

HHS Public Access

Author manuscript *Am J Obstet Gynecol MFM*. Author manuscript; available in PMC 2021 February 01.

Published in final edited form as:

Am J Obstet Gynecol MFM. 2020 February ; 2(1): . doi:10.1016/j.ajogmf.2019.100066.

Population-attributable fraction of risk factors for severe maternal morbidity

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Abstract

Background—Severe maternal morbidity is an important proxy for maternal mortality. Population attributable fraction is the proportion of a disease that is attributable to a given risk factor and can be used to estimate the reduction in the disease that would be anticipated if a risk factor was reduced or eliminated.

Objective—We sought to determine the population-attributable fraction (PAF) of potentially modifiable risk factors for severe maternal morbidity.

Study Design—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 (defined as >3 standard deviations beyond the mean length of stay: >3 days for vaginal deliveries and >5 days for Cesarean deliveries); 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 then calculated the PAF for each risk factor. We also examined the impact of modest reductions and elimination of risk factors on the PAF of severe maternal morbidity.

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Results—The overall rate of severe maternal morbidity was 2.0%. Overweight and obesity, maternal age 35 years, preexisting hypertension, excessive gestational weight gain, and lack of a college degree had PAF ranging from 4.5% to 13%. If all risk factors were eliminated, 36% of cases could have been prevented. Modest reductions in the prevalence of excessive BMI and advanced maternal age 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 by modifying common, individual-level risk factors. Nevertheless, the majority of cases were not attributable to the patient level 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.

Condensation

While risk factor reduction will decrease cases of severe maternal morbidity, most maternal morbidity is not explained by commonly implicated risk factors.

Keywords

population attributable fraction; risk factors; severe maternal morbidity

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.^{1–3} While an important public health problem, maternal mortality remains rare—roughly 17 deaths per 100,000 live births in the U.S. annually. This makes it a difficult subject for epidemiologic studies. Severe maternal morbidity is more common, roughly 14 per 1,000 deliveries, and shares risk factors and etiologies with maternal mortality.⁴ 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.^{1,5}

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.^{6–15} Preliminary evidence by our group suggests that high 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.^{16,17} The extent to which these risk factors contribute to the overall burden of severe maternal morbidity prevention efforts in the U.S. Population attributable fraction is the proportion of a disease that is attributable to a given risk factor and can be used to estimate the reduction in the disease that would be anticipated if a risk factor was reduced or eliminated. Our objective was to determine the population-attributable fraction of potentially modifiable, individual-level risk factors (obesity, maternal age,

education, marital status, preexisting conditions, smoking, and pregnancy weight gain). We estimated 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.

Materials and 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. Higher order multiples were excluded because there is no guidance on gestational weight gain in this group. 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/m²), normal weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/ m^2), and obese (30.0 kg/m²).¹⁸ 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.¹⁹ Total gestational weight gain (kg) was calculated by subtracting prepregnancy weight from delivery weight. We converted total weight gain to gestational age-standardized z-scores based on prepregnancy BMI category-specific charts. We then categorized weight gain as 'below', 'within', or 'above' the Institute of Medicine recommendations.^{20,21} We defined excessive gestational weight gain as weight gain z-scores > +1 SD. Importantly, weight gain z-scores were used so we had a measure of weight gain that was independent of pregnancy duration. 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 1), 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.²²

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.²³ After we log transformed all continuous variables, we jointly imputed missing data using 23 variables in the data set (maternal height, prepregnancy weight, delivery weight, length of stay, education, race, 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.²⁴

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 (weight gain z-scores > +1 SD), and smoking during pregnancy using the following formula:

Population attributable fraction =
$$\frac{P(D) - \sum_{C} P(D \mid C, E) P(C)}{P(D)}$$

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.²⁵ 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.²⁶

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/m² among overweight and obese women, a reduction

that reflects the change in BMI among women enrolled in diet and exercise interventions.²⁷ 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.

Results

Most women in this sample were non-Hispanic White (75%), married (60%), multiparous (54%), and used private insurance as their primary method of payment (69%). Twin pregnancies accounted for 2.2% of the sample. Approximately 44% of women were either overweight or obese before pregnancy (Table 1.). 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.

The unadjusted risk of severe maternal morbidity was 2.0%. 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 (Supplemental Figure 1). 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 1).

Overweight and obesity, maternal age 35 years, preexisting hypertension, and gestational weight gain > +1 SD of gestational age specific z-scores (equivalent to 23kg at 40 weeks in a normal weight woman) had similar PAF, ranging from 4.5% to 7.1%, although precision around these estimates varied. Preexisting diabetes had a relatively 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, gestational weight gain above IOM guidelines, and marital status were not associated with severe maternal morbidity. All of the studied risk factors combined had a total PAF of 36% (95% CI: 14%, 53%) for severe maternal morbidity (Table 2). Eliminating all of the risk factors simultaneously would prevent an estimated 626 cases of severe maternal morbidity during the ten-year study period.

Eliminating risk factors is not feasible for many women and thus we sought to estimate the PAF of more achievable risk reduction scenarios. First, we determined the PAF if all

overweight and obese women had a 3.5 kg/m² reduction in BMI. This decrease in BMI mirrors that seen in weight loss intervention studies.²⁷ This more modest, but achievable reduction in BMI would prevent 3.9% (1.4%, 6.4%) of severe maternal morbidity cases in this group. We then looked at a less stringent definition of advanced maternal age and calculated the PAF if all women were less than age 40 at delivery as opposed to 35. If all women were less than age 40 at delivery we estimate we could prevent 1.8% (0.74%, 2.9%) of cases of severe maternal morbidity.

Comment

Principal Findings

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.^{14,28} Our data suggest that prepregnancy overweight and obesity, advanced maternal age, excessive gestational weight gain, and preexisting hypertension each contribute to approximately 5–7% 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). Additionally, the association with gestational weight was only seen at gestational weight gain z-score > + 1 SD which is equivalent to 23kg at term in a normal weigh woman and not with weight gain defined as above IOM guidelines. This suggests that is extremes in weight gain that are associated with risk.

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.²⁹ 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.³⁰

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.

Results in context

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. ^{8,10} Recently, investigators performed a state-level analysis of factors that contributed to the temporal changes in U.S. maternal mortality from 1997–2012.¹⁶ Similar to our findings, they reported that obesity and low education were important contributors to maternal mortality.

Strengths and Limitations

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.³¹ 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.

With regard to limitations, we used a screening definition of severe maternal morbidity, rather than the gold standard of medical chart review.²² 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.³² 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.

Research Implications/ Conclusions

Our work highlights the need to extend research beyond the commonly measured individuallevel risk factors we examined, to include anemia, substance use, and pre-pregnancy control of pre-existing medical problems. Additionally, it is essential that researchers focus on provider, system, and structural factors--such as state medicaid coverage of pregnancy termination, access to medical insurance prior to pregnancy, access to stable housing-- and many other social determinants of health that likely contribute to severe maternal morbidity and its subtypes.³³ 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: This project was supported by NIH grants R01 HD094777 and R01 NR014245 (PI: Bodnar & Hutcheon). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix

Appendix 1:

The Centers for Disease Control and Prevention indicators and corresponding ICD-9 code to identify severe maternal morbidity.

Severe Maternal Morbidity Indicator	ICD-9-CM Codes
1. Acute myocardial infarct	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

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AJOG at a Glance

Why was this study conducted?

- The extent to which potentially modifiable risk factors contribute to the burden of severe maternal morbidity in the United States (U.S.) is not known.
- Quantifying this burden would help to identify priority areas for maternal morbidity prevention efforts in the U.S.

What are the key findings?

- Overweight and obesity, maternal age 35 years, preexisting hypertension, excessive gestational weight gain, and lack of a college degree had population attributable fractions ranging from 4.5% to 13%.
- Eliminating commonly implicated risk factors would prevent approximately a third of the cases of severe maternal morbidity in this sample.
- Modest reductions in maternal pre-pregnancy weight and age had minimal impact on cases of severe maternal morbidity.

What does this study add to what is already known?

- Maternal age, weight and pre-existing diabetes and hypertension explain a modest portion of severe maternal morbidity.
- Social determinants of health are critical contibutors to the risk of severe maternal morbidity.
- Focusing public health efforts on a single risk factor will have a modest impact on maternal morbidity.

Table 1.

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/m2)	44,797 (52)	778 (1.7)
Overweight (25–29kg/m ²)	20,599 (24)	435 (2.1)
Obese (30kg/m ²)	16,772 (20)	St 450 (2.7)
Gestational weight gain z-score		
<1 SD	13,922 (16)	287 (2.1)
-1 to + 1 SD	20,599 (71)	1,145 (1.9)
> 1 SD	11,007 (13)	307 (2.8)
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)
Plurality		
Singleton	84,328 (98)	1,600 (1.9)
Twin	1,932 (2.2)	139 (7.2)

Characteristic	Population at risk n (%) N=86,260	Cases of severe maternal morbidity (unadjusted incidence per 100 delivery hospitalizations)
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 (4.5)	276 (2.2)
No	73,705 (95)	1,463 (2.0)

Notes and abbreviations:

BMI: Body mass index

IOM: Institute of Medicine

IOM recommendations defined as the following at 40 weeks gestation: I) Singleton pregnancies: Underweight: 12.5–18kg; Normal weight 11.5–16kg; Overweight 7–11.5kg; Obese 5–9kg. II) Twin pregnancies: Underweight and normal weight 17–25kg; Overweight 14–23kg; Obese 11–19kg.

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Table 2.

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 25kg/m ²	1.1 (1.01, 1.3)	44 (37,564)	6.0 (0.83, 11)	104
2. 35 years of age at delivery	1.5 (1.3, 1.6)	19 (16,260)	7.1 (4.6, 9.4)	123
3. No college degree	1.2 (1.1, 1.4)	54 (46,160)	13 (5.7, 19)	226
4. Unmarried	1.0 (0.89, 1.2)	40 (34,094)	1.5 (-4.9, 7.6)	26
5. Preexisting hypertension	2.4 (2.0, 2.8)	3.5 (2,999)	6.3 (4.8, 7.8)	109
6. Preexisting diabetes	2.0 (1.5, 2.5)	1.5 (1,268)	2.4 (1.4, 3.4)	41
7. Smoking during pregnancy	0.92 (0.79, 1.04)	15 (12,554)	-1.4 (-3.7, 0.81)	-24
8. Gestational weight gain z-score $> + 1$ SD ^{<i>a</i>}	1.3 (1.1, 1.5)	13 (11,007)	4.5 (1.9, 7.1)	78
9. All above risk factors	$1.6(1.1, 2.1)^{b}$	93 (80,613) c	$36(14,53)^d$	626 ^e
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Notes: Total number of cases of severe maternal morbidity: 1,739. Preventable cases calculated by multiplying the total number of cases by the population attributable fraction for each risk factor.

 a Equivalent to 23kg at 40 weeks in a normal weight woman

^bAdjusted risk ratio is the predicted risk of severe maternal morbidity with the presence of any one or more of the above risk factors compared with the predicted risk in the absence of all the above risk factors. Model adjusted for the other factors in the table plus mother's race, parity, primary method of payment, and plurality.

 $\mathcal{C}_{\text{Prevalence shown is the presence of any one or more of the above risk factors$

 $d^{}_{
m Population}$ attributable fraction shown is for the presence of any one or more of the above risk factors

^ePreventable cases of severe maternal morbidity if all women had a prepregnancy BMI 18.5–24.9kg/m2, weight gain within the 2009 Institute of Medicine recommendations, were <35 years of age, had a college degree, were married, did not have preexisting hypertension or diabetes, and did not smoke during pregnancy.