidelines	49,604 (57)	1,036 (2.1)
Maternal race/ ethnicity		
Non-Hispanic White	64,681 (75)	1,147 (1.8)
Non-Hispanic Black	16,870 (20)	492 (2.9)
Other	4,709 (5.5)	100 (2.1)
Maternal education		
Less than high school	7,423 (8.6)	226 (3.0)
High school	18,810 (22)	461 (2.5)
Some college	19,924 (23)	418 (2.1)
College graduate	40,103(46)	634 (1.6)
Maternal age (years)		
<20	6,009 (7.0)	152 (2.5)
20-24	15,644 (18)	333 (2.1)
25-29	23,269 (27)	395 (1.7)
30-34	25,243 (29)	474 (1.9)
35-39	13,165 (15)	294 (2.2)
≥40	3,095 (3.6)	91 (3.0)
Marital status		
Unmarried	34,095 (40)	843 (2.5)
Married	52,165 (60)	896 (1.7)
Insurance		
Private	59,225 (69)	1,028 (1.7)
Public/Other	27,035 (31)	711 (2.6)

Table 11 Continued

Parity at conception		
Nulliparous	39,556 (46)	880 (2.2)
Multiparous	46,770 (54)	859 (1.8)
Plurality		
Singleton	84,328 (98)	1,600 (1.9)
Twin	1,932 (2.2)	139 (7.2)
Preexisting hypertension		
Yes	2,999 (3.5)	192 (6.4)
No	83,261 (97)	1,547 (1.9)
Preexisting diabetes		
Yes	1,268 (1.5)	85 (6.7)
No	84,992 (99)	1,654 (1.9)
Smoking during pregnancy		
Yes	12,555 (15)	276 (2.2)
No	73,705 (85)	1,463 (2.0)

Table 12 Population attributable fractions for modifiable risk factors of severe maternal morbidity. Magee- Womens Hospital, 2003-2012 (N=86,260)

Risk factor	Adjusted risk ratio (95% confidence interval)	Prevalence (n)	Population attributable fraction (95% confidence interval)	Total preventable cases of severe maternal morbidity
1. Prepregnancy BMI outside normal range (<18.5 or ≥25kg/m^2)	1.1 (1.002, 1.2)	48 (41,590)	6.1 (0.47, 11)	106
2. Prepregnancy BMI≥25kg/m^2	1.1 (1.01, 1.3)	44 (37,564)	6.0 (0.83, 11)	104
3. ≥35 years of age at delivery	1.5 (1.3, 1.6)	19 (16,260)	7.1 (4.6, 9.4)	123
4. No college degree	1.2 (1.1, 1.4)	54 (46,160)	13 (5.7, 19)	226
5. Unmarried	1.01 (0.89, 1.2)	40 (34,094)	1.5 (-4.9, 7.6)	26
6. Preexisting hypertension	2.4 (2.0, 2.8)	3.5 (2,999)	6.3 (4.8, 7.8)	109
7. Preexisting diabetes	2.0 (1.5, 2.5)	1.5 (1,268)	2.4 (1.4, 3.4)	41
8. Smoking during pregnancy	0.92 (0.79, 1.04)	15 (12,554)	-1.4 (-3.7, 0.81)	-24
9. Gestational weight gain >1 SD	1.3 (1.1, 1.5)	14 (11,754)	4.5 (1.9, 7.1)	78
Term (≥37 weeks)	1.2 (1.0, 1.5)	12 (9,315)	3.0 (0.21, 5.6)	52
Preterm (<37 weeks)	1.3 (1.0, 1.6)	16 (1,752)	4.8 (0.16, 9.2)	83
10. All above risk factors	1.6 (1.1, 2.1)[a]	93 (80,613)[b]	36 (14, 53)[c]	626[d]

6.0 Synthesis

6.1 Overview of Findings

The overarching purpose of this dissertation was to advance the understanding of the role of weight gain during pregnancy and other known, modifiable risk factors on the risk for severe maternal morbidity.

Specific Aim 1. Determine the association between total gestational weight gain and severe maternal morbidity at delivery hospitalization.

In a retrospective cohort of 84,241 delivery hospitalizations, we investigated whether gestational age- and prepregnancy BMI-standardized z-scores were associated with severe maternal morbidity at delivery hospitalization. We found that weight gain during pregnancy that was in the lower or upper extremes of the distribution was associated with increased risk of severe maternal morbidity at delivery hospitalization. When stratified by gestational age at delivery, we observed consistently higher absolute risks of severe maternal morbidity among preterm deliveries compared with term deliveries across the risk curve. Overall, we found the highest adjusted risk difference among those with a z-score of +3 compared with a z-score of 0 (1.6 (0.68, 2.6) per 100 delivery hospitalizations). We found that the same z-score was associated with the highest risk in both, preterm and term deliveries compared with a z-score of 0. Among term deliveries, we found that a z-score of +3 was associated with 0.86 (0.09, 1.6) excess cases and among preterm deliveries, the same z-score was associated with 3.0 excess cases. The confidence intervals were wider for preterm deliveries at this selected z-score, with risk differences ranging from -0.56 excess cases to

6.6 excess cases. Even though our confidence intervals overlapped the null among preterm deliveries, most compatible risk differences for our data were greater than the null and there was a consistent and clear trend of increasing risk among preterm deliveries, which warrants that care be taken to avoid extremely low or high weight gain in all groups. Importantly, any weight gain higher than the mean was associated with increased risk in both term and preterm deliveries, though the magnitude of association in both groups was lower as weight gain was closer to the mean.

Our results agree with the only other known study on the relationship between gestational weight gain and risk of severe maternal morbidity. In 2019, Platner, et al. reported that compared with weight gain within the 2009 Institute of Medicine recommendations, weight gain above the guidelines was associated with a mild increase in odds of severe maternal morbidity or death among term deliveries (Adjusted odds ratio (95% confidence interval): 1.08 (1.02, 1.13).[92] Those who gained ≥20 pounds above the guidelines were at even greater odds compared with those who gained within the guidelines (1.21 (1.12, 1.31)). Additionally, this group did not find a notable association among those who gained below the IOM recommendations (0.98 (0.92, 1.03). Our findings generally agree, but we contribute a very important piece of information to the literature in that we add that both, low and high weight gain is associated with increased risk among preterm deliveries. This is crucial because upwards of 40% of cases of severe maternal morbidity are among preterm deliveries.[32] Preterm delivery in of itself is associated with myriad adverse pregnancy outcomes, but our results suggest that optimizing weight gain in this group might be beneficial in reducing the risk of the most severe maternal outcomes. Finally, when we explored the relationship between gestational weight gain and individual indicators of severe maternal morbidity, we found that elevated weight gain was associated with increased risk of ICU

admission, prolonged postpartum length of stay, eclampsia, heart failure during procedure, puerperal cerebrovascular disorders, and pulmonary edema compared with the mean weight gain (Appendix J). We did not stratify these analyses by gestational age at delivery due to sample size constraints, but overall, Platner, et. al found similar results among term deliveries, with the risk of eclampsia, heart failure, pulmonary edema, blood transfusion, and ventilation all increased among those who gained far above the IOM recommendations compared with those within the IOM recommendations.[92]

Our findings have implications for future research and policy efforts as well as clinical practice. An overarching, existing recommendation for which these data likely provide support is to avoid very high or low weight gain during pregnancy. Though severe maternal morbidity is a set of rare events, along with maternal mortality it is on the highest end of the spectrum of adverse maternal outcomes during pregnancy; therefore, it deserves inclusion when considering best recommendations if our findings are supported by additional research. Current recommendations developed by the Institute of Medicine aimed to balance the risk of various short- and long-term, adverse pregnancy outcomes for mother and child.[107] And while severe maternal morbidity was not an explicit component of the final recommendations, as the specific topic area evolves, future committees to develop guidelines will have improved data on which to guide their recommendations.

Recommendations specific to clinicians who care for pregnant women continue to be that patients should be counseled on healthy weight gain early and often, being vigilant to recognize women at risk of gaining too much weight (i.e. their trajectory is above the recommendations), and knowing how and when to intervene. For other researchers, our data confirm existing literature and extend our knowledge by showing that the relationship between these factors is apparent in

various subgroups of women. The implications for future research efforts will be discussed in later sections, however researchers must consider whether to continue with this avenue of research or to dedicate resources to other risk factors of interest.

Specific Aim 2. Determine the association between early gestational weight gain and severe maternal morbidity at delivery hospitalization.

In a retrospective cohort of 4,774 women who had serial, antenatal weight measurements at Magee-Womens Hospital, we tested whether weight gain at 16-19 weeks gestation was associated with risk of severe maternal morbidity at delivery hospitalization. The overall rate of severe maternal morbidity in this sample was 2.1/100 delivery hospitalizations and was highest among those in the middle of the distribution of weight gain z-scores and decreased in z-scores above and below the mean. After adjusting for confounders, we observed a similar association. Compared with a weight gain z-score of 0 (5.2kg at 19 weeks gestation among normal weight women), z-scores of -2 and +2 (0.1kg and 13kg at 19 weeks gestation, respectively) were associated with -0.80 (-2.3, 0.74) and -1.1 (-2.4, 0.07) excess cases per 100 delivery hospitalizations, respectively.

There are no other studies on the association between weight gain early in pregnancy and risk of severe maternal morbidity, and the discordant findings against our total weight gain paper were surprising. The most likely driver of the difference in association is selection bias in the early weight gain sample, though we cannot explicitly rule out other possibilities, such as our total weight gain results being due to reverse causation.

Our first sensitivity analysis tested the relationship between rate of weight gain in the second half of pregnancy and severe maternal morbidity and whether the association helped

explain the larger discrepancy with the total weight gain results. We found that the predicted, adjusted risk of severe maternal morbidity gradually decreased with increasing weight gain. If weight gain in the second half of pregnancy was driving the results of the total weight gain analysis, and assuming similar distribution of maternal characteristics in each sample, we would expect a positive association between weight gain during the second half of pregnancy and risk of severe maternal morbidity at delivery hospitalization. The fact that we saw the opposite lent further support that the samples might differ and the early weight gain sample is likely not reflective of the general population at risk of severe maternal morbidity.

We also explored the association between severe maternal morbidity at delivery hospitalizations and weight gain at the end of the first trimester and at 24-28 weeks, when screening for gestational diabetes typically occurs at Magee. For the former analyses, we found a similar risk curve to our findings when we measured weight gain at 16-19 weeks gestation. However, the latter analysis resulted in a risk curve more similar to that where we measured weight gain during the second half of pregnancy (decreasing risk of severe maternal morbidity with increasing weight gain). This shift in relationship, particularly that of z-scores corresponding to low weight gain being associated with lower risk to higher risk in the second half of pregnancy, suggests that the relationship between weight gain and risk of severe maternal morbidity might not be consistent throughout pregnancy. Though we cannot confirm the underlying mechanisms in this sample, one possibility is that low weight gain in the second half of pregnancy is indicative of underlying health issues that lead to severe adverse events, but low weight gain early in pregnancy is not necessarily a marker of nutritional status.

The final sensitivity analysis, we performed the same analysis as Specific Aim #1 among women who had the presence of both, serial weight gain measurements and total weight gain

measurements. We would expect a similar relationship if there were no underlying differences in the samples from the two specific aims. That we did not might bolster the likelihood that differences in results are most likely due to differences in the sample characteristics.

Overall, though there are other possible drivers of the differences in association, those mentioned above have the most evidence. It is possible that the relationship is mediated through other factors that lie downstream from early weight gain, but upstream from severe maternal morbidity, though these factors are likely to only obscure the direct relationship rather than result in a different association. Because we cannot directly compare the results from the first Specific Aim, we cannot completely rule out the possibility that weight gain in the second half of pregnancy is a more potent risk factor of severe maternal morbidity than weight gain in the first half. Typically, women gain the higher proportion of their total weight gain in the second and third trimesters, as this is when fetal growth is progressing at the fastest rate.[107] For the same reasons, we cannot explicitly rule out that our total weight gain results are not due to reverse causality. Future research might consider extending this research to examining patterns of gestational weight gain, though ideally in populations where both, the overall and case-specific maternal characteristics are comparable to the larger body of literature. Third, one's physiologic state at the time of delivery might help explain these disparate results, but again, it is less likely that differences in sample characteristics. From a physiologic standpoint, we might have observed a positive relationship between total weight gain and risk of severe maternal morbidity because increased physical mass may act to increase the risk of delivery complications through both challenges for the birth itself to added stress placed on the mother's body during delivery. Interestingly, among women in this sample who had both, early and total weight gain measurements, 72% remained in the same z-score category (<-1 SD, -1 to +1 SD, or >+1 SD)

between measurements (72% among noncases and 78% among cases). Though the majority follow the expected pattern, future research to examine weight gain trajectory might elucidate the relationship further.

Overall, additional research must be conducted in larger samples so that our results can be confirmed/ refuted as well as extended by examining specific indicators of severe maternal morbidity. The women for whom serial weight gain measurements are available might not be representative of the larger population. These data are not regularly or consistently entered across facilities (e.g. outpatient obstetrician offices that regularly use electronic medical records versus those that do not). It is plausible and likely that those facilities who regularly use and upload serial weight measurements so that they are available to researchers serve different patient populations than those who do not. This would substantively impact our results, though without further exploration at the facility level to determine the clinical characteristics of the women being treated, we cannot predict the direction and magnitude that it would change the association between early weight gain and risk of severe maternal morbidity. These limitations also impair our ability to compare our total weight gain results with these results. Future research with these data should explore and account for potential sampling variation between facilities.

Specific Aim 3. Determine the population attributable fraction of modifiable risk factors of severe maternal morbidity (maternal education, marital status, prepregnancy BMI, preexisting hypertension or diabetes, advanced maternal age at delivery, smoking during pregnancy, and gestational weight gain).

In a sample of 86,260 delivery hospitalizations at Magee-Womens Hospital, we calculated the percent of the severe maternal morbidity that could be prevented if 8, known, modifiable risk

factors were reduced to optimal levels. We found that by concurrently reducing all these risk factors to optimal levels, 36% of the severe maternal morbidity in this sample could be prevented. Eliminated or reducing individual risk factors had more modest reductions. The risk factors that conferred the most risk to severe maternal morbidity were lacking a college degree (13%), advanced maternal age (7.1%), preexisting hypertension (6.3%), prepregnancy overweight/ obesity (6.0%), and gestational weight gain >1 SD above the mean (4.5%).

Though preventing roughly 1 in 10-20 cases of severe maternal morbidity by targeting a single risk factor is significant, most of these calculations assume that the risk factor is eliminated entirely from the sample (e.g. no one is overweight or obese), which is not tenable. Therefore, real-world reductions in cases would presumably be lower. For example, published interventions to reduce BMI have varying levels of success and magnitudes of weight loss. Bariatric surgery is effective at reducing BMI among severely obese women (roughly 15% of total weight lost),[135] but is also expensive, time-consuming, and requires strict adherence by the patient. Non-surgical weight loss interventions are less intensive, but require consistent buy-in from participants and when effective, result in less weight loss (roughly 5%).[129] Furthermore, there is insufficient evidence regarding pregnancy outcomes among women who have undergone bariatric surgery and subsequently became pregnant.

Other factors that we studied would require structural changes at the population level. We found that lack of college education was associated with the highest population attributable fraction in this sample. As discussed, this finding was not entirely surprising, as in 2013 the Institute of Medicine highlighted societal factors as major contributors to health disadvantage.[131] However, education level is correlated with other factors associated with adverse pregnancy outcomes and overall health, including other risk factors of severe maternal morbidity examined

here. Though intervening on population-level risk factors like education is not a short-term solution, its impact would likely be significant and long-lasting because of the downstream effects it has on other elements of health.

More short-term goals should include better understanding the interplay between risk factors and recognize that any primary preventive efforts need multidisciplinary approaches to improve the health profile of those at increased risk. Our results lend support to the notion that less than half of severe maternal morbidities are preventable.[13,22,23,136] An additional layer is the evidence that among preventable cases, most are due to provider and system factors[112] rather than individual patient factors. More research is needed to explore these individual factors in large and diverse samples, but our early findings suggest that these investigations need to continue.

6.2 Strengths and Limitations

This study has several strengths that add value to the existing literature. First, using prepregnancy BMI and gestational age-specific z-scores to define weight gain allows us to remove potential confounding by gestational age[137] and, importantly, include preterm deliveries in our sample. Second, we addressed missing data using rigorous methodology, performed complete case analyses and sensitivity analyses where we modified our definition of severe maternal morbidity. Third, we used a large, single institution dataset that linked hospital discharge, birth certificate, and clinical data to include ICU admission and prolonged postpartum length of stay as part of our outcome definition, which are commonly used as indicators of severe maternal morbidity.[30]

There are some overarching limitations that must be considered when interpreting our results. First, as mentioned, our definition of severe maternal morbidity is not based on a gold standard of chart review, but rather a reasonable, externally-validated definition that has been used in previous research.[30] Even so, it is likely that we overestimated the true incidence of severe maternal morbidity, particularly those morbidities considered sentinel events. Perhaps the largest contributor to this possible misclassification is the using of binary variable for blood transfusion, regardless of volume given, as a positive indicator of severe maternal morbidity. Current ACOG recommendations state that blood transfusions consisting of less than 4 units might not constitute a true morbidity.[21] However, it is important to consider that any amount of blood given during delivery could be considered a severe event by some women and their families.[30] Regardless, if there was differential misclassification of our outcome by gestational weight gain, it is possible that our results are biased. Specifically, if in the lower and upper ranges of weight gain the incidence of severe maternal morbidity was overestimated compared with weight gain closer to the mean weight gain, we would expect our results to be biased away from the null. However, without additional data of the direction and magnitude of the bias as well as a format bias analyses, it is not possible to determine with complete certainty whether there was any impact on our results. But, we performed a series of sensitivity analyses where we modified our definition of severe maternal morbidity and found no significant changes. Severe maternal morbidity is a heterogeneous and, outside sentinel events, a somewhat subjective outcome. Even when gold standards are created in the literature, the definition is dependent on the clinicians' and researchers' opinion of what truly constitutes one of these outcomes.[17,19,30] For example, Main et al. found that only 491 of 1,313 screen positive cases were true severe morbidities,[30] Geller et al. reported 186 of 339 screen positive cases were true severe morbidities,[14] and You, et al. 167 of 815 were true

positives.[19] Importantly, however, is that each one of these studies used a different methodology for screening and review (e.g. Main, et al. used a gold standard of conditions agreed upon by 10 obstetric researchers, Geller, et al. used a physician-narrated summary and then used qualitative discussions to review screen positive cases, and You, et al. used a research assistant to provide a narrative of each case to three physicians, who by majority rule, determined the validity of each case). While we as researchers intrinsically trust the judgement of experts, there will always be a subjective component to this area of research so long as there is disagreement in what constitutes a near miss.

Though it is most likely that we overestimated the true incidence in this sample, there is also the possibility of false negatives when using administrative datasets without review of screen negative and screen positive observations. Appearing in even some of the most cited literature, it is often not feasible to review screen negative cases because of the low incidence of severe maternal morbidity and the number of observations needed to perform an analysis with adequate statistical power. Truly rigorous research efforts would review all screen positive and screen negative cases to calculate the actual sensitivity, specificity, and negative predictive value of a definition. Unfortunately, we know of no research that has undertaken the task and we therefore must rely on positive predictive value as the only measure of validity. We cannot comment on the potential false negative rate of identifying severe maternal morbidity, but false positives vary widely between studies, depending on both the method of data ascertainment and the gold standard used to validate the screening criteria. Future epidemiologic research should seek to determine reasonable false positive and false negative rates and incorporate bias analyses to determine the impact of outcome misclassification on effect estimates.

A second, broad category of limitations to this work is related to our exposure definitions, specifically those related to weight gain. The highest leverage factor that would impact our exposure ascertainment is the fact that prepregnancy weight was self-reported. If misreported, both, prepregnancy BMI and gestational weight gain would be skewed; if prepregnancy weight is underestimated (the most likely scenario), prepregnancy BMI would be underestimated and gestational weight gain measures would be inflated which would potentially bias our results away from the null. However, without a formal bias analysis regarding the direction and magnitude of any misclassification, we cannot confirm its impact on our results. Finally, while we believe that utilizing gestational weight gain z-scores is the most rigorous method of accounting for potential confounding by gestational age for exposure/ outcome relationships related to preterm birth, there are others that argue that this method might not mitigate confounding bias in these scenarios.[138] The authors' primary concern is that the creation of z-score charts might not translate from one sample or population to the next. Though future research should compare methods across populations, in our analyses, we used the sample population in which the z-score charts were originally created so there is no reason to suspect these methods inappropriate.

Missing data can also lead to spurious results if not addressed properly. In our total weight gain and population attributable fraction papers (Specific Aims #1 and #2), the variables with the highest percent missing were prepregnancy weight or height (24%) and delivery weight (8.5%). We implemented multiple imputation using chained equations (MICE) for both analyses to address missing data. This was an optimal strategy because, unlike other methods using multiple imputation (i.e. MVN), we could specify unique distributions for each variable (e.g. continuous, binary, etc.) rather than being limited and having to transform variables to achieve a consistent distribution.[139] While more laborious and higher potential for misspecification, the resulting

imputed datasets are likely a better representation of the data. Furthermore, using multiple imputation as a strategy has been shown to be effective in imputing variables with up to 50% missing data.[140] We confirmed that our data were not missing completely at random, but there were no concerning patterns within our key variables that would lead us to believe imputation was not appropriate (i.e. missing at random). However, if we had violated this assumption and our data were not missing at random then our results might be spurious. In Specific Aim #1, where we examined early gestational weight gain and risk of severe maternal morbidity, we chose to limit our analysis to only those with complete data because we determined the added complexity of imputing data in so few individuals and the potential for misspecification did not add rigor to the overall methodology.

Finally, our findings must be applied with caution in facilities whose patient population differs from Magee. Magee is a high-volume delivery center (9,000 deliveries per year) and is responsible for many of the high-risk deliveries in Allegheny County. We would expect the incidence of severe maternal morbidity to be higher than the national average because more high-risk pregnancies culminate at Magee. Also, though Magee serves a diverse racial, ethnic, geographic, and socioeconomic population, its composition is different from other samples. For example, studies from California have a larger proportion of Hispanic women and a lower proportion of non-Hispanic Black women compared with our sample.[30] These differences must be recognized given the racial disparities in the incidence of severe maternal morbidity. As previous research has shown a high contribution of system and provider factors accounting for the incidence of severe maternal morbidity, these differences between Magee and other facilities must be considered. Our results might not be applicable to more rural healthcare centers or those that do not have clinical specialists trained in managing high-risk pregnancies and deliveries. Importantly,

the results from Specific Aim #2 should not be applied to the general population of those at risk of severe maternal morbidity because the underlying patient characteristics likely differ from those of other large, population-based cohorts and the facilities from which serial weight gain data are available are likely not representative of the larger patient population. The sample used in Specific Aim #1 follows published cohorts more closely and might have more relevance to the broader, at risk population.

6.3 Public Health Significance

The importance of understanding how to better prevent severe maternal morbidity and mortality cannot be overstated. The United States has, by many measures, the worst maternal health among high-income15% countries[112] and even with the vast technological and intellectual resources available, the record does not appear to be improving a great deal.[1,141] There are also profound and persistent racial, ethnic, and socioeconomic disparities in the incidence of severe maternal morbidity.[39,130,142] Non-Hispanic Black women are over 60% more likely to face severe maternal morbidity in this sample than non-Hispanic White women, with others reporting similar or greater inequities.[39] We took a practical, epidemiologic approach and directed our focus on known, modifiable risk factors of severe maternal morbidity and applied rigorous methodologies to quantify the burden they place on the incidence of this outcome.

Training our analyses on modifiable risk factors, and particularly including those amenable to intervention during pregnancy, was crucial because most of the available literature has either taken a broad approach (i.e. including many risk factors)[29,35,36] or focused on risk factors that are not modifiable during pregnancy (e.g. prepregnancy body mass index)[89]. As discussed, half of all

pregnancies are unplanned and many do not or cannot seek preconception care,[5,6] so modifying risk factors such as body mass index often isn't feasible. We focused on modifiable risk factors because our intent is to contribute to research efforts whose ultimate goal is to informing risk identification and the development of sustainable intervention strategies.

This dissertation adds support that avoiding very suboptimal or excessive weight gain might be beneficial in reducing one's risk for adverse pregnancy outcomes.[107] Once prenatal care is initiated, patients must be educated about healthy weight gain during pregnancy. Sadly, while most clinicians report sharing this information, current literature suggests that potentially only half of pregnancy women report receiving weight gain advice.[143] Furthermore, in this same prospective cohort study of nearly 1,500 women, current advice had limited effect on preventing inadequate or excessive weight gain during pregnancy according to the current Institute of Medicine guidelines. Furthermore, among some populations, patients report being given inconsistent advice or advice that is outside the current guidelines,[144,145] which might place women at higher risk of gaining outside the recommendations. Though outside the scope of this research, these data, in conjunction with rising morbidity and mortality rates and the suggestion that most preventable cases of morbidity are due to system and provider factors,[18] suggest a troubling pattern between proper healthcare being provided throughout pregnancy and delivery with adverse maternal outcomes.

Adding to our findings on early and total weight gain as risk factors for severe maternal morbidity, we found that by optimizing any one of the eight, modifiable risk factors individually, only modest reductions in the incidence of severe maternal morbidity could be expected. As discussed, most of these calculations assumed that the risk factor was eliminated, which is unrealistic in practice, so real-world reductions would be much lower. Even if all the risk factors

we examined were concurrently reduced to optimal levels, less than 40% of the total cases of severe maternal morbidity in this sample could be prevented. Others have suggested that upwards of 50% of the burden of severe maternal morbidity is not preventable; as our estimates do not account for the other 50%, there appears to be space for prevention (14% of the burden if the estimates from other studies are consistent in our sample).

Assuming we did not exclude a patient-level risk factor that had high leverage on our outcome, we can posit that, echoing previous research, more than half of the cases of severe maternal morbidity are either 1) not due to patient-level risk factors and/or 2) not preventable. With either possibility, our focus must widen to include provider and system-level factors to gain a more holistic understanding of the preventable burden of severe maternal morbidity. Not all severe maternal morbidities are preventable and can be due to individual, provider, or system-level factors. This dissertation focused solely on determining the associations between individual level risk factors and risk of severe maternal morbidity during delivery hospitalization.

Another important finding of our work is that the association between high and low gestational weight gain and severe maternal morbidity is present among term and preterm births and that the absolute risk is consistently higher among preterm births across all z-scores. However, we found no evidence of effect measure modification by gestational age at delivery that would suggest that there are differences in risk between various weight gain z-scores that vary between term and preterm births. Approximately 10% of all births in the U.S. are preterm and nearly 40% of severe maternal morbidity cases are among women who deliver preterm.[32] So, our observations here support previous recommendations that optimizing weight gain during pregnancy is important for all women.[146]

Our immediate attention was on relatively short-term solutions, but we alluded to the importance of larger, sustainable, policy and population-level change. Improving education for clinicians to recognize and manage high risk patients, both during pregnancy and at delivery is an important first step for future research and clinical efforts. In fact, efforts such as the Alliance for Innovation on Maternal Health (AIM), have been designed for this purpose[147]; a way to educate states, hospitals, birthing centers, and maternity care providers on the best practices for maternal care developed by "national multidisciplinary organizations". While these efforts are promising, there are limited data regarding its impact. Without systematic change in how we make affordable healthcare available to all women and improve on the profound disparities that exist, it is unlikely that the upward trend in adverse maternal outcomes during pregnancy will abate.

6.4 Future Research

As recognized by medical and professional societies, having standardized definitions of severe maternal morbidity across all states and facilities is unlikely feasible due to differences in data collection, recording, and reviewing. However, future research in the U.S. should focus on developing the surveillance and reporting tools needed to expand our window of outcome ascertainment. Limiting severe events that happen during delivery hospitalizations is likely leading to underestimation of the true burden of severe maternal morbidity. It is not uncommon for women to have a severe maternal morbidity or even face death after hospital discharge. In fact, the World Health Organization definition of severe maternal morbidity includes events up through 42 days postpartum.[11] Including these cases in future epidemiologic research and clinical case reviews is critical for identifying preventable cases. In a related call to action, a 2019 clinical opinion in the

American Journal of Obstetrics and Gynecology argued that a state-by-state maternal mortality review to be established.[148] Though such an undertaking for reviewing all cases of severe maternal morbidity would not be feasible, better understanding of the causes leading up to mortality would help prevent severe maternal morbidity, as well.

Also related to our outcome, future epidemiologic research should be designed to study individual indicators of severe maternal morbidity. Understanding severe maternal morbidity as a composite measure is useful for broad risk identification strategies, but we are unable to determine the underlying causal mechanisms since the phenotypes of severe maternal morbidity are varied and unique.

Second, our findings on the relationship between early and total gestational weight gain and risk of severe maternal morbidity point to possible follow up studies and provides additional information for weighing research priorities. Studies should examine these relationships according to specific indicators of severe maternal morbidity and might consider the pattern and trajectory of weight gain as an exposure of interest. Overall, although we found larger effect sizes for other risk factors, gestational weight gain remains one of the only risk factors amenable to intervention during pregnancy. Adding these recommendations to future research could, in the future, potentially help identify subgroups that would benefit most from surveillance and intervention.

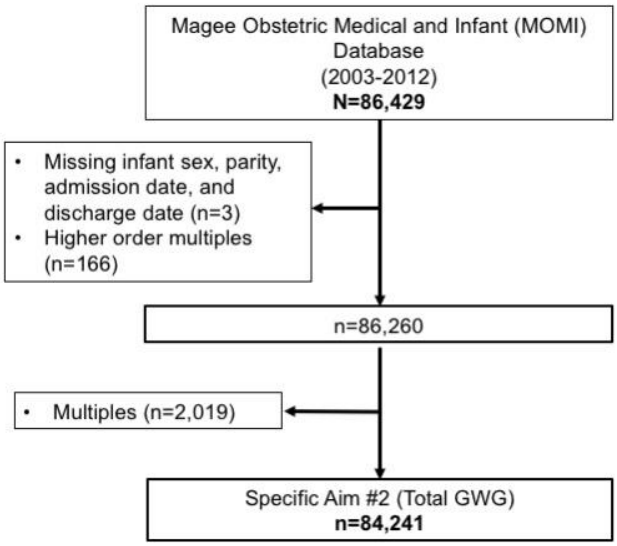
Third, longer-term cohorts should be established to better understand the lasting effects that severe maternal morbidity has on patients, their families, and the healthcare systems they utilize. Along with the immediate impact of severe maternal morbidity, including medical implications and cost to both patient and facility, there are potential lasting effects that have been examined by too few, particularly in the U.S.[149] In developing these efforts, researchers should include patient and stakeholder input during all phases of work. The Patient Centered Outcomes

Research Initiative (PCORI) has placed focus on this type of work in several areas, including pregnancy research.[150] Including stakeholders outside clinical and research staff in the discussion of severe maternal morbidity research would help add context and focus research in new directions. As one example, there is disagreement throughout the literature regarding what constitutes severe maternal morbidity, but nearly all discussion is through a physician or researcher's lens; patients and their families bear the lasting burden of facing one of these events and would have valuable insight as the field progresses.

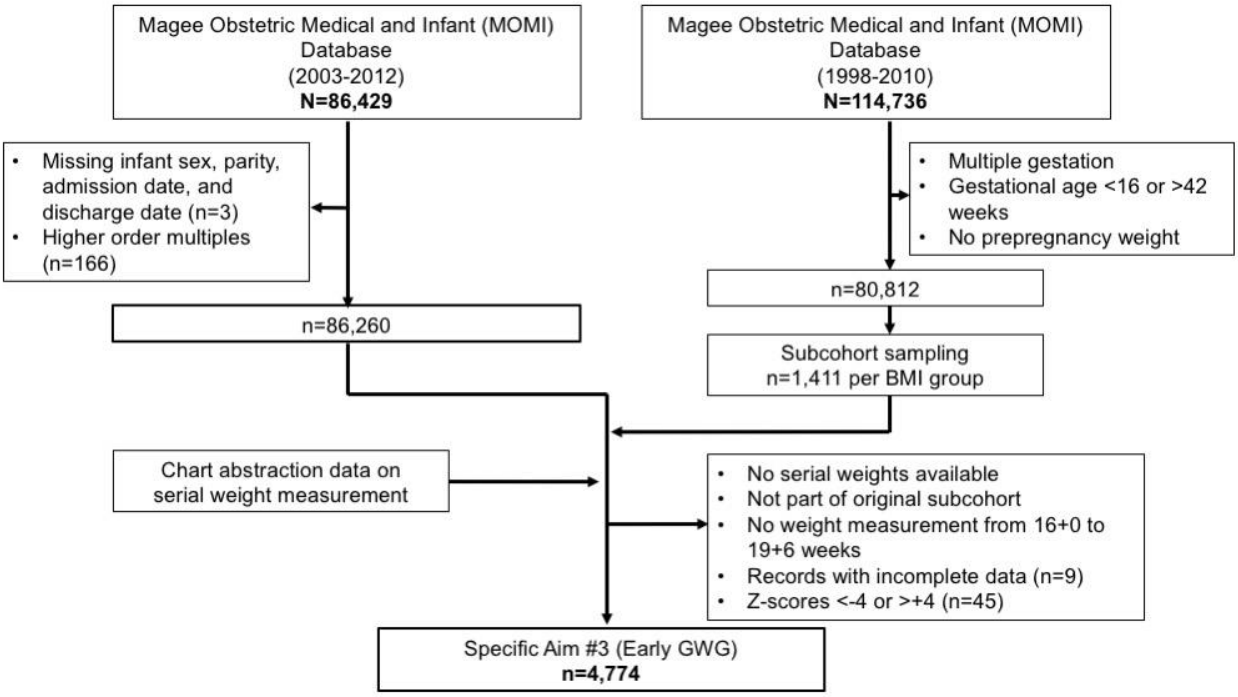
Fourth, while epidemiologic research of individual-level risk factors is important and, as discussed, should be part of any risk reduction strategy, future efforts must expand their focus to facility-level and policy-level risk factors. As our data suggest and previous work has shown, upwards of half of preventable cases are due to provider- and system-level factors.[18,136] By using similar methods as we have shown here (e.g. quantifying the risk that certain factors confer on severe maternal morbidity by calculating the population attributable fraction), this work can and should be done at individual institutions.

Overall, there must be a research environment that focuses on multidisciplinary collaboration between researchers, clinicians, and stakeholders. Research must aim to develop and test sustainable strategies that can lead to quantifiable reductions in the incidence of severe maternal morbidity.

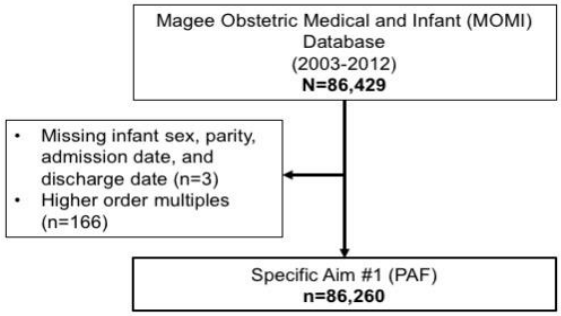
Appendix A Sample Selection



Appendix Figure 1 Specific Aim #1 sample selection



Appendix Figure 2 Specific Aim #2 sample selection

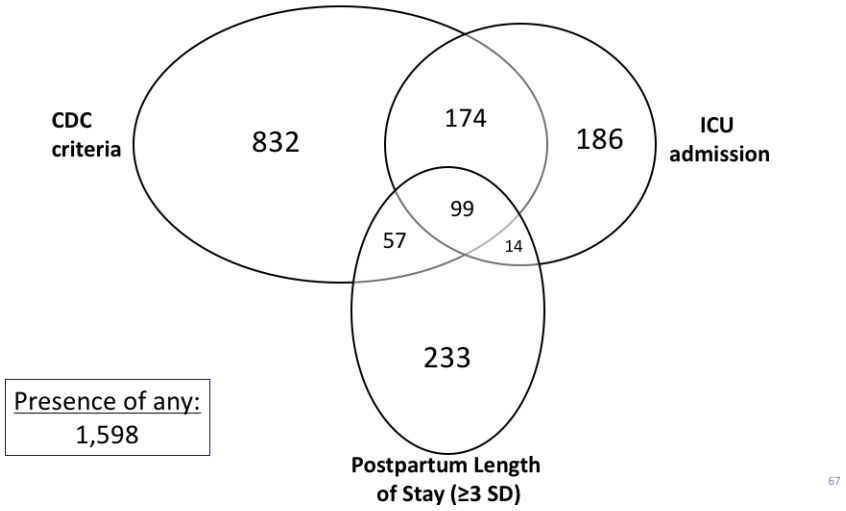


Appendix Figure 3 Specific Aim #3 sample selection

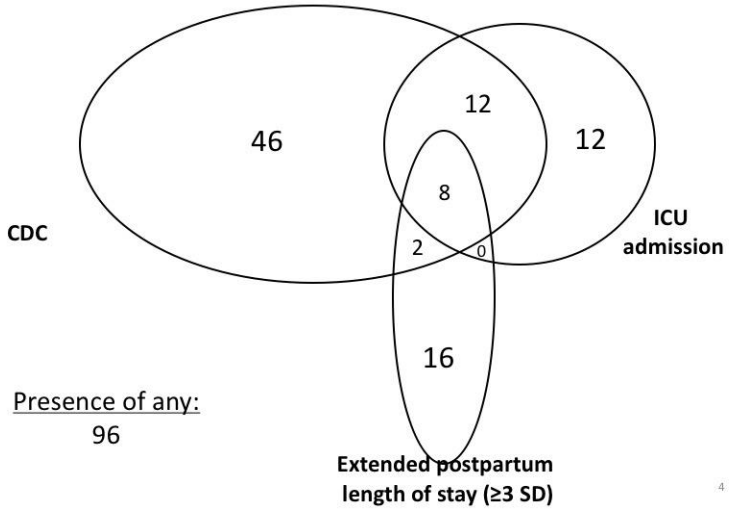
Appendix B Defining severe maternal morbidity and its distribution by indicator and Specific Aim

Appendix Table 1 Severe maternal morbidity indicators and corresponding ICD-9 codes

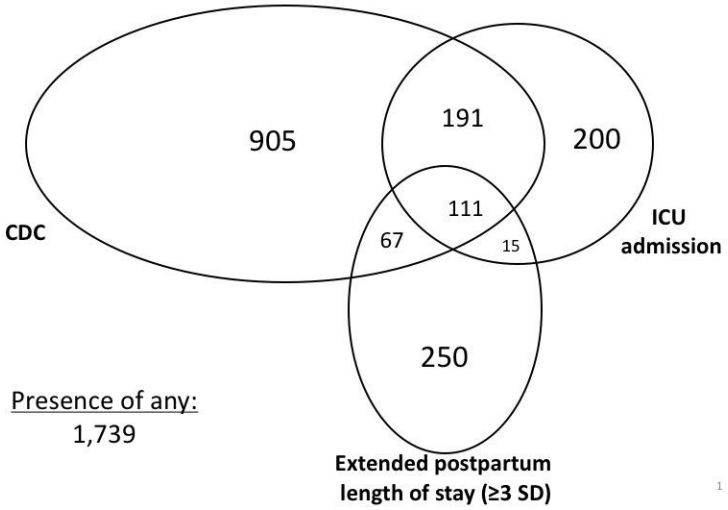
Severe Maternal Morbidity Indicator	ICD-9-CM Codes
1. Acute myocardial infarction	410.xx
2. Acute renal failure	584.x, 669.3x
3. Adult respiratory distress syndrome	518.5, 518.81,518.82, 518.84, 799.1
4. Amniotic fluid embolism	673.1x
5. Aneurysm	441.xx
6. Cardiac arrest/ ventricular fibrillation	427.41, 427.42, 427.5
7. Disseminated intravascular coagulation	286.6, 286.9, 666.3x
8. Eclampsia	642.6x
9. Heart failure during procedure or surgery	669.4x, 997.1
10. Puerperal cerebrovascular disorders	430, 431, 432.x, 433.xx, 434.xx, 436, 437.x, 671.5x, 674.0x, 997.2, 999.2
11. Pulmonary edema	428.1, 518.4
12. Severe anesthesia complications	668.0x, 668.1, 668.2x
13. Sepsis	038.xx, 995.91, 995.92
14. Shock	669.1x, 785.5x, 995.0, 995.4, 998.0
15. Sickle cell anemia with crisis	282.62, 282.64, 282.69
16. Thrombotic embolism	415.1x, 673.0x, 673.2x, 673.3x, 673.8x
17. Blood transfusion	99.0x
18. Conversion of cardiac rhythm	99.6x
19. Hysterectomy	68.3x-68.9
20. Temporary tracheostomy	31.1
21. Ventilation	93.90, 96.01-96.05, 96.7x



Appendix Figure 4 Specific Aim #1 composition of severe maternal morbidity by indicator



Appendix Figure 5 Specific Aim #2 composition of severe maternal morbidity by indicator

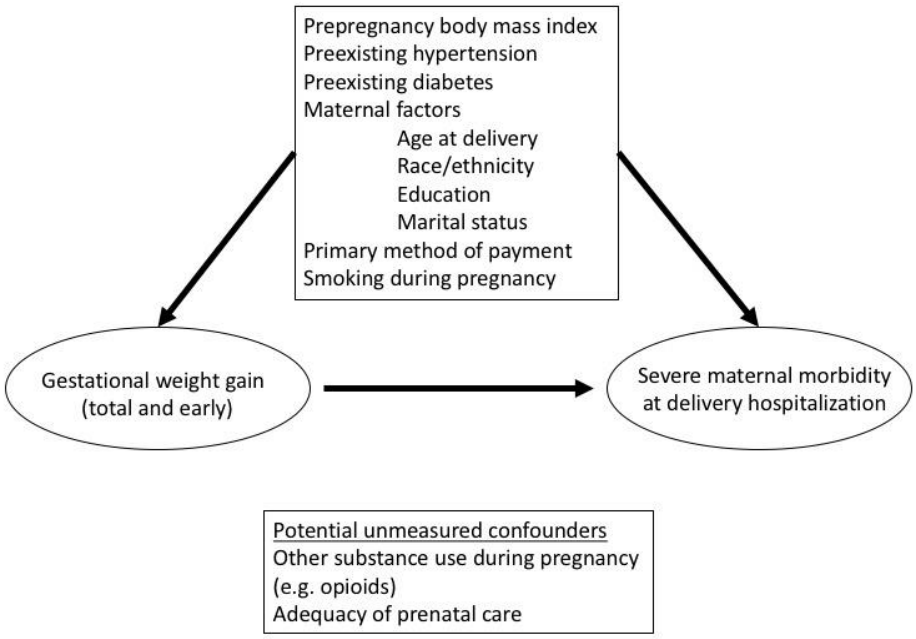


Appendix Figure 6 Specific Aim #3 composition of severe maternal morbidity by indicator

Appendix Table 2 Severe maternal morbidity indicators by Specific Aim

Severe maternal morbidity indicator	Specific Aim #1 (n=84,241)		Specific Aim #2 (n=4,774)		Specific Aim #3 cohort (n=86,260)	
	Cases (n)	%	Cases (n)	%	Cases (n)	%
Intensive care unit admission	474	30	32	33	516	30
Prolonged postpartum length of stay	404	25	26	26	441	25
Acute myocardial infarction	1	0.06	0	0	1	0.06
Acute renal failure	81	5.1	5	5.2	89	5.1
Adult respiratory distress syndrome	89	5.6	6	6.3	94	5.4
Amniotic fluid embolism	7	0.44	1	1.0	7	0.40
Aneurysm	2	0.13	0	0	2	0.11
Cardiac arrest/ ventricular fibrillation	9	0.56	2	2.1	9	0.52
Disseminated intravascular coagulation	100	6.3	8	8.3	112	6.4
Eclampsia	67	4.2	8	8.3	74	4.3
Heart failure during procedure or surgery	431	27	21	22	471	27
Puerperal cerebrovascular disorders	28	1.8	5	5.2	31	1.8
Pulmonary edema	39	2.4	0	0	43	2.5
Severe anesthesia complications	25	1.6	4	4.2	25	1.4
Sepsis	41	2.6	1	1.0	43	2.5
Shock	57	3.5	4	4.2	59	3.4
Sickle cell anemia with crisis	10	0.63	0	0	11	0.63
Thrombotic embolism	17	1.1	3	3.1	19	1.1
Blood transfusion	469	29	27	28	525	30
Conversion of cardiac rhythm	1	0.06	0	0	1	0.06
Hysterectomy	93	5.8	4	4.2	103	5.9
Temporary tracheostomy	2	0.13	0	0	2	0.11
Ventilation	42	2.6	1	1.0	49	2.8

Appendix C Selection of confounders using directed acyclic graphs



Appendix Figure 7 Confounders of the relationship between gestational weight gain and severe maternal morbidity

Appendix D 2009 Institute of Medicine weight gain recommendations

Appendix Table 3 Institute of Medicine weight gain guidelines and corresponding z-scores

Prepregnancy BMI	Total weight gain (kg)	Corresponding z-scores at 40 weeks gestation	Rates of weight gain 2nd and 3rd trimesters (kg/week)*	Corresponding z-scores at 19 weeks gestation
Underweight (<18.5kg/m^2)	12.5 to 18	-0.55 to 0.48	0.44 to 0.58	0.01 to 0.35
Normal weight (18.5-24.9 kg/m^2)	11.5 to 16	-0.95 to -0.07	0.35 to 0.50	-0.26 to 0.08
Overweight (25-29.9kg/m^2)	7 to 11.5	-1.33 to -0.6	0.23 to 0.33	-0.27 to -0.12
Obese 1 (30-34.9kg/m^2)	5 to 9	-1.1 to -0.5	0.17 to 0.27	-0.55 to 0.08
Obese 2 (35-39.9kg/m^2)	5 to 9	-0.6 to -0.1	0.17 to 0.27	0.23 to 0.35
Obese 3 (≥40kg/m^2)	5 to 9	-0.17 to 0.18	0.17 to 0.27	0.40 to 0.49

Appendix E Sensitivity analyses for Specific Aim #1

Appendix Table 4 Characteristics of women delivering singleton infants at Magee-Womens Hospital, 2003-2012 (N=84,241)

Maternal characteristic	n(% of cohort)	
	Term	Preterm
Overall	74,879 (89)	9,362 (11)
Prepregnancy body mass index (BMI cutpoints)		
Underweight (<18.5kg/m^2)	3,529 (4.7)	567 (6.1)
Normal weight (18.5-24.9kg/m^2)	39,357 (53)	4,352 (46)
Overweight (25.0-29.9kg/m^2)	17,860 (24)	2,239 (24)
Obese (≥30.0kg/m^2)	14,133 (19)	2,204 (24)
Age (years)		
<20	5,080 (6.8)	850 (9.1)
20-30	33,622 (45)	4,464 (48)
>30	36,177 (48)	4,048 (43)
Race/ ethnicity		
Non-Hispanic White	56,408 (75)	6,654 (71)
Non-Hispanic Black	14,218 (19)	2,322 (25)
Other	4,253 (5.7)	386 (4.1)
Parity at conception		
0	34,213 (46)	44,385 (47)
1 or more	40,666 (54)	54,977 (53)
Marital status		
Unmarried	28,579 (38)	4,871 (48)
Married	46,300 (62)	4,491 (52)
Education		
High school or less	21,810 (29)	3,884 (42)
Some college	17,069 (23)	2,408 (26)
College graduate	36,000 (48)	3,070 (33)
Preexisting hypertension or diabetes		
Yes	2,581 (3.4)	1,162 (12)
No	72,298 (97)	8,200 (88)
Smoking during pregnancy		
Yes	10,272 (14)	2,051 (22)
No	64,607 (86)	7,311 (78)
Insurance		
Private	39,516 (53)	4,095 (44)
Public/ Other	35,363 (47)	5,267 (56)

Appendix Table 5 Mean z-score among singleton pregnancies at delivery by maternal characteristic and gestational age at delivery. Magee-Womens Hospital, 2003-2012 (N=84,241)

Characteristic	Mean (SD) z-score at delivery	
	Term	Preterm
Prepregnancy body mass index (BMI cutpoints)		
Underweight (<18.5kg/m^2)	0.10 (0.99)	0.06 (1.10
Normal weight (18.5-24.9kg/m^2)	-0.13 (1.1)	-0.25 (1.3)
Overweight (25.0-29.9kg/m^2)	-0.14 (1.0)	-0.14 (1.2)
Obese (≥30.0kg/m^2)	0.02 (1.0)	0.10 (1.2)
Maternal age (years)		
<20	-0.03 (1.1)	-0.18 (1.4)
20-30	-0.05 (1.1)	-0.10 (1.3)
>30	-0.14 (1.0)	-0.14 (1.2)
Maternal race/ ethnicity		
Non-Hispanic White	-0.06 (1.0)	-0.08 (1.2)
Non-Hispanic Black	-0.14 (1.2)	-0.21 (1.4)
Other	-0.37 (1.0)	-0.31 (1.2)
Parity at conception		
0	0.01 (1.0)	0.02 (1.2)
1 or more	-0.18 (1.1)	-0.25 (1.3)
Marital status		
Unmarried	-0.06 (1.1)	-0.16 (1.3)
Married	-0.12 (0.99)	-0.08 (1.2)
Maternal education		
High school or less	-0.10 (1.2)	-0.21 (1.3)
Some college	-0.05 (1.0)	-0.05 (1.3)
College graduate	-0.11 (0.97)	-0.08 (1.2)
Preexisting hypertension or diabetes		
Yes	0.06 (1.2)	0.16 (1.3)
No	-0.10 (1.0)	-0.16 (1.3)
Smoking during pregnancy		
Yes	-0.17 (1.2)	-0.31 (1.3)
No	-0.08 (1.0)	-0.07 (1.2)
Insurance		
Private	-0.08 (0.99)	-0.07 1.2)
Public/ Other	-0.10 (1.1)	-0.16 (1.3)

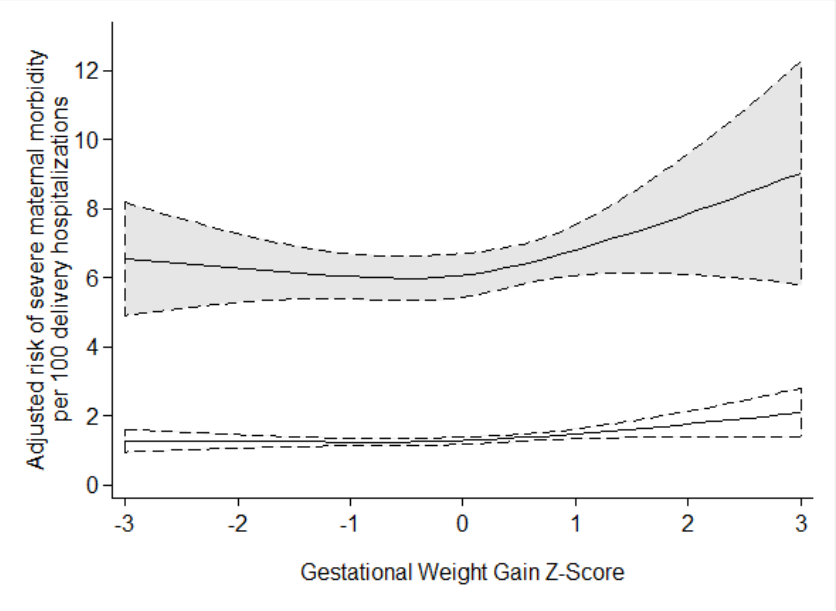
[a] <11kg among normal weight, 9.5kg among overweight, and 3.3kg among obese women at 40 weeks' gestation.

[b] 11-23kg among normal weight, 9.5-25kg among overweight, and 3.3-19kg among obese

[c] >23kg among normal weight, >25kg among overweight, and >19kg among obese women.

Appendix Table 6 Incidence of severe maternal morbidity by maternal characteristic. Magee-Womens Hospital, 2003-2012 (N=84,241)

Maternal characteristic	Cases of severe maternal morbidity (unadjusted incidence)	
	Term	Preterm
Overall	997 (1.3)	600 (6.4)
Prepregnancy body mass index (BMI cutpoints)		
Underweight (<18.5kg/m^2)	44 (1.3)	24 (4.3)
Normal weight (18.5-24.9kg/m^2)	469 (1.2)	231 (5.3)
Overweight (25.0-29.9kg/m^2)	245 (1.4)	155 (7.0)
Obese (≥30.0kg/m^2)	124 (1.7)	99 (8.5)
Maternal age (years)		
<20	93 (1.8)	53 (6.2)
20-30	427 (1.3)	242 (5.4)
>30	477 (1.3)	305 (7.5)
Maternal race/ ethnicity		
Non-Hispanic White	629 (1.1)	404 (6.1)
Non-Hispanic Black	292 (2.1)	176 (7.6)
Other	76 (1.8)	19 (5.0)
Parity at conception		
0	538 (1.6)	255 (5.8)
1 or more	459 (1.1)	344 (6.9)
Marital status		
Unmarried	471 (1.7)	325 (6.7)
Married	526 (1.1)	274 (6.1)
Maternal education		
High school or less	372 (1.7)	265 (6.8)
Some college	223 (1.3)	167 (7.0)
College graduate	402 (1.1)	167 (5.4)
Preexisting hypertension or diabetes		
Yes	74 (2.9)	147 (13)
No	924 (1.3)	452 (5.5)
Smoking during pregnancy		
Yes	147 (1.4)	112 (5.5)
No	851 (1.3)	487 (6.7)
Insurance		
Private	448 (1.1)	250 (6.1)
Public/ Other	549 (1.6)	349 (6.6)



Appendix Figure 8 Adjusted, predicted risk of severe maternal morbidity by gestational age at delivery and weight gain z-score.

Note: For both curves, the solid line represents point estimates, dashed lines represent 95% confidence intervals. Adjusted for maternal age, prepregnancy BMI, maternal race, maternal education, smoking during pregnancy, marital status, parity, preexisting hypertension or diabetes, and primary method of payment. Pittsburgh, PA. N=84,241

Appendix Table 7 Cumulative incidence of severe maternal morbidity among term deliveries by gestational weight gain z-score category. Magee-Womens Hospital 2003-2012 (N=74,879)

Gestational weight gain z-score category	n at risk	Unadjusted risk (cases)	Unadjusted RD (95% CI)	Adjusted RD (95% CI)
<-2	2,745	1.5 (39)	0.26 (-0.26, 0.78)	0.12 (-0.37, 0.61)
-2 to <-1	8,894	1.3 (119)	0.09 (-0.20, 0.38)	0.04 (-0.25, 0.33)
-1 to <0	27,373	1.2 (329)	Reference	Reference
0 to <+1	26,768	1.3 (350)	0.13 (-0.09, 0.34)	0.08 (-0.14, 0.30)
+1 to <+2	8,063	1.6 (131)	0.37 (0.02, 0.73)	0.26 (-0.08, 0.61)
≥+2	1,036	2.7 (29)	1.5 (0.41, 2.5)	1.3 (0.28, 2.2)

40-week gestation equivalent weight gain for normal weight women: -2SD(7.0kg); -1SD(11kg); 0SD(16kg); 1SD(23kg); 2SD(31kg)

Appendix Table 8 Cumulative incidence of severe maternal morbidity among preterm deliveries by gestational weight gain z-score category. Magee-Womens Hospital 2003-2012 (N=9,362)

Gestational weight gain z-score category	n at risk	Unadjusted risk (cases)	Unadjusted RD (95% CI)	Adjusted RD (95% CI)
<-2	611	7.1 (47)	1.2 (-1.4, 3.9)	1.1 (-1.6, 3.8)
-2 to <-1	1,267	5.3 (66)	-0.61 (-2.5, 1.2)	-0.58 (-2.5, 1.3)
-1 to <0	2,925	5.9 (171)	Reference	Reference
0 to <+1	3,015	6.5 (192)	0.61 (-0.80, 2.0)	0.28 (-1.1, 1.7)
+1 to <+2	1,300	7.6 (103)	1.7 (-0.25, 3.6)	1.1 (-0.82, 3.0)
≥+2	244	9.3 (21)	3.4 (-1.1, 7.9)	2.7 (-1.6, 7.0)

40-week gestation equivalent weight gain for normal weight women: -2SD(7.0kg); -1SD(11kg); 0SD(16kg); 1SD(23kg); 2SD(31kg)

Appendix Table 9 Estimated number of excess cases of severe maternal morbidity per 100 delivery hospitalizations by select gestational weight gain z-scores. Term delivery hospitalizations at Magee-Womens Hospital 2003-2012 (N=74,879)

Gestational weight gain z-score category	Adjusted risk per 100 delivery hospitalizations (95% confidence interval)	Adjusted RD per 100 delivery hospitalizations (95% confidence interval)
-3 SD	1.3 (0.97, 1.6)	0.01 (-0.35, 0.36)
-2.5 SD	1.3 (1.0, 1.5)	-0.01 (-0.29, 0.28)
-2 SD	1.3 (1.1, 1.5)	-0.02 (-0.24, 0.20)
-1.5 SD	1.3 (1.1, 1.4)	-0.03 (-0.18, 0.12)
-1 SD	1.2 (1.1, 1.3)	-0.04 (-0.13, 0.04)
-0.5 SD	1.2 (1.1, 1.3)	-0.04 (-0.08, 0.00001)
0	1.3 (1.2, 1.4)	Reference
+0.5 SD	1.2 (1.0, 1.4)	0.09 (0.03, 0.15)
+1 SD	1.5 (1.3, 1.6)	0.22 (0.05, 0.38)
+1.5 SD	1.6 (1.4, 1.9)	0.37 (0.08, 0.66)
+2 SD	1.7 (1.4, 2.0)	0.53 (0.09, 0.96)
+2.5 SD	2.0 (1.4, 2.6)	0.70 (0.09, 1.3)
+3 SD	2.1 (1.4, 2.9)	0.86 (0.09, 1.6)

40-week gestation equivalent weight gain for normal weight women: -2SD(7.0kg); -1SD(11kg); 0SD(16kg); 1SD(23kg); 2SD(31kg)

Appendix Table 10 Estimated number of excess cases of severe maternal morbidity per 100 delivery hospitalizations by select gestational weight gain z-scores. Preterm delivery hospitalizations at Magee-Womens Hospital 2003-2012 (N=9,362)

Gestational weight gain z-score category	Adjusted risk per 100 delivery hospitalizations (95% confidence interval)	Adjusted RD per 100 delivery hospitalizations (95% confidence interval)
-3 SD	6.6 (4.9, 8.2)	0.44 (-1.4, 2.2)
-2.5 SD	6.4 (5.1, 7.7)	0.31 (-1.1, 1.7)
-2 SD	6.3 (5.3, 7.3)	-0.18 (-0.90, 1.3)
-1.5 SD	6.2 (5.4, 6.9)	0.05 (-0.69, 0.79)
-1 SD	6.0 (5.4, 6.7)	-0.06 (-0.50, 0.37)
-0.5 SD	6.0 (5.4, 6.6)	-0.11 (-0.31, 0.10)
0	6.1 (5.5, 6.7)	Reference
+0.5 SD	5.7 (4.6, 6.8)	0.31 (-0.01, 0.63)
+1 SD	6.8 (6.1, 7.5)	0.78 (-0.04, 1.6)
+1.5 SD	7.3 (6.2, 8.5)	1.3 (-0.11, 2.8)
+2 SD	7.5 (6.1, 9.0)	1.9 (-0.22, 4.0)
+2.5 SD	8.6 (6.0, 11)	2.5 (-0.37, 5.4)
+3 SD	9.1 (5.8, 12)	3.0 (-0.54, 6.6)

Appendix F Sampling fractions for Specific Aim #2

Appendix Table 11 Sample selection by prepregnancy BMI category

Sample selection	Prepregnancy BMI category					
	Underweight	Normal weight	Overweight	Grade 1 obese	Grade 2 obese	Grade 3 obese
Total eligible, n	2,016	39,014	22,757	10,067	4,389	2,569
Randomly selected into subcohort	1,411	1,411	1,411	1,411	1,411	1,411
Retained as part of subcohort	1,101	907	968	1,043	1,024	970
Retain those with serial weight measurements	1,042	903	946	1,022	992	934
Retain those with measured antenatal weight at 16-19 weeks	808	821	789	841	816	753
Retain those with complete data	807	819	789	838	814	752
Retain those with z-scores from -4 to +4	800	811	787	828	806	742
Sampling fraction	0.40	0.021	0.035	0.082	0.18	0.29

Appendix G Maternal characteristics by prepregnancy BMI category and cohort

Appendix Table 12 Maternal characteristics for Specific Aim #2, Underweight and Normal weight

Maternal characteristic	Underweight			Normal weight		
	Eligible cohort (n=2,761)	Randomly selected into subcohort with SMM data (n=1,101)	Subcohort used in final sample (n=807)	Eligible cohort (n=35,125)	Randomly selected into subcohort with SMM data (n=907)	Subcohort used in final sample (n=819)
	Percent of cohort					
Age >30 years	35	36	39	51	51	52
Non-Hispanic White	72	73	74	79	78	79
College graduate	39	40	43	54	54	55
Nulliparous	53	52	53	49	49	48
Preterm birth	13	12	10	9.2	8.5	8.3
Preexisting hypertension/ diabetes	1.1	1.2	1.0	1.7	1.1	1.2
Married	50	50	55	66	66	68
Private insurance	48	48	50	58	54	55
Smoked during pregnancy	23	25	21	13	11	11

Appendix Table 13 Maternal characteristics for Specific Aim #2, Overweight and Grade 1 Obese

Maternal characteristic	Overweight			Grade 1 obese		
	Eligible cohort (n=14,300)	Randomly selected into subcohort with SMM data (n=968)	Subcohort used in final sample (n=789)	Eligible cohort (n=6,639)	Randomly selected into subcohort with SMM data (n=1,043)	Subcohort used in final sample (n=838)
	Percent of cohort					
Age >30 years	50	50	51	48	48	51
Non-Hispanic White	75	78	80	72	74	77
College graduate	46	46	50	38	38	41
Nulliparous	44	42	42	42	40	40
Preterm birth	10	11	10	12	12	11
Preexisting hypertension/ diabetes	4.3	5.7	5.8	9.0	9.8	10
Married	61	62	65	57	57	61
Private insurance	53	57	59	50	52	55
Smoked during pregnancy	14	15	13	15	16	15

Appendix Table 14 Maternal characteristics for Specific Aim #2, Grades 2 and 3 obese

Maternal characteristic	Grade 2 obese			Grade 3 obese		
	Eligible cohort (n=2,990)	Randomly selected into subcohort with SMM data (n=1,024)	Subcohort used in final sample (n=814)	Eligible cohort (n=1,804)	Randomly selected into subcohort with SMM data (n=970)	Subcohort used in final sample (n=752)
	Percent of cohort					
Age >30 years	47	48	49	49	48	49
Non-Hispanic White	71	72	74	66	67	68
College graduate	35	35	38	29	28	30
Nulliparous	40	41	42	39	39	39
Preterm birth	12	11	11	15	12	11
Preexisting hypertension/ diabetes	14	14	14	21	21	20
Married	55	56	59	53	54	55
Private insurance	47	47	49	48	50	51
Smoked during pregnancy	16	17	16	15	16	15

Appendix H Severe maternal morbidity indicators by weight gain z-score category at 16-19 weeks gestation

Appendix Table 15 Severe maternal morbidity indicator by z-score category (N=4,774)

Severe maternal morbidity indicator	Gestational weight gain <-1 SD		Gestational weight gain -1 to +1 SD		Gestational weight gain >+1 SD	
	Cases (n)	%	Cases (n)	%	Cases (n)	%
Overall	9		73		14	
Intensive care unit admission	0	0	28	38	4	29
Prolonged postpartum length of stay	0	0	21	29	5	36
Acute myocardial infarction	0	0	0	0	0	0
Acute renal failure	0	0	5	6.9	0	0
Adult respiratory distress syndrome	0	0	5	6.9	1	7.1
Amniotic fluid embolism	0	0	1	1.4	0	0
Aneurysm	0	0	0	0	0	0
Cardiac arrest/ ventricular fibrillation	0	0	2	2.7	0	0
Disseminated intravascular coagulation	0	0	8	11	0	0
Eclampsia	1	11	6	8.2	1	7.1
Heart failure during procedure or surgery	1	11	15	21	5	36
Puerperal cerebrovascular disorders	0	0	5	6.9	0	0
Pulmonary edema	0	0	0	0	0	0
Severe anesthesia complications	1	11	3	4.1	0	0
Sepsis	0	0	1	1.4	0	0
Shock	0	0	4	5.5	0	0
Sickle cell anemia with crisis	0	0	0	0	0	0
Thrombotic embolism	1	11	2	2.7	0	0
Blood transfusion	5	56	21	29	1	7.1
Conversion of cardiac rhythm	0	0	0	0	0	0
Hysterectomy	0	0	3	4.1	1	7.1
Temporary tracheostomy	0	0	0	0	0	0
Ventilation	0	0	1	1.4	0	0

Appendix I Comparison of samples for Specific Aims #1, #2, ASTRID, and MOMI cohorts

Appendix Table 16 Maternal characteristics by cohort

Characteristic	Frequency of sample (%)			
	MOMI (n=180,965)	ASTRID (n=97,793)	Specific Aim #1 (n=84,241)	Specific Aim #2 (n=4,774)*
Prepreg body mass index				
Underweight	4,331 (4.3)	8,918 (9.2)	4,096 (4.8)	800 (2.5)
Normal weight	52,996 (53)	17,814 (18)	43,709 (52)	811 (48)
Overweight	23,016 (23)	15,705 (16)	20,099 (24)	787 (28)
Obese	20,196 (20)	55,045 (56)	16,337 (19)	2,376 (21)
Maternal age				
<20 years	7,276 (6.9)	5,851 (6.0)	5,930 (7.0)	280 (6.2)
20-30 years	47,749 (45)	45,942 (47)	38,086 (45)	2,177 (43)
>30 years	50, 075 (48)	46,000 (47)	40,225 (48)	2,317 (51)
Maternal race/ ethnicity				
Non-Hispanic White	138,242 (77)	72,832 (75)	63,062 (75)	3,602 (78)
Non-Hispanic Black	22,419 (19)	21,503 (22)	16,540 (20)	971 (17)
Other (including Hispanic)	8,344 (4.6)	3,458 (3.5)	4,639 (5.5)	201 (4.9)
Parity				
No births	81,594 (45)	41,928 (43)	38,598 (46)	2,103 (45)
Previous birth	99,358 (55)	55,865 (57)	45,643 (54)	2,671 (55)
Marital status				
Unmarried	38,527 (37)	38,407 (39)	33,450 (40)	1,898 (35)
Married	66,540 (63)	59,386 (61)	50,791 (60)	2,921 (65)
Maternal education				
Less than high school	8,684 (8.3)	7,538 (7.7)	7,244 (8.6)	1,438(6.9)
High school some college	46,786 (45)	51,670 (53)	37,908 (45)	1,283 (43)
College graduate	49,258 (47)	38,415 (39)	38,750 (46)	2,053 (50)
Pre hypertension or diabetes				
Yes	9,903 (5.5)	6,106 (6.3)	3,743 (4.4)	410 (5.0)
No	171,062 (95)	91,399 (94)	80,498 (96)	4,364 (95)
Smoking during pregnancy				
Yes	15,991 (15)	13,630 (14)	12,323 (15)	715 (13)
No	89,010 (85)	82,847 (86)	40,630 (85)	4,059 (87)
Insurance				
Private	104,115 (58)	59,355 (61)	43,611 (52)	2,549 (56)
Public/ Other	76,566 (42)	38,428 (39)	40,630 (48)	2,225 (44)

Appendix Table 17 Appendix A Severe maternal morbidity indicators by gestational weight gain z-score category (N=84,241)

Severe maternal morbidity indicator	Gestational weight gain <-2 SD		Gestational weight gain -2 to <+1 SD		Gestational weight gain +1 to <+2 SD		Gestational weight gain ≥+2 SD	
	Cases (n)	%	Cases (n)	%	Cases (n)	%	Cases (n)	%
Intensive care unit admission	27	33	361	29	71	32	13	28
Prolonged postpartum length of stay	21	25	307	25	60	27	16	32
Acute myocardial infarction	0	0	1	0.08	0	0	0	0
Acute renal failure	5	6.3	60	4.9	13	5.8	1	2.0
Adult respiratory distress syndrome	4	5.5	65	5.3	16	7.3	1	2.0
Amniotic fluid embolism	1	1.2	4	0.39	1	0.43	0	0
Aneurysm	0	0	1	0.08	1	0.43	0	0
Cardiac arrest/ ventricular fibrillation	1	1.2	5	0.46	2	1.2	0	0
Disseminated intravascular coagulation	7	8.6	81	6.6	9	4.4	1	2.0
Eclampsia	1	1.9	43	3.5	18	8.4	1	2.0
Heart failure during procedure or surgery	15	19	340	27	59	26	15	31
Puerperal cerebrovascular disorders	1	1.2	18	1.5	6	3.1	1	2.4
Pulmonary edema	1	1.2	26	2.1	7	3.3	3	6.5
Severe anesthesia complications	3	3.7	19	1.6	1	0.43	1	2.0
Sepsis	2	2.4	33	2.7	3	1.6	1	2.0
Shock	3	3.6	47	3.8	4	2.2	1	2.0
Sickle cell anemia with crisis	1	1.2	7	0.59	0	0	0	0
Thrombotic embolism	0	0	13	1.1	3	1.4	0	0
Blood transfusion	30	36	367	30	59	26	12	25
Conversion of cardiac rhythm	0	0	1	0.08	0	0	0	0
Hysterectomy	4	5.4	75	6.1	12	5.5	0	0
Temporary tracheostomy	0	0	1	0.08	1	0.43	0	0
Ventilation	3	3.5	30	2.5	8	3.6	1	2.0

Appendix Table 18 Appendix A Severe maternal morbidity indicators by gestational age at delivery (N=84,241)

Severe maternal morbidity indicator	n(% of cases)*	
	Term delivery (≥37 weeks) 998 (54)	Preterm delivery (<37 weeks) 599 (36)
ICU admission	250 (25)	224 (37)
Prolonged postpartum length of stay	207 (21)	197 (33)
Acute myocardial infarction	0	1 (0.17)
Acute renal failure	26 (2.6)	55 (9.2)
Adult respiratory distress syndrome	30 (3.0)	59 (9.8)
Amniotic fluid embolism	5 (0.50)	2 (0.33)
Aneurysm	1 (0.10)	1 (0.17)
Cardiac arrest/ ventricular fibrillation	6 (0.60)	3 (0.50)
Disseminated intravascular coagulation	58 (5.8)	42 (7.0)
Eclampsia	34 (3.4)	33 (5.5)
Heart failure during procedure or surgery	317 (32)	114 (19)
Puerperal cerebrovascular disorders	20 (2.0)	8 (1.3)
Pulmonary edema	13 (1.3)	26 (4.3)
Severe anesthesia complications	21 (2.1)	4 (0.67)
Sepsis	10 (1.0)	31 (5.2)
Shock	30 (3.0)	27 (4.5)
Sickle cell anemia with crisis	2 (0.20)	8 (1.3)
Thrombotic embolism	10 (1.0)	7 (1.2)
Blood transfusion	303 (30)	166 (28)
Conversion of cardiac rhythm	1 (0.10)	0
Hysterectomy	46 (4.6)	47 (7.8)
Temporary tracheostomy	0	2 (0.33)
Ventilation	19 (9)	23 (3.8)

Appendix J Sensitivity analyses, Specific Aim #1

Appendix Table 19 Estimated number of excess cases of severe maternal morbidity by outcome definition used. Magee-Womens Hospital (N=84,241)

Gestational weight gain z-score	Adjusted risk difference per 100 delivery hospitalizations (95% confidence interval)				
	Primary definition (PD)	PD less ICU admission	PD less extended postpartum length of stay	PD less blood transfusion	Complete case analysis (n=57,922)
-3 SD	0.30 (-0.07, 0.67)	0.23 (-0.11, 0.57)	0.25 (-0.10, 0.59)	0.22 (-0.10, 0.55)	0.25 (-0.11, 0.62)
-2.5 SD	0.22 (-0.07, 0.51)	0.17 (-0.10, 0.43)	0.18 (-0.09, 0.45)	0.16 (-0.09 (0.41)	0.18 (-0.11, 0.47)
-2 SD	0.14 (-0.07, 0.35)	0.10 (-0.10, 0.30)	0.12 (-0.08, 0.32)	0.09 (-0.09, 0.28)	0.11 (-0.10, 0.32)
-1.5 SD	0.06 (-0.08, 0.21)	0.04 (-0.09, 0.17)	0.06 (-0.08, 0.19)	0.03 (-0.09, 0.16)	0.04 (-0.10, 0.18)
-1 SD	-0.01 (-0.10, 0.08)	-0.02 (-0.10, 0.06)	0.001 (-0.08, 0.08)	-0.03 (-0.10, 0.05)	-0.02 (-0.11, 0.06)
-0.5 SD	-0.04 (-0.08, -0.002)	-0.04 (-0.08, -0.004)	-0.03 (-0.07, 0.01)	-0.05 (-0.08, -0.01)	-0.05 (-0.09, -0.01)
0	Reference	Reference	Reference	Reference	Reference
+0.5 SD	0.14 (0.08, 0.21)	0.13 (0.07, 0.19)	0.10 (0.04, 0.17)	0.14 (0.09, 0.20)	0.15 (0.09, 0.21)
+1 SD	0.38 (0.20, 0.56)	0.34 (0.18, 0.51)	0.27 (0.10, 0.44)	0.38 (0.23, 0.53)	0.39 (0.22, 0.57)
+1.5 SD	0.67 (0.33, 1.0)	0.61 (0.29, 0.92)	0.48 (0.16, 0.79)	0.68 (0.38, 0.97)	0.70 (0.37, 1.0)
+2 SD	1.0 (0.46, 1.5)	0.88 (0.40, 1.4)	0.68 (0.21, 1.2)	1.0 (0.53, 1.5)	1.0 (0.51, 1.5)
+2.5 SD	1.3 (0.58, 2.0)	1.2 (0.51, 1.9)	0.92 (0.26, 1.6)	1.4 (0.69, 2.0)	1.4 (0.66, 2.1)
+3 SD	1.6 (0.68, 2.6)	1.5 (0.60, 2.4)	1.1 (0.29, 2.0)	1.7 (0.82, 2.6)	1.7 (0.78, 2.7)

Notes: Primary definition (PD)= severe maternal morbidity as "presence of any one of the Centers for Disease Control and Prevention criteria, ICU admission, or extended postpartum length of stay (>3 days for vaginal deliveries and >5 days for cesarean deliveries).

Appendix Table 20 Estimated number of excess cases of severe maternal morbidity by specific indicator. Preterm deliveries Magee-Womens Hospital (N=84,241)

Severe maternal morbidity indicator	Adjusted risk difference per 100 delivery hospitalizations (95% confidence interval)			
	Gestational weight gain z-score category			
	-2	-1	+1	+2
Intensive care unit admission	0.08 (-0.02, 0.18)	0.01 (-0.03, 0.05)	0.12 (0.02, 0.23)	0.33 (0.04 (0.63)
Prolonged postpartum length of stay	0.02 (-0.08, 0.11)	-0.02 (-0.05, 0.02)	0.14 (0.06, 0.23)	0.39 (0.12, 0.65)
Acute myocardial infarction	‡	‡	‡	‡
Acute renal failure	0.01 (-0.03, 0.05)	0.001 (-0.02, 0.02)	0.01 (-0.03, 0.05)	0.02 (-0.07, 0.12)
Adult respiratory distress syndrome	0.01 (-0.03, 0.05)	-0.002 (-0.02, 0.02)	0.03 (-0.01, 0.08)	0.10 (-0.03, 0.23)
Amniotic fluid embolism	‡	‡	‡	‡
Aneurysm	‡	‡	‡	‡
Cardiac arrest/ ventricular fibrillation	-0.0005 (-0.01, 0.01)	-0.001 (-0.01, 0.005)	0.01 (-0.01, 0.02)	0.03 (-0.04, 0.09)
Diss. intravascular coagulation	0.03 (-0.02, 0.07)	0.01 (-0.01, 0.03)	-0.01 (-0.05, 0.03)	-0.02 (-0.11, 0.07)
Eclampsia	-0.01 (-0.06, 0.03)	-0.01 (-0.03, 0.01)	0.04 (0.01, 0.08)	0.14 (0.0005, 0.27)
Heart fail during procedure/ surgery	-0.08 (-0.21, 0.05)	-0.05 (-0.11, 0.002)	0.15 (0.05, 0.24)	0.38 (0.09 (0.67)
Puerperal cerebrovascular disorders	-0.0006 (-0.02, 0.02)	-0.003 (-0.01, 0.01)	0.02 (0.003, 0.04)	0.08 (-0.02, 0.18)
Pulmonary edema	0.01 (-0.01, 0.02)	-0.00008 (-0.01, 0.01)	0.02 (0.00005, 0.05)	0.07 (-0.02 (0.17)
Severe anesthesia complications	0.01 (-0.02, 0.04)	0.003 (-0.01, 0.01)	0.00008 (-0.02, 0.02)	0.003 (-0.05, 0.06)
Sepsis	0.001 (-0.04, 0.04)	-0.0008 (-0.02, 0.02)	0.003 (-0.03, 0.03)	0.01 (-0.07, 0.08)
Shock	-0.01 (-0.06, 0.05)	-0.003 (-0.03 (0.02)	0.003 (-0.04, 0.04)	0.01 (-0.1, 0.1)
Sickle cell anemia with crisis	0.03 (-0.10, 0.13)	0.02 (-0.05, 0.10)	-0.02 (-0.11, 0.07)	-0.02 (-0.19, 0.15)
Thrombotic embolism	-0.0001 (-0.02, 0.02)	-0.001 (-0.01, 0.01)	0.01 (-0.01, 0.03)	0.02 (-0.04, 0.09)
Blood transfusion	0.08 (-0.04, 0.20)	0.03 (-0.02, 0.08)	0.02 (-0.07, 0.12)	0.06 (-0.17, 0.29)
Conversion of cardiac rhythm	‡	‡	‡	‡
Hysterectomy	0.01 (-0.06, 0.07)	0.002 (-0.03, 0.03)	0.002 (-0.05, 0.05)	0.01 (-0.11, 0.12)
Temporary tracheostomy	‡	‡	‡	‡
Ventilation	-0.01 (-0.05, 0.04)	-0.01 (-0.03, 0.01)	0.02 (-0.01, 0.04)	0.04 (-0.04, 0.13)

Appendix Table 21 Estimated number of excess cases of severe maternal morbidity by outcome definition used. Preterm deliveries. Magee-Womens Hospital (N=84,241)

Gestational weight gain z-score	Adjusted risk difference per 100 delivery hospitalizations (95% confidence interval)				
	Primary definition (PD)	PD less ICU admission	PD less extended postpartum length of stay	PD less blood transfusion	Complete case analysis (n=57,922)
-3 SD	0.44 (-1.4, 2.2)	0.23 (-1.4, 1.9)	0.16 (-1.6, 1.9)	0.5 (-1.1, 2.2)	1.1 (-0.94, 3.2)
-2.5 SD	0.31 (-1.1, 1.7)	0.15 (-1.2, 1.5)	0.10 (-1.3, 1.5)	0.36 (-0.98, 1.7)	0.86 (-0.76, 2.5)
-2 SD	-0.18 (-0.90, 1.3)	0.10 (-0.93, 1.1)	0.04 (-1.0, 1.1)	0.21 (-0.79, 1.2)	0.60 (-0.59, 1.8)
-1.5 SD	0.05 (-0.69, 0.79)	-0.01 (-0.70, 0.68)	-0.02 (-0.74, 0.70)	0.07 (-0.61, 0.76)	0.35 (-0.45, 1.2)
-1 SD	-0.06 (-0.50, 0.37)	-0.08 (-0.49, 0.33)	-0.07 (-0.50, 0.35)	-0.05 (-0.45, 0.35)	0.12 (-0.35, 0.58)
-0.5 SD	-0.11 (-0.31, 0.10)	-0.10 (-0.29, 0.10)	-0.08 (-0.28, 0.11)	-0.11 (-0.29, 0.08)	-0.03 (-0.24, 0.19)
0 (Mean)	Reference	Reference	Reference	Reference	Reference
+0.5 SD	0.31 (-0.01, 0.63)	0.25 (-0.06, 0.56)	0.20 (-0.10, 0.51)	0.32 (0.03, 0.61)	0.25 (-0.08, 0.58)
+1 SD	0.78 (-0.04, 1.6)	0.62 (-0.16, 1.4)	0.50 (-0.27, 1.3)	0.81 (0.06, 1.5)	0.67 (-0.18, 1.5)
+1.5 SD	1.3 (-0.11, 2.8)	1.1 (-0.31, 2.4)	0.85 (-0.50, 2.2)	1.4 (0.05, 2.7)	1.2 (-0.32, 2.7)
+2 SD	1.9 (-0.22, 4.0)	1.5 (-0.50, 3.5)	1.2 (-0.74, 3.1)	2.0 (0.01, 4.0)	1.7 (-0.51, 3.9)
+2.5 SD	2.5 (-0.37, 5.4)	2.0 (-0.72, 4.7)	1.6 (-1.0, 4.1)	2.6 (-0.09, 5.4)	2.2 (-0.76, 5.2)
+3 SD	3.0 (-0.54, 6.6)	2.4 (-0.95, 5.7)	1.9 (-1.3, 5.0)	3.2 (-0.20, 6.7)	2.7 (-1.0, 6.4)

Notes: Primary definition (PD)= severe maternal morbidity as “presence of any one of the Centers for Disease Control and Prevention criteria, ICU admission, or extended postpartum length of stay (>3 days for vaginal deliveries and >5 days for cesarean deliveries).

Appendix Table 22 Estimated number of excess cases of severe maternal morbidity by outcome definition used. Term deliveries. Magee-Womens Hospital (N=84,241)

Gestational weight gain z-score	Adjusted risk difference per 100 delivery hospitalizations (95% confidence interval)				
	Primary definition (PD)	PD less ICU admission	PD less extended postpartum length of stay	PD less blood transfusion	Complete case analysis (n=57,922)
-3 SD	0.01 (-0.35, 0.36)	-0.01 (-0.35, 0.33)	0.03 (-0.31, 0.37)	-0.06 (-0.37, 0.24)	0.01 (-0.36, 0.38)
-2.5 SD	-0.01 (-0.29, 0.28)	-0.02 (-0.29, 0.25)	0.01 (-0.25, 0.28)	-0.06 (-0.31, 0.18)	-0.01 (-0.30, 0.28)
-2 SD	-0.02 (-0.24, 0.20)	-0.03 (-0.24, 0.18)	0.001 (-0.20, 0.20)	-0.06 (-0.25, 0.12)	-0.03 (-0.25, 0.19)
-1.5 SD	-0.03 (-0.18, 0.12)	-0.04 (-0.18, 0.10)	-0.01 (-0.15, 0.13)	-0.06 (-0.20, 0.07)	-0.04 (-0.20, 0.11)
-1 SD	-0.04 (-0.13, 0.04)	-0.05 (-0.13, 0.04)	-0.03 (-0.11, 0.06)	-0.06 (-0.14, 0.01)	-0.06 (-0.15, 0.03)
-0.5 SD	-0.04 (-0.08, 0.00001)	-0.04 (-0.08, -0.003)	-0.03 (-0.06, 0.01)	-0.05 (-0.08, -0.01)	-0.05 (-0.09, -0.01)
0 (Mean)	Reference	Reference	Reference	Reference	Reference
+0.5 SD	0.09 (0.03, 0.15)	0.09 (0.03, 0.14)	0.06 (0.004, 0.12)	0.09 (0.04, 0.15)	0.12 (0.06, 0.18)
+1 SD	0.22 (0.05, 0.38)	0.21 (0.06, 0.36)	0.16 (0.005, 0.31)	0.23 (0.09, 0.37)	0.30 (0.13, 0.46)
+1.5 SD	0.37 (0.08, 0.66)	0.37 (0.09, 0.64)	0.27 (-0.004, 0.54)	0.39 (0.13, 0.66)	0.51 (0.20, 0.83)
+2 SD	0.53 (0.09, 0.96)	0.52 (0.11, 0.93)	0.38 (-0.02, 0.78)	0.57 (0.17, 0.97)	0.75 (0.26, 1.2)
+2.5 SD	0.70 (0.09, 1.3)	0.70 (0.11, 1.3)	0.50 (-0.05, 1.0)	0.77 (0.19, 1.3)	1.0 (0.31, 1.7)
+3 SD	0.86 (0.09, 1.6)	0.87 (0.12, 1.6)	0.61 (-0.08, 1.3)	0.96 (0.21, 1.7)	1.3 (0.35, 2.2)

Notes: Primary definition (PD)= severe maternal morbidity as "presence of any one of the Centers for Disease Control and Prevention criteria, ICU admission, or extended postpartum length of stay (>3 days for vaginal deliveries and >5 days for cesarean deliveries).

Appendix Table 23 Estimated number of excess cases of severe maternal morbidity by outcome definition used. Magee-Womens Hospital (N=84,241)

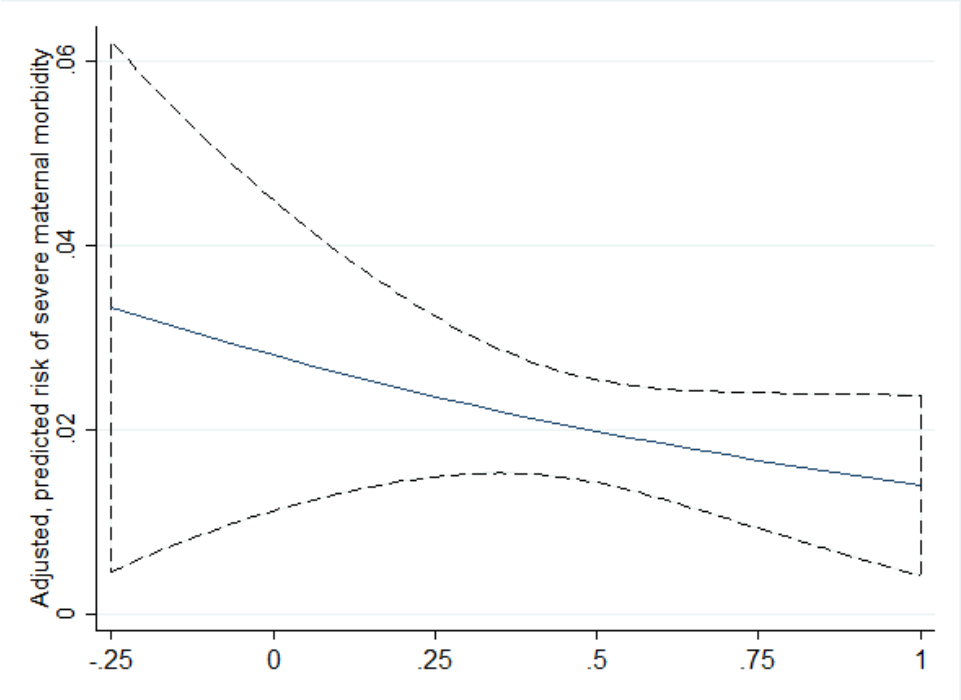
Gestational weight gain z-score	Adjusted risk difference per 100 delivery hospitalizations (95% confidence interval)				
	Primary definition (PD)	Underweight	Normal weight	Overweight	Obese
-3 SD	0.30 (-0.07, 0.67)	1.7 (-1.7, 5.1)	0.21 (-0.20, 0.62)	0.61 (-0.31, 1.5)	-0.04 (-1.0, 0.94
-2.5 SD	0.22 (-0.07, 0.51)	1.2 (-1.1, 3.6)	0.15 (-0.17, 0.47)	0.46 (-0.25, 1.2)	-0.06 (-0.85, 0.73)
-2 SD	0.14 (-0.07, 0.35)	0.85 (-0.71, 2.4)	0.09 (-0.15, 0.32)	0.32 (-0.20, 0.83)	-0.08 (-0.68, 0.53)
-1.5 SD	0.06 (-0.08, 0.21)	0.52 (-0.42, 1.5)	0.03 (-0.13, 0.19)	0.18 (-0.16, 0.52)	-0.09 (-0.51, 0.33)
-1 SD	-0.01 (-0.10, 0.08)	0.24 (-0.23, 0.71)	-0.02 (-0.12, 0.07)	0.06 (-0.13, 0.26)	-0.10 (-0.35, 0.15)
-0.5 SD	-0.04 (-0.08, -0.002)	0.06 (-0.13, 0.24)	-0.05 (-0.09, 0.00005)	-0.01 (-0.10, 0.08)	-0.08 (-0.20, 0.03)
0 (Mean)	Reference	Reference	Reference	Reference	Reference
+0.5 SD	0.14 (0.08, 0.21)	0.09 (-0.19, 0.38)	0.14 (0.06, 0.22)	0.13 (-0.01, 0.26)	0.17 (-0.01, 0.36)
+1 SD	0.38 (0.20, 0.56)	0.30 (-0.47, 1.1)	0.36 (0.15, 0.57)	0.35 (-0.01, 0.70)	0.43 (-0.05, 0.91)
+1.5 SD	0.67 (0.33, 1.0)	0.60 (-0.87, 2.1)	0.64 (0.25, 1.0)	0.62 (-0.03, 1.3)	0.73 (-0.14, 1.6)
+2 SD	1.0 (0.46, 1.5)	0.90 (-1.4, 3.2)	0.93 (0.33, 1.5)	0.91 (-0.09, 1.9)	1.0 (-0.26, 2.3)
+2.5 SD	1.3 (0.58, 2.0)	1.3 (-2.0, 4.5)	1.3 (0.40, 2.1)	1.2 (-0.18, 2.6)	1.4 (-0.42, 3.2)
+3 SD	1.6 (0.68, 2.6)	1.6 (-2.7, 5.8)	1.6 (0.44, 2.7)	1.5 (-0.30, 3.3)	1.7 (-0.58, 4.0)

Notes: Primary definition (PD)= severe maternal morbidity as "presence of any one of the Centers for Disease Control and Prevention criteria, ICU admission, or extended postpartum length of stay (>3 days for vaginal deliveries and >5 days for cesarean deliveries).
Ref: Reference category

Appendix Table 24 Adjusted risk differences by select, specific indicators of severe maternal morbidity by total gestational weight gain z-score (N=84,241)

Selected indicator of severe maternal morbidity	Adjusted risk difference per 100 delivery hospitalizations (95% confidence interval)			
	Gestational weight gain z-score			
	-2 SD	-1 SD	+1 SD	+2 SD
Primary definition	0.14 (-0.07, 0.35)	-0.01 (-0.10, 0.08)	0.38 (0.20, 0.56)	1.0 (0.46, 1.5)
Intensive care unit admission	0.08 (-0.02, 0.18)	0.01 (-0.03, 0.05)	0.12 (0.02, 0.23)	0.33 (0.04, 0.63)
Prolonged postpartum length of stay	0.02 (-0.08, 0.11)	-0.02 (-0.05, 0.02)	0.14 (0.06, 0.23)	0.39 (0.12, 0.65)
Acute renal failure	0.01 (-0.03, 0.05)	0.001 (-0.02, 0.02)	0.01 (-0.03, 0.05)	0.02 (-0.07, 0.12)
Adult respiratory distress syndrome	0.01 (-0.03, 0.05)	-0.002 (-0.02, 0.02)	0.03 (-0.01, 0.01)	0.01 (-0.03, 0.23)
Disseminated intravascular coagulation	0.03 (-0.02, 0.07)	0.01 (-0.01, 0.03)	-0.01 (-0.05, 0.03)	-0.02 (-0.11, 0.07)
Eclampsia	-0.01 (-0.06, 0.03)	-0.01 (-0.03, 0.01)	0.04 (0.01, 0.08)	0.13 (0.0005, 0.27)
Heart failure during procedure or surgery	-0.08 (-0.21, 0.05)	-0.05 (-0.11, 0.002)	0.15 (0.05, 0.24)	0.38 (0.09 (0.67)
Puerperal cerebrovascular disorders	-0.0006 (-0.02, 0.02)	-0.003 (-0.01, 0.01)	0.02 (0.003, 0.04)	0.08 (-0.02, 0.18)
Pulmonary edema	0.01 (-0.01, 0.02)	-0.00008 (-0.01 (0.01)	0.02 (0.0005, 0.05)	0.07 (-0.02, 0.17)
Severe anesthesia complications	0.01 (-0.02, 0.04)	0.002 (-0.008, 0.01)	0.00008 (-0.02, 0.02)	0.003 (-0.05, 0.06)
Sepsis	0.001 (-0.04, 0.04)	-0.00008 (-0.02, 0.02)	0.003 (-0.03, 0.03)	0.01 (-0.07, 0.08)
Shock	-0.01 (-0.06, 0.05)	-0.003 (-0.03, 0.02)	0.003 (-0.04, 0.04)	0.008 (-0.08, 0.10)
Blood transfusion	0.08 (-0.04, 0.20)	0.03 (-0.02, 0.08)	0.02 (-0.07, 0.12)	0.06 (-0.17, 0.29)
Ventilation	-0.01 (-0.05, 0.04)	-0.01 (-0.03, 0.01)	0.02 (-0.01, 0.04)	0.04 (-0.04, 0.13)

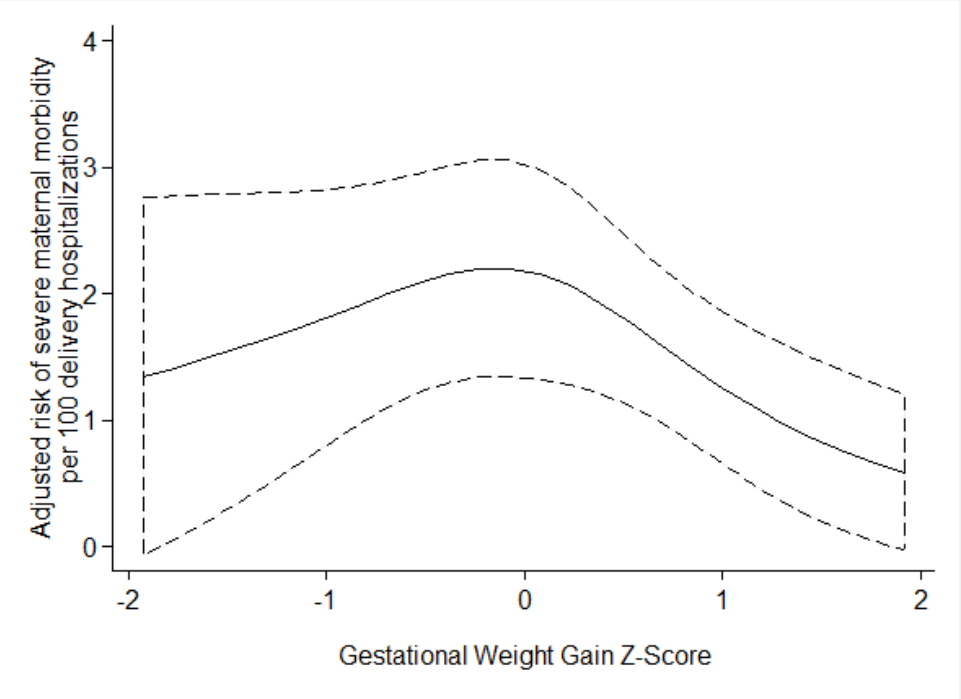
Appendix K Sensitivity analyses, Specific Aim #2



Appendix Figure 9 Adjusted predicted risk of severe maternal morbidity by rate of weight gain (kg per week) from 16-19 weeks to delivery (N=4,714)

Appendix Table 25 Association between gestational weight gain trajectory in the second half of pregnancy and risk of severe maternal morbidity at delivery hospitalization (N=4,714)

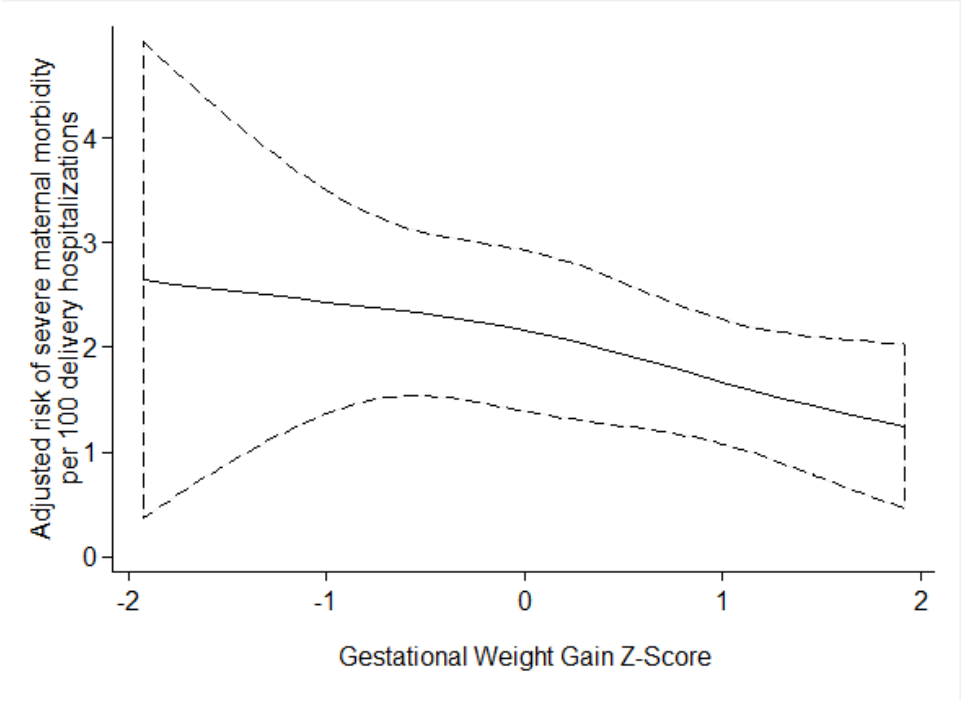
Weight gain quartile	At risk (n)	Cases (n)	Adjusted risk (95% CI)	Adjusted RD (95% CI)
<25%	1,183	28	2.9 (1.0, 4.7)	0.65 (-1.5, 2.8)
25-50%	1,182	22	2.2 (1.0, 3.4)	Reference
50-75%	1,174	20	1.8 (0.76, 2.9)	-0.39 (-2.0, 1.2)
>75%	1,175	25	1.6 (0.72, 2.6)	-0.59 (-2.1, 0.94)



Appendix Figure 10 Adjusted predicted risk of severe maternal morbidity by gestational weight gain z-score at 10-13 weeks gestation (N=4,268)

Appendix Table 26 Association between gestational weight gain z-score at 10-13 weeks gestation and risk of severe maternal morbidity at delivery hospitalization (N=4,268)

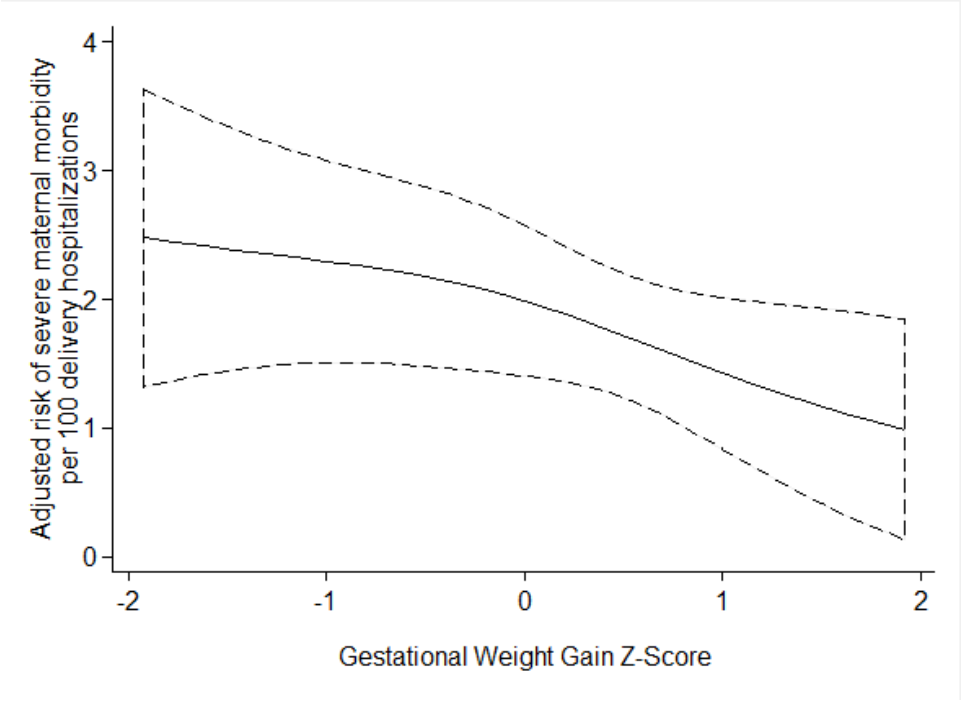
Weight gain z-score category	At risk (n)	Cases (n)	Adjusted risk (95% CI)	Adjusted RD (95% CI)
<-1	341	5	1.1 (-0.57, 2.9)	-0.88 (-2.7, 0.94)
-1 to +1	3,367	62	2.0 (1.3, 2.7)	Reference
>+1	560	10	0.74 (0.12, 1.4)	-1.3 (-2.2, -0.36)



Appendix Figure 11 Adjusted predicted risk of severe maternal morbidity by gestational

Appendix Table 27 Association between gestational weight gain z-score at 24-28 weeks gestation and risk of severe maternal morbidity at delivery hospitalization (N=4,272)

Weight gain z-score category	At risk (n)	Cases (n)	Adjusted risk (95% CI)	Adjusted RD (95% CI)
<-1	439	11	3.6 (1.1, 6.1)	1.6 (1.0, 4.2)
-1 to +1	3,135	61	2.0 (1.4, 2.7)	Reference
>+1	698	15	1.1 (0.39, 1.7)	-0.97 (-1.9, -0.04)



Appendix Figure 12 Adjusted predicted risk of severe maternal morbidity by total gestational weight gain z-score among women with both, total weight gain and serial weight gain measurements (N=5,741)

Appendix Table 28 Association between total gestational weight gain z-score and risk of severe maternal morbidity at delivery hospitalization among women with both, early and total weight gain measurements (N=5,741)

Weight gain z-score category	At risk (n)	Cases (n)	Adjusted risk (95% CI)	Adjusted RD (95% CI)
<-1	745	12	2.3 (0.66, 3.9)	0.36 (-1.4, 2.1)
-1 to +1	4,276	83	1.9 (1.3, 2.5)	Reference
>+1	702	18	1.5 (0.41, 2.6)	-0.43 (-1.7, 0.80)

Appendix L Sensitivity analyses, Specific Aim #3

Appendix Table 29 Risk ratio of modifiable risk factors by definition of severe maternal morbidity (N=86,260)

Risk factor	Risk ratio (95% CI)			
	Principal analysis	Minus blood transfusion	Minus ICU admission	Minus prolonged postpartum length of stay
1. Prepregnancy BMI≥25kg/m^2	1.1 (1.01, 1.3)	1.1 (0.96, 1.2)	1.1 (0.99, 1.2)	1.1 (1.0, 1.3)
2. ≥35 years of age at delivery	1.5 (1.3, 1.6)	1.5 (1.3, 1.7)	1.5 (1.3, 1.6)	1.4 (1.2, 1.6)
3. No college degree	1.2 (1.1, 1.4)	1.2 (1.1, 1.4)	1.2 (1.0, 1.4)	1.3 (1.1, 1.4)
4. Unmarried	1.01 (0.89, 1.2)	0.97 (0.83, 1.1)	1.1 (0.91, 1.2)	1.0 (0.89, 1.2)
5. Preexisting hypertension	2.4 (2.0, 2.8)	2.5 (2.1, 3.0)	2.3 (1.9, 2.7)	2.1 (1.8, 2.5)
6. Preexisting diabetes	2.0 (1.5, 2.5)	2.1 (1.6, 2.6)	2.0 (1.5, 2.5)	1.9 (1.4, 2.4)
7. Smoking during pregnancy	0.92 (0.79, 1.0)	0.97 (0.82, 1.1)	0.89 (0.76, 1.0)	0.89 (0.75, 1.0)
8. Gestational weight gain >1 SD	1.3 (1.1, 1.5)	1.4 (1.2, 1.6)	1.3 (1.1, 1.6)	1.3 (1.1, 1.5)
9. All above risk factors	1.6 (1.1, 2.1)	1.4 (1.1, 1.7)	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)

Appendix Table 30 Population attributable fraction of modifiable risk factors by definition of severe maternal morbidity (N=86,260)

Risk factor	Population attributable fraction (95% CI)			
	Principal analysis	Minus blood transfusion	Minus ICU admission	Minus prolonged postpartum length of stay
1. Prepregnancy BMI≥25kg/m^2	6.0 (0.83, 11)	3.8 (-1.8, 9.2)	5.1 (-0.39, 10)	6.2 (0.64, 11)
2. ≥35 years of age at delivery	7.1 (4.6, 9.4)	8.1 (5.3, 11)	6.8 (4.2, 9.3)	6.5 (3.9, 9.1)
3. No college degree	13 (5.7, 19)	12 (4.6, 19)	10 (3.0, 17)	13 (5.7, 20)
4. Unmarried	1.5 (-4.9, 7.6)	-1.2 (-8.4, 5.6)	2.7 (-4.1, 9.1)	1.7 (-5.1, 8.1)
5. Preexisting hypertension	6.3 (4.8, 7.8)	6.9 (5.1, 8.6)	5.9 (4.3, 7.5)	5.3 (3.7, 6.9)
6. Preexisting diabetes	2.4 (1.4, 3.4)	2.7 (1.6, 3.9)	2.2 (1.2, 3.3)	2.2 (1.1, 3.3)
7. Smoking during pregnancy	-1.4 (-3.7, 0.81)	-0.54 (-3.1, 2.0)	-1.9 (-4.3, 0.48)	-2.0 (-4.4, 0.42)
8. Gestational weight gain >1 SD	4.5 (1.9, 7.1)	5.0 (2.2, 7.7)	4.5 (1.8, 7.0)	4.1 (1.4, 6.6)
9. All above risk factors	36 (14, 53)[c]	26 (10, 39)	23 (7.3, 37)	26 (9.2, 39)

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