INCIDENT PREPREGNANCY OBESITY AND PERINATAL MORTALITY: APPLICATION OF NONPARAMETRIC DOUBLY ROBUST METHODS

by

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ABSTRACT

This dissertation's objective is to address methodological challenges in estimating the association of prepregnancy obesity with stillbirth and infant mortality. Our goal was to advance understanding of this topic of high public health importance to decrease the gap of high perinatal mortality between United States and other counties. Our focus was on the association of incident prepregnancy obesity with stillbirth and infant mortality. We constructed our analytic cohort of multiparous women who were non-obese in their first pregnancy from a population-based cohort study in Pennsylvania from 2003-2013 (n=1,551,919 singleton pregnancies).

A visualization tool was developed for variable selection considering bias-variance tradeoff for inverse probability weights. Applying this tool to our study, we identified two high influential confounders which informed us to adjust for them carefully.

Next, we examined the impact of parametric modeling assumptions on these associations by analytic methods with different reliance on parametric assumptions. Consistent, increased risk of stillbirth among women who became obese compared to those staying non-obese was observed with all methods. However, discrepancies in magnitude between methods were found: risk differences from semiparametric inverse probability weighting and nonparametric targeted minimum loss-based estimation (TMLE) were larger than those from parametric methods.

Then, the analysis was constrained to those at normal first pregnancy weight, and we examined the effect of becoming overweight and obese on stillbirth and infant mortality in the second pregnancy. Nonparametric TMLE estimates showed that becoming overweight increased the risk of stillbirth (RD=1.4, 95% CI: 0.6, 2.2) while those becoming obese had increased risks of both stillbirth (RD=4.0, 95% CI: 1.4, 6.6) and neonatal mortality (RD=2.3, 95% CI: 0.1, 4.5) in the second pregnancy. A dose-response relationship was observed where increasing interpregnancy BMI change was associated with increased risk of stillbirth and infant mortality.

Our findings provided the evidence that transitioning from normal weight to overweight or obese increases risk of stillbirth and infant mortality. Health care providers can communicate the importance of weight maintenance. These are important public health opportunities to prevent the onset of obesity and minimize fetal and infant risks, particularly since pregnancy is an important period to optimize maternal health.

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PREFACE

It has been a great journey to complete this dissertation. First of all, thank you to my diligent advisor, Dr. Ashley Naimi. It is a great honor to be able to learn from you and work with you. All of your time and efforts helped me to shape this dissertation and inspire my research interest in causal inference and epidemiology methods. I will always look up to you for your work ethic and the passion for science. I also want to thank to my dissertation committee: Dr. Lisa Bodnar, Dr. Maria Brooks, and Dr. Katherine Himes. They provided critical insight for my work. They are also very caring and had many helpful suggestions for my career development. I truly appreciate having these great mentors to lead me through this process.

To my friends - without your support, I would not be able to continue facing these challenges. Finally, I would like to dedicate this work and degree to my mother and sister in Taiwan. You are my strengths.

1.0 INTRODUCTION

1.1 BACKGROUND

Perinatal mortality, infant mortality (neonatal mortality) and stillbirth, continue to burden families in the United States, with 2013 rates of 6 per 1000 live births and 5.96 per 1000 live births and fetal deaths, respectively[1,2]. The overweight (56%) and obesity (30%) epidemics among women of childbearing age[3] continue to be important for further investigation. Evidence have linked pre-pregnancy obesity or inadequate or excessive gestational weight gain to an increased risk of infant death and stillbirth[4,5]. Additionally, a stark racial disparity exists for perinatal mortality[1,2] as well as the prevalence of pre-pregnancy obesity and inadequate or excessive gestational weight gain[6,7]. Recent work found prepregnancy obesity explained 10% of the racial disparity in absolute scales of infant mortality and stillbirth [8].

Existing research addressing the relationship between prepregnancy obesity and perinatal mortality is limited. First, a large majority of studies have examined the association between prevalent prepregnancy obesity and the risk of adverse birth outcomes. However, there is likely a critical difference between the effects of obesity among women who recently became obese (incident obesity), and the effects of longstanding obesity. Second, because body mass (and thus obesity status) varies over time, pre-pregnancy obesity may be subject to **time-dependent confounding**. This bias—often ignored in research when examining effects of pre-pregnancy obesity and adverse reproductive outcomes—can be properly and simply adjusted for by using inverse probability weighting.[9]

In theory, constructing inverse probability weights in complex longitudinal data requires adjusting for the high-dimensional vector representing an individual's entire covariate history[10]. However, in practice, adjusting for high-dimensional covariate vectors can result in unstable weights, and thus problems with estimation. To date, only ad hoc **bias-variance trade-off methods** are available in literature (e.g., propensity score trimming or weight truncation)[11,12] which do not give information on the role of individual predictors in trading off bias and variance when the impact of a large number of covariates on the empirical performance of IPW methods is of interest.

1.2 SPECIFIC AIMS

Given these aforementioned issues, **our objective** is to (i) estimate the association of incident obesity with stillbirth and infant mortality, and (ii) explore the extent to which parametric models may have different estimates of the association of incident prepregnancy obesity with stillbirth and infant mortality when compared to more nonparametric methods. We will use inverse probability weighting, g Computation, and targeted maximum likelihood estimation to account for potential confounding of the effect of incident obesity. Additionally, to mitigate problems that would result from adjusting for the breadth of information available on each woman in the cohort, we will develop methods to optimize the bias-variance tradeoff when using inverse probability weighted marginal structural models in a wide range of settings. More specifically, we will:

Aim 1: To develop an algorithm to visualize the impact of the bias-variance tradeoff for each confounder, and the effect on the estimate of interest and propensity score overlap

Aim 2: To explore the extent to which parametric models may have different estimates of the association of incident prepregnancy obesity with stillbirth and infant mortality when compared to more nonparametric methods.

Hypothesis: The estimates from different methods will have different magnitudes.

Aim 3: To evaluate the relation of newly-developed prepregnancy overweight and obesity with stillbirth and infant mortality of second pregnancies in a cohort of 212,889 pregnancies from PA, during 2003-2013.

Hypothesis: newly-developed prepregnancy overweight and obesity will increase the risk of stillbirth and infant mortality

1.3 EXPECTED OUTCOME

This work will extend our understanding of the role that pre-pregnancy obesity plays in shaping the risk of stillbirth and infant mortaltiy. We will quantify the magnitude of the association of incident pre-pregnancy obesity on stillbirth and infant mortaltiy, as well as the impact of parametric modeling assumptions on estimating this association. In addition, the visual tools developed in this work will provide researchers in a wide range of settings with a valuable means of making informed bias-variance trade-off decisions when using inverse probability weighted estimators.

2.0 BACKGROUND

2.1 OVERVIEW OF PERINATAL MORTALITY

Perinatal mortality, defined as fetal death and neonatal death, is **a commonly used indicator of a country's overall health and well-being** in relation to access to and quality of health care, maternal health, and socioeconomic conditions. **Perinatal loss can have detrimental effects for maternal physical and mental health, in addition to having psychosocial consequences for the family**[13]. After stillbirth, one in five women suffer from depression, anxiety or post-traumatic stress disorder[14–16]. Higher parental mortality is also observed after early loss of her children[17]. Furthermore, women experiencing perinatal loss have higher risk of the recurrence of adverse pregnancy outcomes and complications in subsequent pregnancies[18–20].The impacts of perinatal death are long-term. It is therefore crucial to address perinatal loss to improve overall maternal health.

Stillbirth is defined as an intrauterine fetal death that occurs at 20 or more weeks of gestation in United States (28 or more weeks in other countries). Antepartum stillbirths (fetal death before labor) mostly happen at later gestational ages, while intrapartum stillbirths (fetal death during labor) occur at earlier gestational ages. Stillbirth is thought to be mainly a result of placental pathology-related causes such as abruption or retroplacental hematoma. Some other causes include infection, maternal medical complication, congenital anomalies, cord abnormality and disorders. Around 30% stillbirths occurred without a specified cause [21].

Infant mortality is formally defined as live-born babies who die within their first year of life. This outcome can be further divided as neonatal death (before 28 days of their life) and post-

neonatal death (during 28- 364 days of their life). A 2013 National Vital Statistics report in United States showed that congenital malformation (20%), preterm or low birth weight-related disorder (18%), sudden infant death syndromes (SIDS) (7%), maternal complication (7%) and unintentional injuries are the leading causes of infant death. Neonatal death is mostly caused by congenital malformation and pre-term birth; post-neonatal death is mostly caused by SIDS (sudden infant death syndrome) and unintentional injuries. Effective interventions have decreased these leading cause-specific infant mortalities except preterm-related disorder, which increased or remained the same. Perinatal mortality is more prevalent in low-income countries but is still overlooked as a public health burden among families in high-income countries[22,23].

Perinatal mortality varies across different maternal characteristics. Women with the following characteristics are at higher risk: aged under 20 or 40-54 years, non-Hispanic Black race, having first pregnancy, having comorbidities, and multiple deliveries or those who are not married[1]. Among high-income countries, maternal obesity is one of the most important risk factors. Literature has shown maternal obesity can affect maternal and fetal health from many aspects: Women who are obese have increased the risk of maternal complication during pregnancy such as gestational diabetes and preeclampsia. The birthweight of the child is highly affected by maternal obesity, with outcomes such as macrosomia or small size for gestational age due to growth-restriction. Obese women also have higher risk of having babies/fetuses with congenital anomalies[24] However, these congenital anomalies are hard to detect via ultrasound in obese women, which might affect the decision for early pregnancy termination[25]. Maternal obesity is also related to inflammation which might affect placenta function. Overall, maternal obesity has potentially important impact on maternal and fetal health, as well as the process of delivery, clearly showing it is an important risk factor to prevent perinatal mortality.

Disparities are observed for perinatal mortality along with other health outcomes in high-income countries. In these countries, race/ethnicity and socioeconomic status disparities are most apparent. These disparities originate from complex structural risk factors: underlying socioeconomic factors (low education levels, living in poor neighborhoods) and then reflect on the proximate factors related to perinatal outcomes, such as maternal factors (age, lifestyle, BMI), nutritional factors such as food availability, and health care factors such as care-seeking attitudes) [26]. These downstream factors provide opportunities for intervention on race/ethnicity and those with socioeconomic disadvantages. Understanding the mechanism of how these disparities affect perinatal outcomes is the promising way to diminish the health gap.

Currently, the United States has an uncharacteristically high infant mortality rate of 6 per 1000 live births and 5.96 stillbirth per 1000 live births and fetal deaths in 2013,[2] relative to other high-income countries (2.8 infant deaths per 1000 live births in Japan, 3 infant deaths per 1000 live births in Sweden[27]). Since the early 20th century, infant mortality in the U.S. dropped dramatically, but stabilized again in 2005, with only slightly decreased rates observed in recent years. Stillbirth has a similar trend although rates remained relatively similar since 2006[27].

Socially-patterned disparities for both infant mortality and stillbirth might partially explain the limited decline[23]. Socially disadvantaged groups tend to have higher risks of infant mortality and stillbirths. Another plausible reason of infant mortality and stillbirths might due to the epidemic of women who are overweight (56%) and obese (30%), an identified risk factor for perinatal mortality[3]. Of note, maternal obesity may be one of mechanisms for socially-patterned disparities in perinatal mortality. To improve perinatal outcomes in U.S., we need to identify specific prevalent risk factors and understand the mechanisms of disparity on perinatal mortality.

2.2 MATERNAL OBESITY AND INCREASED RISK OF PERINATAL MORTALITY

2.2.1 Prepregnancy obesity

2.2.1.1 Measurement

Body mass index (BMI), calculated as weight (in kilograms) divided by height (in meters) squared, is usually used to measure obesity status and approximate overall maternal nutritional status before pregnancy. BMI, a common measure in clinical and research settings, has been shown to reflect percent of body fat among pregnant women. The relationship between BMI and body fat is stronger at early gestational ages and therefore often used to study the association between pre-pregnancy obesity with adverse pregnancy outcomes[28]. Almost all current literature use BMI to define pre-pregnancy obesity status by the World Health Organization (WHO) definition categories: underweight (<18.5 kg/m^2), normal weight (18.5-25 kg/m^2), overweight (25-30 kg/m^2), class I obesity (30-35 kg/m^2), class 2 obesity (35-40 kg/m^2), class 3 obesity (>40 kg/m^2) Most of the height and weight are self-reported or measured at the first perinatal visit. Though self-reported BMI tends to be lower due to overestimated height and underestimated weight, grouping women into appropriate BMI categories by self-reported BMI has an accuracy around 80% [29].

Revised birth certificate data includes information for calculating maternal pre-conception BMI provides an opportunity for using large population-based data to evaluate maternal obesity and adverse pregnancy outcome[30]. Park et al.,[31] examined the validity and reliability of BMI obtained from birth certificates by comparing with BMI values acquired from WIC program in Florida 2005. They showed BMI obtained from birth certificates are generally reliable and valid except for overestimating prevalence of underweight and obesity. Bodnar et al.,[32] showed BMI

category of birth certificate is highly consistent with medical record among normal weight/ overweight and obese women. However, the agreement of BMI category between birth certificate and medical records varies by race/ethnicity and gestational age at delivery. The bias introduced by misclassification of BMI categories needs to be carefully evaluated when using BMI values obtained from birth certificate. **Overall, use of BMI values obtained from birth certificates is an imperfect but practical measurement to represent pre-pregnancy obesity status.**

2.2.1.2 Prepregnancy obesity and perinatal mortality

There have been several studies focused on determining pre-pregnancy obesity and increased risk of perinatal mortality with odds ratios ranging from 1.1 to 2.7. Two meta-analyses provided summarized estimates for these relationships: Aune et al.,[33] found per 5-unit increases in pre-pregnancy BMI increased risk of perinatal death by 16%, stillbirth by 24% and infant mortality by 18%. Non-linear relationships of BMI were observed in most of outcomes except stillbirth. Meehan et al., [34] showed 42% and 103% increased risk of infant death compared to normal weight women among all obese women and class 1 obese women, respectively. One population-based case control study using sister controls to better account for potential uncontrolled environmental and genetic confounders shared within family. They found the association of obesity and stillbirth is stronger when it is compared to their non-obese sister (OR=4.04, 95%CI: 2.25, 7.25) than to population non-obese controls (OR=2.41, 95%CI: 1.83, 3.16)[35]. This study demonstrated pre-pregnancy obesity itself increased risk of perinatal death after controlling for family-shared confounders.

Prepregnancy obesity also synergistically increases the risk of adverse perinatal outcomes when some other known risk factors present, such as depressive symptoms[36], advanced maternal age (>35 years)[37] and inadequate gestational weight gain[38]. Gestational age is another important

contributor to perinatal death. When stratified by gestational age, the associations between maternal prepregnancy BMI and infant death/ stillbirth are more pronounced in terms birth/gestation periods (≥37 weeks) as shown in three large cohort studies[5,39,40] Although biological mechanisms are not well understood, studies examining cause-specific mortality relative to reported pre-pregnancy overweight and obesity are related to birth asphyxia and other neonatal morbidities; grades 2 and 3 obesity are more related to congenital anomalies and sudden infant death syndrome[5,39]. In terms of cause-specific stillbirth, a case-cohort study in the US demonstrated that the association between BMI and stillbirth is stronger among antepartum stillbirth and obesity and is related to placental disease, hypertension, fetal anomalies and umbilical cord abnormalities[41].

2.2.1.3 Prepregnancy obesity across pregnancies

Despite its prevalence and potential importance in shaping adverse birth outcomes, current literature on the relation between prepregnancy obesity and fetal / infant death are difficult to interpret from a policy standpoint. Among those studies, pre-pregnancy obesity is a left-truncated event because the timing of obesity onset is undetermined. Consequently, we cannot differentiate whether the relation between obesity and perinatal mortality is driven by long-standing obesity, newly-occurring obesity, or some combination of both. Population-level reductions of the prevalence of prepregnancy obesity can be accomplished by reducing the body mass of women of childbearing age *or* by preventing the onset of obesity in women without obesity of childbearing age (or both). These different obesity prevalence reduction strategies will likely have different impacts on stillbirth and infant mortality.

One of the methods to approximately quantify the association of newly-occurring obesity is by examining prepregnancy BMI longitudinally. By considering the prepregnancy obesity status

of previous pregnancies, we can identify if pre-pregnancy obesity of current pregnancy is "incident" or "prevalent" obesity. Currently, only three studies have examined the association of pre-pregnancy obesity on adverse pregnancy outcomes across multiple pregnancies. Two studies focused on inter-pregnancy weight change[42,43], which is defined as the difference of prepregnancy BMI of their first and second pregnancies (e.g. 2-4 unit of BMI increase) while other study looked at BMI category changes between first and second pregnancies[44] (e.g. normal weight to overweight).

A national Swedish study[42] with 151,025 women examined the association of inter-pregnancy weight changes between first and second pregnancies and risk of stillbirth of the second pregnancy. They found those women with a 3 or more unit increase in BMI had 1.63 (95% CI: 1.20-2.21) times higher risk compared to those had stable BMI (-1.0 and 0.9 unit change). They indicated that the association of weight changes are independent from the association of being overweight or obese in the second pregnancy, since the result is consistent after they constrained their analysis to women whose BMI were less than 25 in both pregnancies. The other large Sweden population-based study[43] of 456,711 women examined inter-pregnancy weight change and perinatal mortality stratified by BMI in their first pregnancy (less than or equal to/greater than 25). They demonstrated that among women who were underweight or normal weight in their first pregnancy, women with 4 or more BMI unit increase between first and second pregnancies have a 55% higher risk of stillbirth and a 29% higher risk of infant mortality, compared to women with stable BMI (changes within 1 unit). They also found there is dose-response relationship between risk of stillbirth increase in BMI. In addition, for those women who were overweight or obese in their first pregnancy, inter-pregnancy weight loss could reduce infant mortality. Whiteman et al.,[44] showed that increased risk of stillbirth is associated with BMI gain between first and second

pregnancy as well in a Missouri maternally-linked birth cohort (N=218,389). The hazard ratios for stillbirth are from 1.2- 1.5 among the following subgroups of BMI category change between pregnancies: normal to overweight (1.2, 95% CI: 1.0-1.4), normal weight to obese (1.5, 95% CI: 1.1-2.1), overweight to obese (1.4, 95% CI: 1.1-1.7), obese to obese (1.4, 95% CI: 1.2-1.7).

These studies have provided an indication of the relation between obesity onset and adverse pregnancy outcomes by examining BMI status across pregnancies. However, the studies are limited for several reasons: First, due to different purposes of their studies, they examined the association between inter-pregnancy weight change and perinatal mortality. Those results were presented as the range of BMI changes and we cannot determine if prepregnancy BMI reaches the range for being defined as obese for current pregnancy. Therefore, we cannot differentiate whether the association is from a large weight change between pregnancy or prepregnancy obesity status of current pregnancy. Furthermore, these studies excluded women with stillbirth or infant death in their first pregnancy. This opens the door to potential selection bias, and results in poor generalizability for women at high risk of adverse pregnancy outcomes in second and higher order pregnancies. Second, these studies only include first and second pregnancies. Parity might modify these relationships. Finally, (and arguably most importantly) these studies did not control for prior pregnancy characteristics (e.g. GWG, preterm birth, mortality). It is well known that prior adverse pregnancy outcomes are strongly associated with subsequent adverse pregnancy outcomes. This lack of adjustment for prior pregnancy characteristics introduces the potential for strong confounding. We will address all these issues in the current work.

2.2.2 Gestational weight gain (GWG) during pregnancy

2.2.2.1 Current gestational weight gain recommendations

Weight gain during pregnancy affects pregnancy outcomes[45] (e.g. birthweight[46], infant mortality[7]), post-partum weight retention[47] and long-term health of mother[48] and offspring[49]. Outcomes often used to evaluate optimal GWG are fetal growth [includes small for gestational age (SGA) and large for gestational age (LGA)], gestational age (preterm or term birth), mode of delivery (emergency C-section), infant death, post-partum weight retention and childhood obesity. However, the optimal GWG to prevent adverse health outcomes is still yet to decide. Current recommendations are based on the 2009 Institute of Medicine (IOM) guideline which suggested the ranges of total GWG (lb) in 40th week specific to different maternal pre-conception BMI categories: 28-40 (underweight), 25-35 (normal weight), 12-25 (overweight) and 11-20 (obese). The recommended rate of weight gain in 2nd and 3rd trimester (lbs/ week) are: 1 (underweight or normal weight), 0.6 (overweight) and 0.5 (obese)[50]. Due to lack of evidence, GWG recommendation for subgroups, such as race or severity of obesity were not provided in current version of the recommendations. In addition, the IOM committee noted that more research is warranted, to evaluate effective dietary or physical activity interventions for achieving optimal GWG for better health outcome.

Unfortunately, measurements of total GWG and rate of weight gain provided in this guideline is inappropriate to be applied to research for two reasons: first, total GWG is inherently related to gestation duration which is also an important contributor for adverse pregnancy outcomes (e.g. perinatal death, child development due to preterm birth etc.). Failing to control for gestation duration would bias the results. Second, current recommendations only addressed weight gain rate during 2nd and 3rd trimester, ignoring weight gain rates across different trimesters are

differnet[50]. Also, studies showed trimester-specific weight gain has different impacts on health outcomes. Weight gain during 1st trimester is related to the cardiometabolic profile of offspring[51] and their risk of gestational diabetes,[52] while weight gain during 2nd and 3rd trimesters is related mainly to maternal body mass and neonatal size[53].

Two studies quantified biases by using three different GWG measurements- total GWG, average GWG (total GWG/ gestational age at delivery) and IOM adequacy ratio (total GWG/ recommended total GWG from the IOM guideline). Hutcheon et al. [54]applied these three measurements to examine the association between GWG and preterm birth by using a simulated dataset with null association (true odds ratio=1). They found that all three measurements introduced bias to the results and magnitudes were non-negligible from odds ratio of 4.4 (95% CI 3.6-5.4) to 1.6 (95% CI 1.3-2.0). Bodnar et al.[55] compared results of using these three GWG measurements with results of using GWG z-score (a method controlling for effect of gestation duration) in examining associations with pregnancy outcomes (pre-term birth, SGA, and LGA). Results showed discrepant magnitudes of association between three traditional measurements and z-score in preterm birth but not in SGA or LGA. Overall, using these three measurements will introduce bias when the outcome of interest is related to gestational length. To address the bias, it is important to use a gestation duration-independent GWG measurement to provide valid results for future guideline updates.

2.2.2.2 Methods to improve gestational weight gain measurement

Several methods have been used to mitigate limitations in measuring GWG. Regression-based adjustment for gestational duration is as simple, appealing, and often used technique to account for its effect. Nevertheless, it may introduce collider bias when we include gestation duration in the model since it may be a mediator between total GWG and pregnancy outcomes[56]. Hinkle et

al., [57]provided a different view that there is no direct relation between total GWG and pregnancy outcome (e.g. neonatal death) but rather their work was subject to potentially strong confounding by unmeasured factors (longitudinal interactions between GWG and gestational age). Under this strong assumption, they demonstrated model-based adjustment for gestation duration can provide an unbiased and precise estimate of total GWG and neonatal death.

Inspired by the concept of fetal growth curve[58,59], gestational-age-specific z-score chart was created by using serial weight measurements at different gestational ages among healthy women with healthy pregnancy outcomes. Currently, five studies established gestational age-specific z-score charts: two specific to different prepregnancy BMI (normal weight[60], overweight or class 1-3 obese[61]), one generated from Malawi population[62] and one generated from a population-based Swedish cohort and stratified by early pregnancy BMI categories (6 levels)[63] and one international standard generated from eight countries[64]. By using these charts, total gestational weight gain can be expressed as gestation age-adjusted z-score for gestational age at delivery to provide a valid GWG measurement independent of gestation duration. Most currently existing gestational age-specific z-score charts are from small populations or another country. If the population used to generate charts is discrepant from the study population, the z-score-generated estimates might be biased and imprecise[57]. A gestational-age-specific z-score chart from a nationally representative population is warranted.

GWG patterns and trajectories provide an overall picture of the relationship between GWG in each trimester and health outcomes. Different analytic methods were proposed to clarify these relationships such as using the conditional percentile approach to isolate independent effect of GWG in each trimester[65]; SITAR model (Super-Imposition by Translation and Rotation) to classify GWG pattern by biologically meaningful parameter (e.g. absolute GWG amount, timing,

and acceleration)[66]. Better knowledge of the relationship of GWG trajectories and health outcomes can inform clinicians to tailor trimester-specific GWG recommendation.

2.2.2.3 Pre-pregnancy BMI as an effect modifier

Pre-pregnancy BMI is known for modifying the association of GWG and pregnancy outcome. Studies suggested obese women would benefit from lower GWG while underweight women have a wider range of increase in GWG to achieve healthier outcomes[67]. The 2009 IOM guideline therefore defined optimal GWG by prepregnancy BMI levels: underweight, normal weight, overweight and obesity, but not by obesity severity. Some studies demonstrated that effects of GWG on pregnancy outcomes differed by severity of obesity as well. A study[68] using Belgian cohort with 500,000 pregnancies showed weight loss in obese women decreased perinatal risks of LGA, macrosomia for all obese classes but risk of emergency cesarean delivery only in classes 1 and 2. Two other studies defined optimal GWG by severity of obesity: Bodnar et al.,[69] used gestational-age-specific z-score to examine GWG and adverse pregnancy outcomes among women in obesity classes 1-3 . They suggested optimal total GWG (kg) at 40 weeks is −4.3 to 9 for class 1, −8.2 to 5.6 for class 2, and −12 to −2.3 for class 3 obese women. Faucher et al.,[70] included 10 articles summarized optimal total GWGs (kg): 5-9 for class 1,1-5 for class 2 and no weight gain for class 3 obesity, in order to minimize combined risk of SGA, LGA, and cesarean. Among overweight and obese women, excess GWG is related to increasing maternal fat rather than lean body mass; increasing fat increases risk of post-partum weight retention and long-term maternal obesity[71]. In addition to prepregnancy BMI, parity was shown to be a modifier in a study[72] which suggests multiparous women should have lower GWG compared to nulliparous women in the same prepregnancy BMI category but this was not seen in other study[73]. There is not enough evidence to show that age, race/ethnicity, height, smoking status are effect modifiers for GWG[72,73].

2.2.2.4 Joint association between prepregnancy BMI and GWG with perinatal mortality

Few studies investigated joint associations of prepregnancy BMI and GWG and perinatal mortality, one of the most critical pregnancy outcomes. A population-based cohort study[74] using Missouri birth certificate data (1990-2004) showed no association of GWG and risk of neonatal death among overweight women with term birth. David et al.,[7] found that among non-obese women, insufficient GWG increased risk of infant death compared to women with adequate GWG in the same BMI category with odds ratios of 6.18, 1.47, 2.11 for underweight, normal weight, and overweight women respectively. Of note in this study, among obese women, excess GWG was protective for infant death with 49% decreased risk. A case-control study[75] using the 1998 US National Maternal and Infant Health Survey data (with 4265 infant deaths and 7293 controls) showed obese women with GWG≧0.45 kg/week have highest odds of infant death (2.87, 95% CI: 1.98-4.16) compared to non-obese women with GWG of 0.33-0.44 kg/week. Also, non-obese women have higher risk at very low GWG. Most of the studies defined insufficient, adequate and excessive GWG by compared GWG to 2009 IOM recommendations. When adjusting for the effect of gestational age, some constrained study samples to term births or included gestational age into regression models. Their results might be biased since infant death is related to gestational age-related pregnancy outcomes (such as preterm birth or SGA)[76]. To better control for gestational age, one population-based cohort study[38] investigated gestational-age-specific z-score of GWG and infant death by using linked birth-infant death records (2003-2011) in Pennsylvania (n=1,232,346). They found U-shaped associations between GWG and infant death among all prepregnancy BMI categories except in women with class 3 obesity, where both insufficient and excessive GWG had higher risk of infant death. Obese women, even with adequate GWG, still have higher risk of infant death compared to normal-weight women. They suggested avoiding very low or very high GWG

to lower risk of infant death. In terms of stillbirth, there are very few studies examining joint associations of pre-pregnancy BMI and GWG on stillbirth. The associations of GWG and stillbirths[77,78](antepartum[79] or intrapartum[80]) are still uncertain.

2.3 RACIAL DISPARITY IN MATERNAL OBESITY AND PERINATAL DEATH

2.3.1 Racial disparity in perinatal mortality

There have been persistent racial disparity gaps in perinatal mortality. From 1960 to 2014, infant mortality among Non-Hispanic Black (NH-Black) decreased from 44.3 to 11.4 per 1000 live births, while for Non-Hispanic White (NH-White), the rate went from 22.9 to 4.8 per 1000 live births. Although infant mortality is decreasing in both groups, the racial disparity gap is wider: the rate ratios of NH-Black to NH-White are 1.9 (1960), 1.8 (1970), 2.1 (1987), 2.2 (2011) and 2.4 (2014)[81,82]. This gap might continue to increase in 2020 as one study[83] projected infant mortality in 2020. They showed infant mortality will decrease to 5.6 (95% CI: 5.4.0-6.5) for overall population, 5.5 (95% CI: 5.1-5.7) for NH-White and 12.8 (95% CI: 11.8-13.4) for NH-Black. The highest infant mortality rate will be observed among NH-Black with less than high school education (12.5, 95% CI: 12.4-13.0). Causes of infant mortality differ by race as well, specifically for neonatal but not in post-neonatal mortality[84]. The main causes of neonatal mortality are congenital malformations, low birth weight and maternal complications in NH-Black, as shown by Black-White differences of 1.3, 3.9 and 2.8 (per 1000 live births) respectively.

Similarly, overall stillbirth rates decreased from 7.49 (1990) to 6.22 (2005) and was 5.96 per 1,000 stillbirths and live births in 2013. Substantial declines were seen in late fetal death rate

(≥28 weeks). Racial disparity gaps in stillbirth have remained for decades; NH-Black had around 2.2 times higher rate compared to NH-White. Although stillbirth rates are improving over time among NH-Black, rates are declining slowly from 12.8 (1990), 11.3 (2005) to 10.53 (2013) compared to NH-White: 5.9 (1990), 4.79 (2005) to 4.88 (2013)[2,85,86].

Racial disparity can be related to several factors: genetics, as well as individual and community-level social determinants[87–89]. Some of the risk factors are disproportionally distributed between NH-Black and NH-White, and it is also possible that some risk factors have more prominent effects among NH-Black[84]. Targeting these risk factors through community or individual-level interventions or earlier medical interventions are potential solutions to mitigate the disparity in perinatal mortality.

2.3.2 Racial disparity in maternal obesity

Maternal obesity may serve as a potential risk factor explaining racial disparity in perinatal mortality. First, pre-pregnancy BMI is higher among NH-Black with 34.8% obese and 26.9% overweight compared to NH-White with 22.7% obese and 24.1% overweight[90]. NH-Black also showed lower adherence to GWG recommendation and they tend to have less GWG compared to NH-White[91–93].Headen et al. found racial disparity on inadequate GWG was modified by pre-pregnancy BMI. NH-Black women have higher risk of GWG below IOM guidelines compared to NH-White and associations were only observed among pre-pregnancy underweight and normal weight groups with RR of 1.38 (95% CI: 1.07, 1.79) and 1.34 (1.18, 1.52) respectively[91]. Furthermore, several studies showed NH-Black have higher post-partum weight retention compared to NH-White[94].

Second, the association of prepregnancy BMI and infant mortality may have a stronger association in NH-Blacks. One study[95] using Missouri linked cohort dataset (n=1,577,082 birth from 1978 to 1997) found increased risk of neonatal mortality among women who were obese pre-pregnancy. This was only seen among NH-Black: RR=1.8 (95% CI: 1.6, 2.0) but not in NH-White. Also, the association of pre-pregnancy obesity and stillbirth was stronger among NH-Black women (RR: 1.9 (95% CI:1.7, 2.1)) compared to NH-White women (1.4 (95% CI: 1.3, 1.5))[96]. Access and quality of perinatal care might be the plausible explanation to this discrepancy in neonatal mortality, while for stillbirth, higher prevalence of chronic hypertension might explain why NH-Black women have higher prevalence of placental dysfunction increasing risk of stillbirth. In addition to these factors, GWG might be another reason why the effect of pre-pregnancy obesity on perinatal death varied by race/ethnicity groups. It is known pre-pregnancy BMI modifies the association between GWG and perinatal mortality. Discrepancies by race are shown in pre-pregnancy BMI and GWG as well. The joint association of GWG and pre-pregnancy BMI might explain racial disparity on perinatal mortality. However, none of the studies have examined these complex interrelationships between racial disparity, pre-pregnancy BMI, GWG and perinatal mortality.

While research identified plausible risk factors explaining racial disparity in perinatal death, it is important to prioritize interventions to target these risk factors. Quantifying the burden can be reduced if we could have eliminated certain risk factor from population is of public health significance. There has been a recent focus on quantifying the extent of racial disparity on perinatal mortality that is explained by pre-pregnancy obesity. Lemon et al.[8] used a population-based cohort in Pennsylvania (n=1,058,461) and found pre-pregnancy obesity may explain 10% of racial disparity in stillbirths and infant death, while severe obesity may explain 5%. In other words, 6 of

61 excess infant deaths and 5 of 44 excess stillbirths in NH-Black may be a result of pre-pregnancy obesity. It is crucial to know the role of GWG in explaining racial disparity in perinatal mortality. Since it is relatively easier to intervene on GWG, we can take advantage of opportunities during regular perinatal visits by motivating mothers to maintain healthy behaviors during pregnancy. However, conventional methods to quantify the extent of racial disparity explained by GWG might fail to meet the assumptions. Prepregnancy BMI is modified the effect of GWG on perinatal mortality and it is disproportionally distributed among different race/ethnic groups. A more appropriate method is required to explain this complex relationship to determine valid estimates.

2.4 GAPS OF CURRENT LITERATURE

There are several critical issues that need to be addressed after reviewing current literature examining maternal obesity and perinatal mortality:

First, among most of the literature studying prepregnancy obesity and adverse pregnancy outcomes, the timing of obesity onset is undetermined. Consequently, we cannot differentiate whether the relation between obesity and perinatal mortality is driven by long-standing obesity, newly-occurring obesity, or some combination of both. It is important to quantify this association since from a policy perspective, we can reduce prevalence of obesity in population by focusing on preventing onset of obesity among non-obese women, or by weight reduction among obese women.

Second, there are few studies examining pre-pregnancy BMI longitudinally to investigate the association between prepregnancy BMI change between first and second pregnancies and perinatal mortality of second pregnancy. These studies further stratified analyses by prepregnancy

BMI at first pregnancy. By using this method, it is assumed the onset of obesity can fall between first and second pregnancy and the measured effect is close to newly obese. However, these studies are limited, in generalizability and potentially introduced collider stratification bias since they excluded women who had event (stillbirths or infant mortality) in their first pregnancy and did not control for the characteristics of last pregnancy.

2.5 METHODOLOGY TO ADVANCE KNOWLEDGE OF CURRENT LITERATURE

2.5.1 Bias-variance trade-off for inverse probability treatment weighting (IPTW)

Properly adjusting for all plausible confounders between exposure and outcome allows for calculations of valid estimates. Theory-based causal graph approach[97] is preferred over traditional modeling strategies for covariate selection, such as stepwise or change in estimate approaches which rely heavily on statistical significance testing[9899]. However, issues arise when including all covariates along with exposure variable to model the outcome of interest. High-dimensional covariates will lead to two problems (1) data sparsity especially when outcome is rare; (2) multicollinearity with exposure variable[98]. In addition, conventional regression methods cannot be used for adjusting time-varying confounders which are affected by prior exposure. This would introduce collider bias if time-varying confounders are included in regression along with exposure variable[100].

Inverse probability treatment weighted-regression[9] is an alternative approach applied for controlling high-dimensional or time-varying confounders. It is a two-staged modeling strategy: First, we model exposure by using all the covariates and exposure history and generate weight for

each participant which is the inverse probability of receiving exposure; Second, we use these weights to create a pseudo-population and examine the relationship between exposure and outcome to acquire accurate estimate[101]. By doing this, we can assume in this pseudo-population that there is no association between exposure and other covariates but we also need to be aware other required assumptions: consistency, exchangeability, positivity and correct model specification to be able to make this inference. To better control for confounders, we would include all the plausible confounders and exposure history to get unbiased estimate with the price of losing precision of our estimate. This is because of high dimensional covariates will generate unstable weight. Covariate selection in constructing IPTW is a process of bias-variance trade-off[11].

There are several diagnostic tools used to examine those assumptions for constructing IPTW: covariate balanced diagnostics tool for time-fixed[102] and time-varying[103] to examine exchangeability and diagnostic tool for examining bias due to violation of experimental treatment assignment. In terms of bias-variance trade-off, weight truncation with different percentiles[11] or using AIC and cross-validation methods for overall marginal structure model fitting[104,105] are available. However, there are no published tools available to evaluate the impact of each variable on bias and variance of the estimate. Developing an easy-to use tool can help with examining these assumptions while constructing IPTW is warrant since it will encourage more researchers to accurately use IPTW through step-by-step evaluations.

2.6 SIGNIFICANCE

This proposed study will advance knowledge of the associations of maternal obesity on perinatal mortality from a policy decision-making perspective. First, we will establish our analytic cohort

by using a large population-based cohort in Pennsylvania to synchronize and quantify association of becoming pre-pregnancy obese and stillbirth and infant mortality. First, we will apply and compare four different approaches with different reliance on the parametric modeling assumption to estimate the effect of interest. Second, we will further explore the effect of transiting from normal weight to overweight or obese on the risk of stillbirth and infant mortality. Third, the visualization tool developed in this study will assist researcher in variable selection to construct inverse probability weights. Our goal is to use practice-based study designs and analytic methods to provide evidence for the association of maternal obesity and perinatal mortality and to help clinicians and policy experts with decision making.

3.0 VISUALIZATION TOOL OF VARIABLE SELECTION IN BIAS-VARIANCE TRADEOFF FOR INVERSE PROBABILITY WEIGHTS

3.1 ABSTRACT

The main advantage of inverse probability weighted (IPW) method is how it adjusts for time-fixed or time-varying confounder issues, compared to conventional regression methods. However, high-dimensional covariates may cause a positivity violation resulting in unstable weights. Our objective was to develop a SAS macro to generate plots demonstrating the impact of each confounder on the bias and variance of IPW estimates, as well as the propensity score overlap. We show how this SAS macro can be used to visualize the impact of problematic confounders of the relation between obesity and stillbirth in a study of 363,610 pregnancies from Pennsylvania, between 2006 and 2013. Our results suggest careful consideration of the analytic impact of all confounders should be made when fitting IPW estimators.

3.2 INTRODUCTION

The proper controlling of confounding is essential for consistently estimating exposure effects in observational studies. Directed acyclic graphs (DAGs)[106] have generally been preferred over statistical modeling strategies for confounder identification (such as stepwise or change in estimate approaches)[107,108]. However, while DAGs are an improvement, issues may arise when the minimally sufficient adjustment set is large relative to the sample size. Adjusting for all

confounding variables identified by a DAG may incur a variance penalty such that the overall mean squared error of the estimator is greater. This well-known bias-variance tradeoff can have an important impact on the quality of an inference from any study[109].

Inverse probability weighting (IPW) is one of the approaches often used in confounding adjustment, particularly in the presence of time-varying confounding affected by prior exposure[110]. Provided all confounders are properly accounted for, weighting creates a "pseudo-population" in which no confounding is present[111]. Weights for each study subject are constructed by taking the inverse probability of receiving their observed exposure. However, when the probability of being exposed or unexposed is close to zero or one, IPW estimators are known to suffer from problems due to highly variable weights[112,113].These problems are worsened in the presence of high-dimensional covariates[114].

To date, a limited number of diagnostic tools are available that signal problems with IPW estimators. These include simply taking the mean of the stabilize IPWs,[115] evaluating the maximum IPW value, and visualizing the overlap in the propensity score between exposed and unexposed groups. To date, all such tools have relied on evaluating some function of the propensity score[116]. Here, we propose an algorithm that extends this evaluation to the point estimate of interest. We develop a software program that will allow researchers to visualize the bias-variance tradeoff incurred by including or excluding a confounder from the propensity score model.

3.3 METHODS

3.3.1 Empirical Setting

We applied our SAS macro ***%bais_var*** to an empirical study using data from a population-based cohort from linked birth-infant death records and fetal death records in Pennsylvania, 2006-2013 to investigate the association between incident obesity and stillbirth. Our analytic cohort consisted of second or third pregnancies from a group of women who were non-obese (defined as body mass index (BMI) less than 30 kg per m^2) in their first pregnancy (363,610 pregnancies). Details on the process of constructing our analytic cohort were described in previous studies[117]. This study has been approved by the Institutional Review Board at University of Pittsburgh. Women with incident obesity were those who were normal weight at conception of the previous pregnancy and were obese (BMI $\geqq$30 kg/m^2) at conception of the index pregnancy. The outcome of interest was stillbirth, defined as fetal death at 20 or more weeks gestation. Because the outcome is rare, we refer to all odds ratios as risk ratios.

We used causal diagrams to identify all potential confounders of the current pregnancy as well as those from their prior pregnancy (Appendix A). Several confounders were selected including maternal race and height as well as the maternal characteristics of prior and current pregnancy: pregnancy order, inter-pregnancy interval, age, maternal education, urban residence, percent Black residents, pre-pregnancy diabetes mellitus, pre-pregnancy hypertension, smoking status, and health insurance type. We also adjusted for *prior* pregnancy characteristics, including gestational weight gain, gestational diabetes, gestational hypertension, smoking status during pregnancy, gestational age, birth weight, birth facility level of neonatal care, neonatal intensive

care units (NICU) admission, use of the Special Supplemental Program for Women, Infants, and Children (WIC), breast feeding, mode of delivery, Apgar score, stillbirth, and infant death. Details on variable collection can be found in the previously mentioned study[117].

3.3.2 Analytic Methods

Propensity score models for binary exposure were constructed by logistic regression to predict the probability of being exposed given adjusting for confounders. For those who were exposed, the denominator of IPW is the predicted probability of being exposed; for those who were not exposed, we used one minus the probability of being exposed in the denominator. To stabilize the weights, the marginal probability of being exposed/unexposed was used as the numerator for those who were exposed/unexposed.

We used the mean squared error (MSE) as a summary statistic for bias and variance of the IP-weighted estimate. We presumed the estimate from the fully adjusted model (as determined via our DAG) was the unbiased (true) estimate. We calculated bias as the deviance between this "unbiased" estimate with the estimate from model excluding a certain confounder. In addition, we also showed impact of on bias-variance tradeoff from two-sided IPW truncation at 1st or 5th percentiles of the distribution as a comparison to the approach of removing certain confounders. Propensity score overlapping plots between exposed and unexposed groups were also generated to evaluate the impact of potential positivity violations on overall results.

In total, we adjusted 30 categorical variables and 6 continuous variables, and estimated marginal risk ratios for the relation between incident pre-pregnancy obesity and stillbirth. ***%bias_var*** was used to generate plots and we input the following required parameters: dataset, list of categorical variables, list of continuous variables, binary exposure variable, binary outcome

variable, and unique identifier for each observation. The output of this macro consisting of two plots: the first plot displayed the odds ratios with 95% confidence interval from models that exclude the variable shown on the y-axis. The second plot shows the distribution (min, 25^{th}, 50^{th}, 75^{th} percentile, mean and max) of propensity score of obese and non-obesity pregnancies from the corresponding models. These plots were both sorted by ascending values of mean squared errors of the outcome model.

3.4 RESULTS

Graphs of adjusted risk ratios obtained after excluding each confounder are provided Figure 1a. In our example, we identified two confounders (prior pre-pregnancy BMI and prior gestational weight) to have an important impact on the point estimate. Excluding one of them greatly improved overall MSE. As shown in Figure 1(left panel), the much larger MSE value for the model that included prior pregnancy BMI was largely the result of a severe lack of propensity score overlap (Figure 1: right panel). Based on these findings, we further modified our propensity model by excluding the BMI of prior pregnancy (Figure 2) or excluding both prior pregnancy BMI and prior gestational weight gain (Figure 3) and running the visualization tool again. Once these variables were removed, all models had a smaller MSE, and the propensity score plots for the exposed and unexposed suggested good overlap.

3.5 DISCUSSION

We developed a tool to visualize the impact of each confounder on characteristics of the point estimate of interest and applied it to estimating the IP-weighted association between prepregnancy obesity and stillbirth in a cohort of 363,610 pregnancies from Pennsylvania. Our results demonstrated the advantages of adopting this visualization tool for identifying highly influential confounders based on the bias and variance of the point estimate, and the overlap in the propensity score of the exposure of interest. Based on extensive prior research, it is reasonable to assume that prior pre-pregnancy BMI and prior gestational weight gain act as important confounders of the relation between current pre-pregnancy obesity and stillbirth. However, our findings suggest that the degree of association between these confounders and pre-pregnancy obesity makes it such that adjusting for them leads to sub-optimal estimation.

When presented with a problematic confounder, a handful of options exist to manage its impact. One option is to simply remove the confounder from the model. Provided the actual confounding impact is negligible, this is the simplest approach. For a true confounder, however, one may use doubly robust collaborative targeted minimum loss-based estimation (cTMLE)[118]. With cTMLE, one may adjust for the confounder in the outcome model but exclude it from the propensity score model. In doing so, confounding is adjusted for without sub-optimal performance caused by non-overlapping propensity scores [119].

An important limitation of our tool is that it is designed to only exclude one confounder at a time. We simplified the algorithm without imposing a functional form on these covariates or including interaction terms in the propensity score models. Importantly, we are also aware that the incentive of using propensity scores is to create balanced groups between exposed and unexposed groups in terms of covariates. Our assessment of the impact of each confounder on the point

estimate might conflict with the purpose of the propensity score as a "design" phase tool[120]. However, our tool addressing the issue of selection of variables for propensity scores plays important roles in obtaining unbiased and efficient estimates[121].

This user-friendly macro can serve as the first step to visually diagnose the impact of each confounder on the point estimates as well as propensity score distributions. It is especially useful for identifying extreme violations of the positivity assumption.

3.6 FIGURES

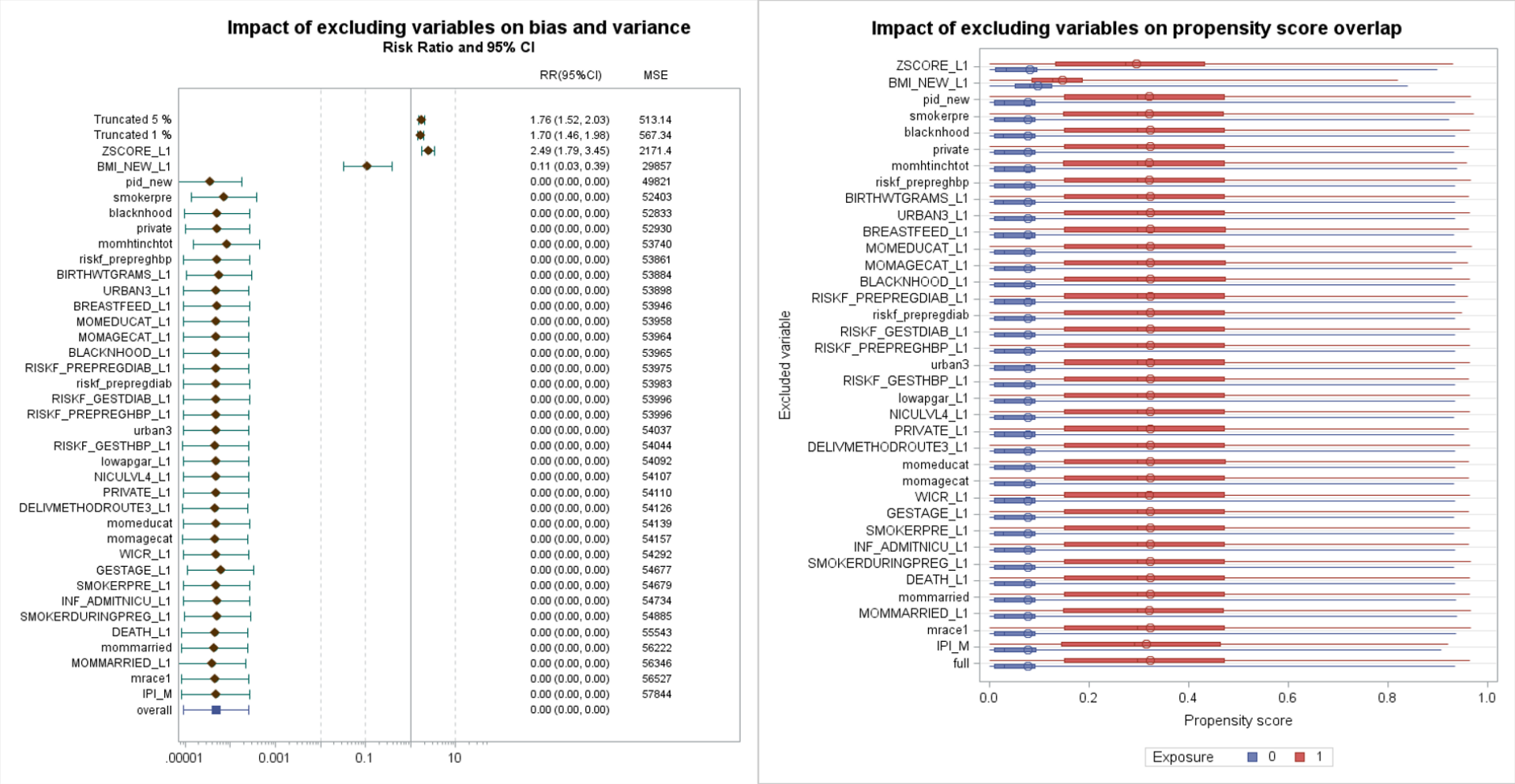


Figure 1. Risk Ratios and propensity score overlap for stillbirths among obese vs. non-obese pregnancies by models with full model of adjusting all the confounders

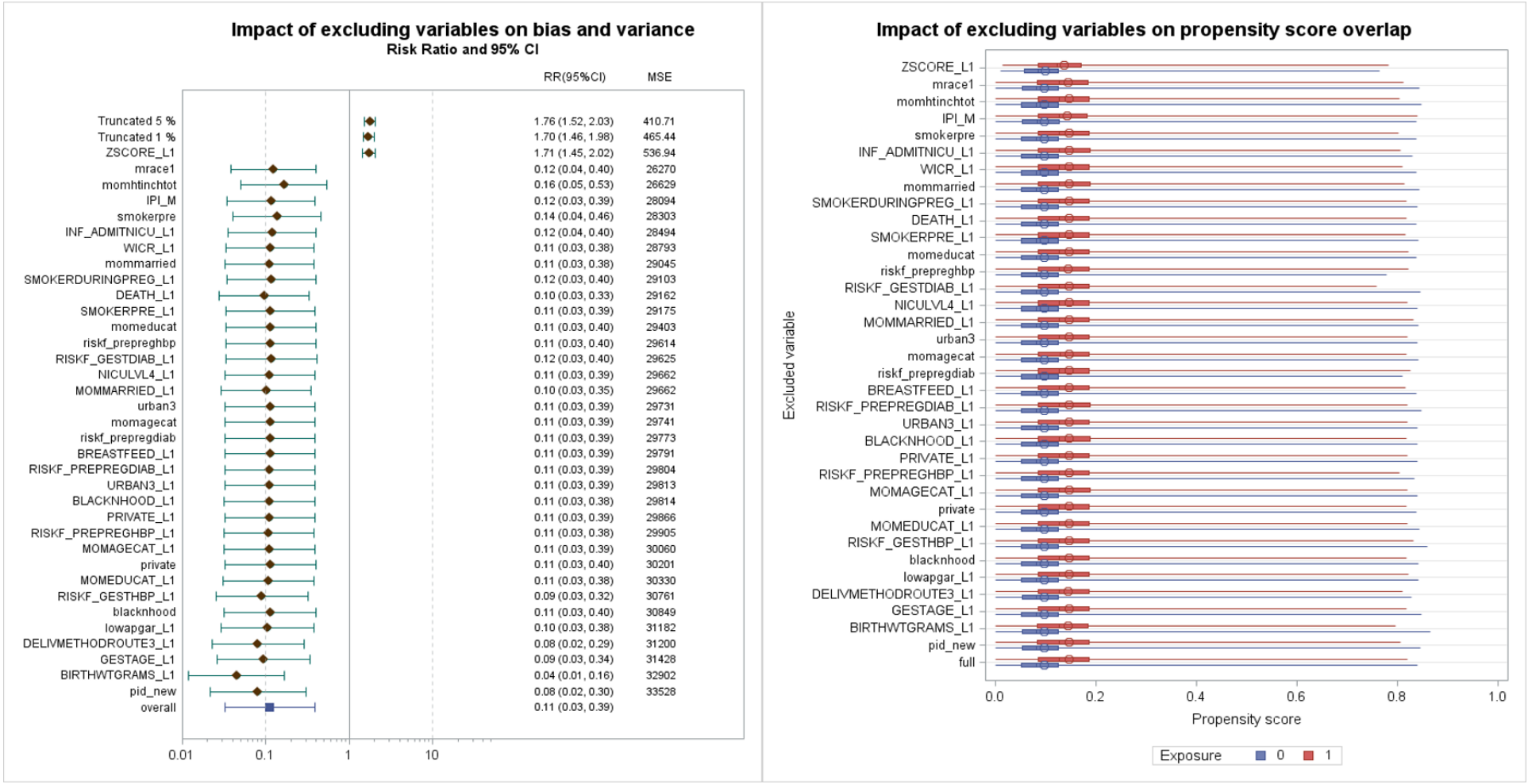


Figure 2. Risk Ratios and Propensity Score Overlap for stillbirths among obese vs. non-obese pregnancies by models with full model of adjusting all the confounders excluding prepregnancy BMI of last pregnancy

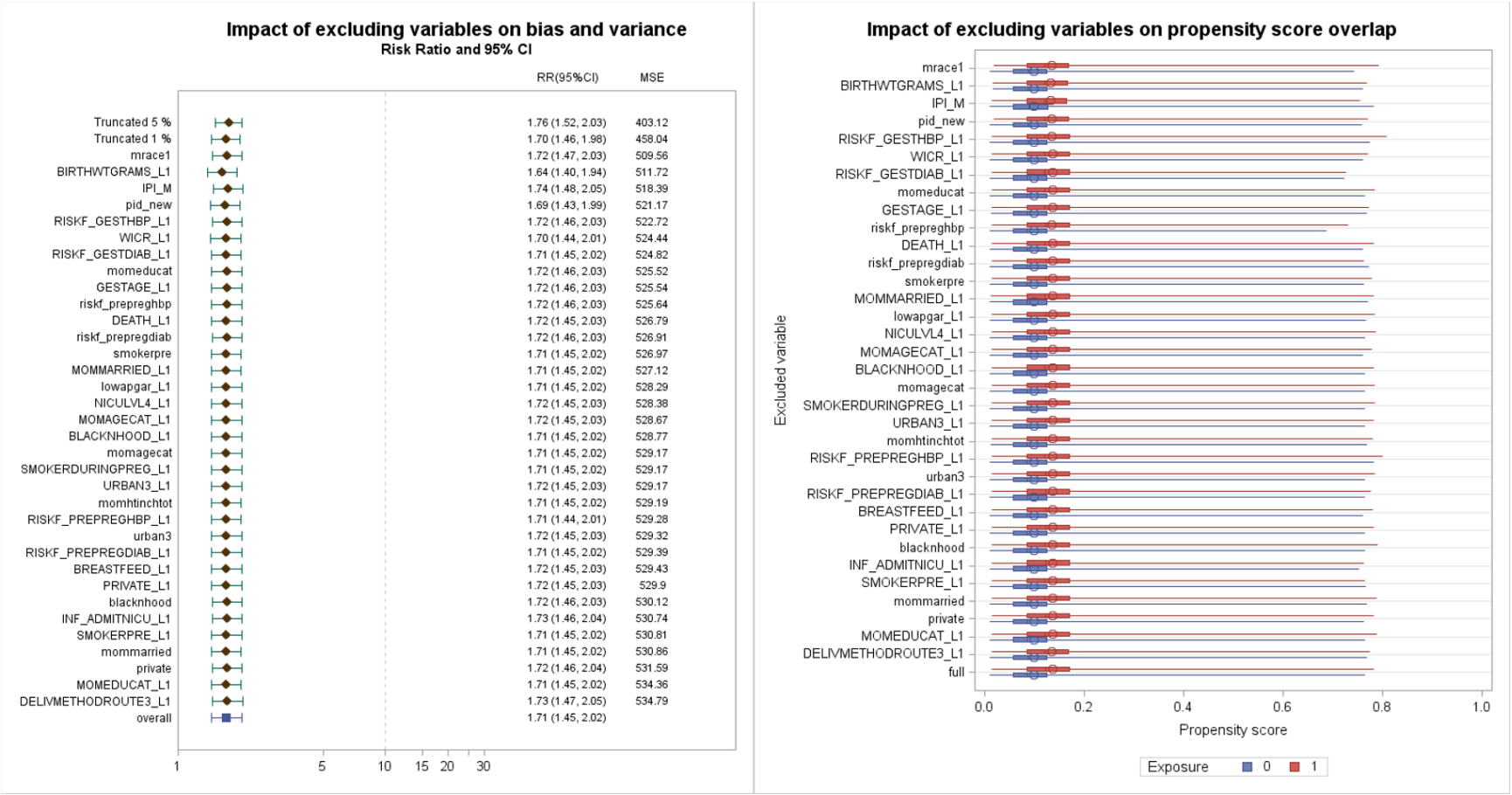


Figure 3. Risk ratios for stillbirths among obese vs. non-obese pregnancies by models with adjusting for different confounder sets all the confounders excluding prepregnancy BMI and gestational weigh gain of last pregnancy

4.0 NONPARAMETRIC ESTIMATION OF THE ASSOCIATION OF INCIDENT PREPREGNANCY OBESITY WITH STILLBIRTH AND INFANT MORTALITY IN A POPULATION-BASED COHORT

4.1 ABSTRACT

Prepregnancy obesity increases risk of perinatal mortality; few studies have evaluated whether estimates are from longstanding obesity or newly-developed obesity. Additionally, researchers relied exclusively on parametric models, requiring correct assumptions for consistent estimation. Our study explored the impact of parametric assumptions on the association of prepregnancy obesity with stillbirth and infant mortality. We focused on incident obesity by analyzing a cohort of women who were non-obese at first pregnancy from linked birth and death records in Pennsylvania (2003-2013). Incident obese pregnancies were from women whose body mass index became ≥30 kg/m^2. We used parametric g computation, semiparametric inverse probability weighting (IPW), and parametric/nonparametric targeted minimum loss-based estimation (TMLE) to estimate the association of incident prepregnancy obesity with each outcome. Compared to non-obese pregnancies, incident obese pregnancies had 1.8 (95% CI: -0.7, 4.3) more stillbirths per 1,000 pregnancies using parametric g computation. Parametric TMLE generated similar findings. However, for IPW and nonparametric TMLE, the risk differences were 2.4 (95% CI: 0.7, 2.7) and 3.3 (95% CI: 1.5, 5.0) excess stillbirths, respectively. Only weak associations were found in infant

mortality. Our results suggest incident obesity increased risk of stillbirth. Parametric assumptions can play an important role in influencing estimates of this relationship.

4.2 INTRODUCTION

Relative to other wealthy countries, women of childbearing age in the U.S. are subject to a higher risk of stillbirth and infant mortality[122,123]. Perinatal death can have important effects on mental and physical heath, as well as a family's psychological, emotional, and social wellbeing [124–126]. As such, a better understanding of the etiology of perinatal death is central. Evidence suggests a strong association of prepregnancy obesity with higher risk of stillbirth [127] and infant mortality [128]. In light of the overweight (56%) and obesity (30%) epidemics among women of childbearing age in the United States [129], maternal obesity may be a particularly important driver of the excess stillbirth and infant mortality in the US.

Despite the importance of this relationship, two major challenges have limited our ability to identify and estimate the *causal* effect of prepregnancy obesity on stillbirth and infant mortality. First, because obesity status cannot be assigned via randomization, cause-effect interpretations rely more heavily on parametric assumptions about the nature of the exposure-outcome relation [130]. Indeed, such assumptions are commonplace, and often involve distributional (e.g., normal or binomially distributed outcome), functional form (e.g., identity or logit link, linear or polynomial terms for continuous independent variables), and no interaction (e.g., no exposure-confounder or confounder-confounder interactions) components. Second, the onset of obesity is unknown in most studies. As a result, it is unclear whether estimated associations are the result of longstanding obesity, obesity that recently developed, or some combination of the two. The causal effect of

obesity on stillbirth and infant mortality is likely to be different if a woman became obese in the previous year versus in the previous decade [131–134].

In this study, we use data from a population-based Pennsylvania cohort to estimate the association of obesity with stillbirth and infant mortality in a way that overcomes two major obstacles in prior research. First, we explore the extent to which parametric models can alter the association of prepregnancy obesity with stillbirth and infant mortality when compared to more nonparametric methods. Second, we focus on incident obesity by restricting all analyses to a subset of women whose obesity onset time is bounded.

4.3 METHODS

4.3.1 Conceptual framework

The perfect (albeit impossible) study for quantifying the *effect* of prepregnancy obesity on stillbirth and infant mortality would be an ideal randomized trial among fully compliant reproductive-aged women who are not obese and not pregnant at baseline. Women would be randomized into exposure groups (e.g., remain non-obese or become obese), and would be followed until their terminal event (stillbirth, infant mortality, or a competing event) or the end of study follow up (whichever came first). The effect of prepregnancy obesity could then be estimated by simply contrasting the proportion of events in each group.

Were such a study possible, several challenges in defining and estimating the effect of obesity on stillbirth and infant mortality could be handled with relative ease. These include: 1) The ability to define cause-effect relations using the counterfactual modeling framework and,

importantly, to articulate what compliance with the study protocol would precisely entail [134]; 2) The ability to properly account for competing risks, including infertility (i.e., no pregnancy) and miscarriage [135] 3) The absence of confounding (in expectation), which would enable effect estimation without resorting to statistical (namely parametric) adjustment for a (possibly) high-dimensional set of covariates; 4) The ability to clearly define the onset of the risk period in each group, which corresponds to the onset of the obesity status in the exposed group.

As with all observational studies examining the relation between obesity and health outcomes, the information of our study is insufficient to fulfill first and second criteria. Here, we evaluate the impact of unnecessary parametric assumptions on the relation of prepregnancy obesity with stillbirth and infant mortality in a cohort of women who were non-obese in their first pregnancy.

4.3.2 Study population

We use data from a population-based cohort study linking birth and infant/fetal death records in Pennsylvania from 2003-2013 (n=1,551,919 singleton pregnancies). We confirmed birth-death matching and plurality for all data and created a unique identifier for each woman to link consecutive pregnancies by using a sequential, deterministic linkage strategy [117,136,137]. Details of the linkage process are described in the Appendix B. Pennsylvania used revised birth certificates in 2003 and fetal death certificate in 2006 which included body mass index (BMI) information. Therefore, we excluded women with stillbirths before 2006 (4,006 women, 5,168 pregnancies) due to unavailable BMI measurements, and restricted stillbirth analysis to records from 2006-2013.

To assess the relation between incident prepregnancy obesity and adverse pregnancy outcomes, we restricted our analysis to the sample of women with two or more pregnancies from

2003 to 2013 and a prepregnancy BMI of <30 kg/m^2 in their first identified pregnancies during this period (332,357 women, 769,758 pregnancies). We further excluded women with questionable data (non-logical age: 1,167 women, 3,349 pregnancies; non-logical inter-pregnancy interval: 92 women, 316 pregnancies), or prior twin gestation (5,359 women, 8,636 pregnancies).

Our final analytic sample consisted of the second and/or third pregnancies among women who were not obese at their first pregnancy. Of note, for the women who became obese in their second pregnancies, their third pregnancies were not included in our analysis. Excluding pregnancies after the onset of obesity is consistent with our study objective, which was to examine this association among pregnancies without an obesity history. Overall, 394,072 pregnancies for the infant mortality analysis (2003-2013), and 363,610 pregnancies for the stillbirth analysis (2006-2013) were available (Figure 6). This study has been approved by the institutional review board at the University of Pittsburgh.

4.3.3 Outcome, Exposure, and Confounders

Stillbirth was defined as fetal death at 20 or more weeks gestation. Infant mortality was defined as the death of live-born infant at <365 days after delivery. Prepregnancy BMI was calculated as self-reported weight (kg) divided by height (m) squared and categorized as non-obese (< 30 kg/m^2) or obese (≥ 30kg/m^2) [138].

Confounders were identified as the minimally sufficient adjustment set of the causal diagram depicted in Appendix A [106]. These confounders were maternal characteristics (age, race/ethnicity, height, education), parity, inter-pregnancy interval, urban residence, percent Black residents, prepregnancy diabetes, prepregnancy hypertension, smoking status, marital status and insurance. We also adjusted for characteristics of the *prior* pregnancy, including gestational weight

gain, gestational diabetes, gestational hypertension, smoking status during pregnancy, gestational age, birth weight, birth facility level of neonatal care, neonatal intensive care unit admission, Women, Infants, and Children program usage, breast feeding, mode of delivery, apgar score, stillbirth, and infant death.

For all parametric models, categorical variables were grouped based on the levels outlined in Table 1 and 6, while continuous variables (inter-pregnancy interval, maternal height, gestation age, gestational weight gain, and birthweight of last pregnancy) were fit with 4 knot restricted quadratic splines [139].

Details on variable collection have previously been published [140]. Briefly, medical records were used to obtain information on maternal characteristics (race/ethnicity, age, education, marital status, smoking status), parity, delivery payment method (private, Medicare, other), prepregnancy diabetes or hypertension, the address of primary residence gestational age at delivery, and level of neonatal care available in the birth facility (three levels). We used county-level federal information processing standards codes of the primary residence address to compute a measure of urbanity and the proportion of Black residents by applying Urban-Rural Continuum Codes (U.S. Department of Agriculture, Economic Research Service) [141].Inter-pregnancy interval was calculated as the interval between delivery date of last pregnancy and conception date of current pregnancy. Gestational weight gain was calculated as z scores by applying a gestational-age- and -BMI specified z-score chart [142,143].

4.3.4 Missing Data

Our final analytic sample consisted of 394,072 pregnancies from 320,677 unique women. Of these, 24% of the pregnancies had records with missing values on variables of interest. We imputed these

missing data 10 times using multiple imputation via chained equations [144].Our imputation models included variables of analytic interest without missing values (year of birth, infant death/stillbirths, breastfeeding intentions, smoking during pregnancy, neonatal level of care, infant admission into the neonatal intensive care unit) as well as several auxiliary variables (mother ID, county-level federal information processing standards codes, census tract, facility code, presence of a congenital malformation, mother being foreign born, whether labor was attempted, plans for adoption, infertility treatment, labor induction, and premature rupture of the membranes) to impute missing values on prepregnancy weight and height, weight at delivery, age, race/ethnicity, parity, smoking status prior to pregnancy, education, insurance, marital status, urban residence, enrollment in Women, Infants, and Children program, prepregnancy diabetes/hypertension, Apgar scores, birth weight, gestational age and infant sex. All analyses were conducted separately in each imputed dataset, and the results from each imputation were combined using standard equations [145].

4.3.5 Statistical analysis

4.3.5.1 Estimands

Our interest lies in estimating the marginal association between incident obesity and adverse pregnancy outcomes on both the risk difference and risk ratio scales:

$$\sum_{c} P(Y = 1|X = 1, C) - \sum_{c} P(Y = 0|X = 0, C)$$

$$\frac{\sum_c P(Y = 1|X = 1, C)}{\sum_c (Y = 1|X = 0, C)}$$

where the binary obesity status (X) was coded as 1 if obese and zero otherwise, the binary outcome status (Y) was coded as 1 if the event occurred and zero otherwise, and where C indexes all confounders outlined in the previous section. Events were stillbirth and infant death, analyzed as separate outcomes. These estimands can be interpreted as the association between obesity and pregnancy outcomes not attributable to the confounding variables listed above.

4.3.5.2 Estimators

To quantify the estimands defined above, we used parametric g-computation [146], semi-parametric inverse probability weighted (IPW) estimation [110], and parametric and nonparametric targeted minimum loss-based estimation (TMLE) [147]. Each approach relies on the specification of an exposure and/or outcome model, defined nonparametrically as:

$$P(X = 1|C) = f(C),$$

$$P(Y = 1|X, C) = g(X, C),$$

where f ( ) and g ( ) are arbitrary functions of the confounders (C) and the exposure (X) defining the relationship between right- and left-hand side of each respective equation. These models are typically referred to as the propensity score model, and the outcome model, respectively, and are often assumed to be logistic regression models when the exposure and outcome are binary. However, as in any observational study, we do not know the true form of these relationships encoded in f() and g().

We first used parametric g computation to estimate the association of prepregnancy obesity with stillbirth and infant mortality. g Computation relies on correct parametric specification of the outcome model function $g(X, C)$. This can be achieved by (i) regressing the observed outcome

against the exposure and confounders [148] (ii) predicting outcomes for all pregnancies under exposed and unexposed settings, (iii) computing the average of each of these predicted outcomes, and (iv) contrasting these averages to quantify the estimand of interest. With a time-fixed exposure such as in our setting, the g computation estimator is equivalent to model-based standardization [149]. All listed confounders were included in the outcome model. Standard errors were obtained using the normal interval bootstrap with 100 resamples [150].

Semiparametric IPW estimation was implemented by constructed IPWs using the quantile binning method [151] which specifies the propensity score functional $f(C)$ as a standard (i.e., parametric) logistic model. These models are semiparametric because they are obtained from the combination of a parametric (finite-dimensional) propensity score model with a nonparametric (infinite-dimensional) outcome model [152]. All listed confounders were included in the propensity score model. Parameters corresponding to the risk difference and risk ratio from linear and log-linear regression models were quantified via nonparametric maximum likelihood estimation, with each pregnancy's contribution to the likelihood weighted by the inverse of the probability of being in their observed obesity category. Standard errors were obtained using the robust variance estimator [153].

TMLE is obtained by updating the g computation estimator using information from the exposure model (via the "clever covariate") to better target the estimand of interest [147]. We implemented TMLE parametrically and nonparametrically.

In the parametric approach, both the propensity score model and the outcome model were estimated via standard logistic regression. When implemented nonparametrically, both the propensity score and outcome models were specified using an ensemble machine learning method (SuperLearner) [154] to create an optimally weighted combination of predictions from a library of

algorithms. In our case, “optimal” was defined using a 5-fold cross-validated L2 loss function [155]. Our SuperLearner library included the arithmetic mean, neural networks, multivariate adaptive regression splines, least absolute shrinkage and selection operator, generalized additive models, random forests, and gradient boosted machines. We also included generalized linear models with second order polynomials and two-way interactions of the main terms. A cross-validated search over the (hyper)parameter space was also conducted for random forests, gradient boosting, least absolute shrinkage and selection operator, and generalized additive models. All listed confounders were included in both the propensity score and outcome models. Standard errors were estimated by taking the variance of the efficient influence function.

4.4 RESULTS

In our analytic cohort comprised of second and third pregnancies, around 11% of the pregnancies developed obesity. Compared to pregnancies from women who were not obese prior to pregnancy, those with incident prepregnancy obesity were more likely to be Non-Hispanic Black, Hispanic, younger, with only a high-school education or less, and living in neighborhoods with higher percentage of Blacks. They were also subject to more prepregnancy diabetes and hypertension, had non-private insurance, were unmarried, and had shorter intervals between pregnancies (Table 1and 7). In their last pregnancy, these women experienced more adverse pregnancy outcomes including infant death, fetal death and large for gestational age, as well as higher gestational weight gain, gestational diabetes, gestational hypertension (Table 6 and 8).

As shown in Figure 4, among pregnancies from non-obese women, the adjusted stillbirth rate increased with pregnancy order, from 3.4 and 4.0 per 1,000 pregnancies for second and third

pregnancies respectively. Pregnancies from incident obese women had a higher adjusted stillbirth rate, which increased with pregnancy order as well: 5.5 and 7.7 per 1,000 pregnancies for second and third pregnancy respectively. Adjusted infant mortality patterns were similar, except infant mortality did not increase with pregnancy order among pregnancies from incident obese women.

We found important differences in the estimated associations of incident obesity with stillbirth and infant mortality between parametric and semi- or nonparametric methods. When using parametric g computation to estimate the risk differences comparing pregnancy outcomes among obese and non-obese pregnancies, we found that women with incident prepregnancy obesity had 1.8 (95% CI: -0.7, 4.3) excess stillbirths per 1,000 pregnancies relative to women who were not obese before pregnancy. Parametric TMLE yielded a similar risk difference of 1.6 (95% CI: 0.2, 2.9) excess stillbirths. In contrast, when using semiparametric IPW or nonparametric TMLE, the corresponding risk differences nearly doubled to 2.4 (95% CI: 0.7, 2.7) and 3.3 (95% CI: 1.5, 5.0) excess stillbirths per 1,000 pregnancies, respectively. In terms of infant mortality, we observed a similar pattern between parametric and semi- or nonparametric methods. However, the magnitude of the associations between incident obesity and infant mortality were smaller (Table 2). G computation and parametric TMLE yield similar results with 0.2 (95% CI: -1.1, 1.6) and 0.3 (95% CI: -1.9, 2.7) excess infant deaths per 1,000 livebirths, respectively when comparing incident obesity pregnancies with non-obese pregnancies. Estimates from semiparametric IPW and nonparametric TMLE were both much higher with risk differences of 0.9 (95% CI: -0.5, 2.3) and 1.0 (-1.1, 3.1), respectively (Table 2). A similar pattern was observed for risk ratios (Table 3).

4.5 DISCUSSION

We used different analytic methods to quantify the association between prepregnancy obesity and the risk of stillbirth and infant mortality among women who were not obese in their prior pregnancies. While we found positive associations of incident prepregnancy obesity with stillbirth and infant mortality using all methods, meaningful differences were observed between methods that relied on parametric modeling assumptions (g computation, parametric TMLE) versus those that were more flexibly specified (semiparametric IPW, nonparametric TMLE). In particular, the magnitudes of association were smaller when estimated via parametric methods compared to those estimated via nonparametric methods.

Because prepregnancy obesity cannot be assigned, the effect of prepregnancy obesity on stillbirth and infant mortality can only be studied using observational data. When randomizing the exposure is not possible, the counterfactual approach to causal modeling can be particularly useful in identifying deviations from the ideal (i.e., gold standard) randomized design.

In our case, we were able to identify four key challenges to nonparametrically identifying and estimating the causal effect of prepregnancy obesity on stillbirth and infant mortality. One of these included the reliance on unnecessary parametric assumptions, which was shown to play an important role in influencing the estimated associations. However, the remaining challenges continue to have important implications on estimating the causal effect of obesity [134]. These include 1) the inability to precisely articulate what it means for the relation between obesity and stillbirth and infant mortality to be "causal," and 2) the problem introduced by competing risks.

In order to interpret the associations estimated in this study as causal effects, the former complication would require assuming that the nature of the relation between changes across a particular threshold of a woman's body mass index reflect physiologic alterations that lead to

material changes in the risk of stillbirth and infant mortality. While this may, in fact, be the case, empirically evaluating these beliefs would require data much more detailed than our population-based cohort contains. In particular, there are many ways in which prepregnancy body mass index can be changed, each of which may induce a variety of physiologic changes, with different effects on stillbirth and infant mortality [134].

Interpreting the effects of prepregnancy obesity as causal would also require assuming that it plays a minimal to no role in influencing the probability of conception. This is unlikely, given existing evidence on the relation between obesity and fertility [156]. However, this issue is not specific to prepregnancy obesity, but an important limitation of any research that examines the relation between pre-conception exposure status on post-conception outcomes [157].

Despite these remaining challenges, we have accounted for two key issues that prevail in research examining the relation between prepregnancy obesity and perinatal outcomes. Indeed, adequate confounder control is a central challenge in observational studies. To address this, one can use outcome modeling approaches (e.g. parametric g computation) that require researchers to correctly model all aspects of the data generating distribution [148,158]. One can also use inverse probability weighting which relies on correct specification of a propensity score model. The outcome model need not be correctly specified. In particular, one can avoid the need to include all exposure-confounder interactions, and still obtain a consistent estimator of the marginal exposure-outcome association [110].

When relying on parametric models, researchers must correctly specify the functional form of the relation between the confounders and the exposure (when adjustment is carried out via propensity scores) or the confounders and the outcome (when adjustment is carried out via outcome modeling). Correct model specification is an unverifiable assumption that usually

requires choosing the correct link function, including the correct set of exposure-confounder and/or confounder-confounder interactions, and appropriately modeling potential nonlinearities.

Instead of relying exclusively on either a correctly specified outcome or exposure model, a doubly robust estimator may be used. With doubly robust estimation, one need only correctly specify one of the two models. Unfortunately, when the exposure and outcome are modeled parametrically, one must not only include all relevant confounders, but also include all relevant interactions, correctly model nonlinearities, and choose appropriate link functions. Thus, while the likelihood of correct double-robust specification is better, there are still many opportunities for misspecification to occur.

However, use of double robust methods offer an opportunity to rely on nonparametric (e.g., machine learning) techniques [147,154]. In doing so, researchers may entirely avoid relying on unwarranted assumptions about precisely how the exposure and confounders relate to the outcome, or how the confounders relate to the exposure [159]. Indeed, in the presence of such uncertainty, numerous theoretical and simulation studies have shown that nonparametric TMLE has greater efficiency and less bias when compared with (mis-specified) parametric singly robust methods [160] as well as nonparametric singly robust methods [159,161].

In our study, we found meaningful differences in the magnitude of the relation of prepregnancy obesity and stillbirth and infant mortality when quantified using parametric versus less (semi, non) parametric methods. One other study examined stillbirth in the second pregnancy among women who became obese compared to women who maintained normal weight and found a hazard ratio of 1.5 (95% CI: 1.1, 2.1) [162].This magnitude is similar to our results estimated by parametric g computation, but different from our nonparametric TMLE estimates. In terms of infant mortality, to our knowledge there are no literature with a similar study design. The

differences between our study and previously published results might be due to parametric assumptions or some other phenomena (e.g., hazard versus risk ratios, additional adjustment of characteristics during prior pregnancy in our study). Our results suggest that parametric assumptions play an important role in influencing estimates of the relation of prepregnancy obesity with stillbirth and infant mortality and should be handled with caution.

4.6 FIGURES AND TABLES

Table 1. Characteristics of Non-obese vs. Incident Obese Pregnancies, Infant Mortality Analysis (2003-2013)

	Non-obese N (%) (n=354,079)		Obese N (%) (n=39,993)	
Maternal race				
Non-Hispanic White	266,272	(75.2)	26,693	(66.7)
Non-Hispanic Black	43,282	(12.2)	8,054	(20.2)
Hispanic	28,303	(8.0)	4,255	(10.6)
Others	16,222	(4.6)	991	(2.5)
Maternal age (year)				
<= 20	12,313	(3.5)	1,451	(3.6)
20-29	175,184	(49.5)	23,182	(58.0)
>= 30	166,582	(47.0)	15,360	(38.4)
Maternal education				
Less than high school	53,518	(15.1)	6,807	(17.0)
High school or equivalent	87,317	(24.7)	13,287	(33.2)
Some college	86,375	(24.4)	11,929	(29.8)
College graduate	126,869	(35.8)	7,970	(19.9)
Metropolitan area				
>= 1mile	184,612	(52.1)	19,935	(49.9)
250,000- 1 mile	103,333	(29.2)	11,656	(29.2)
< 250,000	66,134	(18.7)	8,402	(21.0)
Neighborhood (% of Black)				
Lowest	123,142	(34.8)	12,453	(31.1)
Middle	124,053	(35.0)	11,793	(29.5)
Highest	106,884	(30.2)	15,747	(39.4)
Prepregnancy diabetes				
No	352,763	(99.6)	39,636	(99.1)
Yes	1,316	(0.4)	357	(0.9)
Prepregnancy hypertension				
No	351,508	(99.3)	39,071	(97.7)
Yes	2,571	(0.7)	922	(2.3)
Prepregnancy smoking				
Non-smoker	281,945	(79.6)	30,620	(76.6)
Very light	19,425	(5.5)	2,719	(6.8)
10-<20	21,160	(6.0)	2,688	(6.7)
>=20	31,549	(8.9)	3,966	(9.9)
Insurance				
Non-private	138,277	(39.1)	19,934	(49.8)
Private	215,802	(60.9)	20,059	(50.2)
Marital status				
Unmarried	114,519	(32.4)	17,603	(44.0)
Married	239,560	(67.7)	22,390	(56.0)
Inter-pregnancy interval				
< 18 months	222,879	(63.0)	27,638	(69.1)
>= 18 months	131,200	(37.0)	12,355	(30.9)

Table 2. Risk Differences of Stillbirth and Infant Mortality by Incident Obesity Status, Various Methods

Outcomes	Event	Population at risk	Risk difference (95% CI)[a]				
			Unadjusted	IPW	G computation	parametirc-TMLE[b]	nonparametric-TMLE[c]
Stillbirth							
Obesity	226	37,432	2.6 (1.3, 4.0)	2.4 (0.7, 2.7)	1.8 (-0.7, 4.3)	1.6 (0.2, 2.9)	3.3 (1.5, 5.0)
Non-obesity	1,092	326,178	reference	reference	reference	reference	reference
Infant death							
Obesity	243	39,993	0.9 (-0.4, 2.3)	0.9 (-0.5, 2.3)	0.3 (-1.9, 2.7)	0.2 (-1.1, 1.6)	1.0 (-1.1, 3.1)
Non-obesity	1,782	354,079	reference	reference	reference	reference	reference

Abbreviations: IPW: Inverse Probability Weighted; TMLE: Targeted Minimum Loss-based Estimation

[a.] Risk difference: per 1000 live births (or pregnancies)

[b.] TMLE with parametric regressions

[c.] TMLE with SuperLearner with algorithms of SL.mean, SL.nnet, SL.earth, SL.ranger, SL.xgboost, SL.glmnet, SL.gam, SL.glm.interaction

Table 3. Risk Differences of Stillbirth and Infant Mortality by Incident Obesity Status From Various Methods

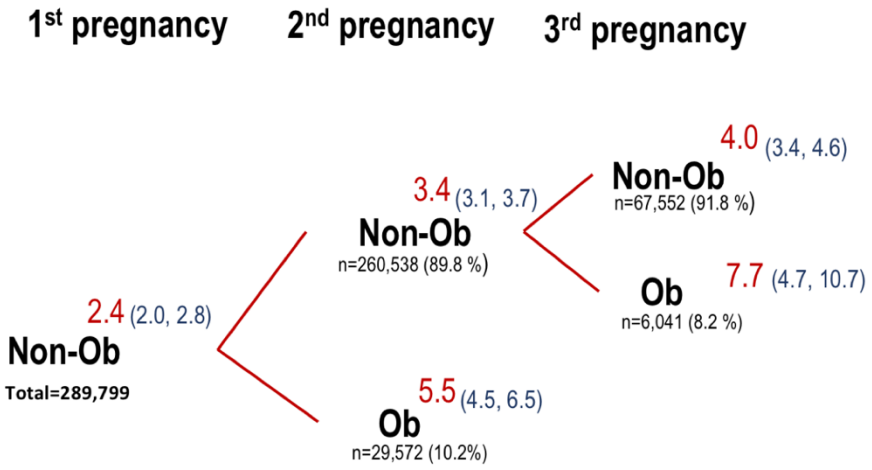
Outcomes	Event	Population at risk	Risk difference (95% CI)[a]				
			Unadjusted	IPW	G computation	parametirc-TMLE[b]	nonparametric-TMLE[c]
Stillbirth							
Obesity	226	37,432	2.6 (1.3, 4.0)	2.4 (0.7, 2.7)	1.8 (-0.7, 4.3)	1.6 (0.2, 2.9)	3.3 (1.5, 5.0)
Non-obesity	1,092	326,178	reference	reference	reference	reference	reference
Infant death							
Obesity	243	39,993	0.9 (-0.4, 2.3)	0.9 (-0.5, 2.3)	0.3 (-1.9, 2.7)	0.2 (-1.1, 1.6)	1.0 (-1.1, 3.1)
Non-obesity	1,782	354,079	reference	reference	reference	reference	reference

Abbreviations: IPW: Inverse Probability Weighted; TMLE: Targeted Minimum Loss-based Estimation

a. TMLE with parametric regressions

b. TMLE with SuperLearner with algorithms of SL.mean, SL.nnet, SL.earth, SL.ranger, SL.xgboost, SL.glmnet, SL.gam, SL.glm.interaction

A. Stillbirth



B. Infant mortality

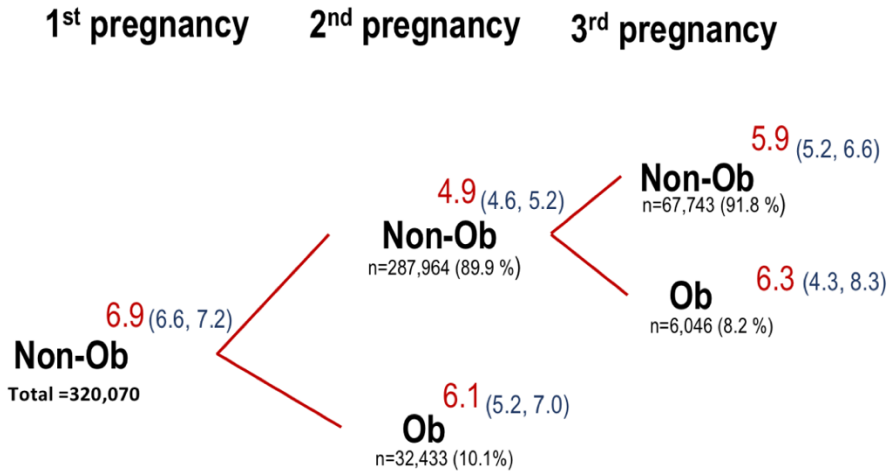


Figure 4. IPW stillbirth rate and infant mortality by parity and obesity status

5.0 THE EFFECT OF INCIDENT PREPREGNANCY OBESITY ON STILLBIRTH AND INFANT MORTALITY IN A COHORT OF MULTIPAROUS WOMEN

5.1 ABSTRACT

Objective

To identify the association of newly-developed prepregnancy overweight and obesity with stillbirth and infant mortality.

Methods

We studied subsequent pregnancies of mothers who were normal weight at conception of their first pregnancy, from a population-based cohort that linked the birth registry with death records in Pennsylvania, 2003-2013. Newly-developed overweight and obese pregnancies were identified from women whose prepregnancy body mass index (BMI) at second pregnancy was $\leq$ 25 kg/m^2 to <30 kg/m^2 or $\geq$30 kg/m^2. Our main outcomes of interest were stillbirth defined as in-utero death $\geq$ 20 weeks of gestation and infant mortality: death <365 days after birth. Adjusted associations of both prepregnancy BMI categories and continuous BMI unit changes with each outcome were estimated by nonparametric targeted minimum loss-based estimation and inverse-probability weighted dose-response curves, respectively.

Results

Compared with women who stayed normal weight in their second pregnancies, those becoming overweight had 1.4 (95% confidence interval [CI]: 0.6, 2.2) excess stillbirths per 1,000 pregnancies. Mothers who became obese had 4.0 (95% CI: 1.4, 6.6) excess stillbirths per 1,000 pregnancies as well as 2.3 (95% CI: 0.1, 4.5) excess neonatal deaths per 1,000 livebirths. There

was a dose-response relationship between a prepregnancy BMI increase of more than 2 units and increased risk of stillbirth and infant mortality. In addition, BMI increases were associated with higher risks of infant mortality among women with shorter interpregnancy intervals (less than 18 months) compared with those with longer intervals.

Conclusion

Our results suggest that transitioning from normal weight to overweight or obese between the first and second pregnancy increases risk of stillbirth and neonatal mortality. Health care providers should monitor and provide weight counseling about proper gestation weight gain during pregnancy or postpartum weight loss for pregnant women to minimize risk of adverse outcomes for future pregnancies.

5.2 INTRODUCTION

The obesity epidemic has impacted millions worldwide, including 30% of adults in the U.S.[163]. Importantly, obesity has higher prevalence in women of childbearing age compared with general population estimates. From 2007-2008 to 2015-2106, the prevalence of obesity among women aged 20-39 years increased from 31% to 36%[164]. Prepregnancy obesity is a common high-risk obstetric condition with wide-ranging health impacts, [165] including stillbirth[127] and infant death.[128]

Obesity is often defined via body mass index (BMI), which is correlated with body fat percent in women prior to conception[166]. However, obesity is a complex and heterogeneous disorder presenting with multiple sub-phenotypes. The effect of obesity sub-phenotypes such as with or without metabolic syndromes or other comorbidities, on adverse pregnancy outcomes can vary [167,168]. The duration a woman is exposed to the obese phenotype may also impact her risk for

obstetrical and perinatal complications. For example, higher cardiometabolic risk is associated with longer duration and greater severity of obesity[169,170]. To date, however, there is little information regarding the timing of obesity onset relative to pregnancy outcomes[171]. Given this, in this study, we evaluated the relation between newly-developed pre-pregnancy overweight and obesity and stillbirth and infant mortality.

5.3 MATERIALS AND METHODS

The Penn MOMS study, which included fetal death records and linked birth-infant death records in Pennsylvania from 2003-2013 (n=1,551,919 singleton pregnancies), were used to construct our analytic cohort. Unique identifiers were used to link pregnancies from the same women. In Pennsylvania, fetal death records before 2006 did not contain information to calculate BMI; therefore, women with stillbirth before 2006 (4,001women; 5,168 pregnancies) were excluded. Details on data cleaning and linkage processes can be found in previous studies[117,140].

We established our study cohort by including women who had at least two pregnancies during the study period 2003-2013 and were normal weight at the start of the first identified pregnancy (215,706 women; 505,942 pregnancies). Women with questionable data (non-logical age: 654 women, 1,879 pregnancies; non-logical interpregnancy interval: 54 women, 188 pregnancies) or prior twin gestations (1,064 women, 2,682 pregnancies) were excluded. We then limited our analytic sample to second pregnancies. Overall, there were 212,889 pregnancies for the infant mortality analysis (2003-2013), and 192,941 pregnancies for the stillbirth analysis (2006-2013) (Figure 7.). This study has been approved by the institutional review board at the University of Pittsburgh.

Outcomes of interest were stillbirth, which was defined as in-utero death at 20 or more weeks gestation and infant mortality, defined as the death of live-born infant before 1 year of age. We further divided infant mortality into two groups based on the timing of death: neonatal death (< 28 days) and post neonatal death (28 to <365 days).

Prepregnancy BMI was computed by using self-reported weight (kg) and divided by height (m) squared. We categorized BMI as underweight (<18.5 kg/m^2), normal weight (18.5 ≤ BMI< 25 kg/m^2), overweight (25 ≤ BMI< 30 kg/m^2) or obese (≥ 30kg/m^2)[138]. Women who were normal weight in their first pregnancy and became overweight or obese in their second pregnancy were considered to have newly-developed overweight or obesity. Interpregnancy BMI changes were calculated as the difference in prepregnancy BMI units of first and second pregnancy.

We used causal diagrams to identify confounders (Appendix A)[106]. We adjusted for maternal height and race/ethnicity as well as other characteristics during *prior and current* pregnancies including inter-pregnancy interval, maternal education, urban residence, percent Black residents in census tract, prepregnancy diabetes, prepregnancy hypertension, smoking status, marital status and payer status. In addition, we adjusted for *prior* pregnancy characteristics including gestational weight gain, gestational diabetes, gestational hypertension, smoking status during pregnancy, gestational age, birth weight, birth facility level of neonatal care, neonatal intensive care units (NICU) admission, use of the Special Supplemental Program for Women, Infants, and Children (WIC), breast feeding, mode of delivery, Apgar score, stillbirth, and infant death. When adjusting for confounding in our analysis, inter-pregnancy interval, maternal height as well as gestation age, gestational weight gain, and birthweight of last pregnancy were treated as continuous variables. Other confounders were categorized based on the groups listed in Table 4 and Table 9.

Information on maternal characteristics (race/ethnicity, age, education, marital status, smoking status), delivery payment insurance, prepregnancy diabetes or hypertension, gestational age at delivery, and level of neonatal care available in the birth facility were acquired from hospital discharge records. Neighborhood socioeconomic status (urbanity and the proportion of Black residents) were computed based on the county-level federal information processing standards (FIPS) codes of the primary residence address. Inter-pregnancy interval was calculated as the months between delivery date of previous pregnancy and conception date of current pregnancy. Gestational weight gain was calculated as z scores by applying a gestational-age- and BMI-specified z-score chart[142,143] . Roughly 20% of pregnancies were missing data on variables of interest, which were imputed using a Markov chain Monte Carlo approach[144]. Details on variable collection and imputation have been previously provided[117,140].

Our primary analysis aimed to determine the association between incident overweight and obesity before pregnancy and stillbirth and infant mortality. Nonparametric targeted minimum loss-based estimation (TMLE)[147], was used to estimate risk differences and risk ratios for the relation between categorical prepregnancy BMI (underweight, overweight, obesity versus normal weight) and our outcomes of interest. TMLE is a "doubly robust" approach in that it combines both a propensity score model with a regression model for the outcomes (stillbirth, infant mortality), thus providing two chances to adjust for potential confounding[172]. Furthermore, unlike standard regression, it enables use of nonparametric machine learning techniques that do not rely on unverifiable modeling assumptions (e.g., linearity, additivity, no interaction). In our analyses, we used stacking[154,155] to combine several machine learning algorithms into one. We included the arithmetic mean, neural networks, multivariate adaptive regression splines, least absolute shrinkage and selection operator (LASSO), generalized additive models, random forests, and

gradient boosted machines. These algorithms were used to estimate both the propensity score model for BMI, and the outcome models (stillbirth, infant mortality).

To examine the dose-response relation between the continuous interpregnancy BMI change and the risk of stillbirth and infant mortality, we further modeled interpregnancy BMI change using restricted cubic splines with 4 knots, and weighted by inverse of the propensity score to adjust for confounding.[173] Knots were located at the 20th, 40th, 60th, and 80th percentiles of the distribution of BMI among the events[139]. These curves were also stratified by interpregnancy interval length. We adopted the commonly used cut-points of less than 18 months to define short inter-pregnancy interval.[174]

5.4 RESULTS

Among women who were normal weight in their initial pregnancy, only 3%, 18% and 4% became underweight, overweight, or obese in their next pregnancy. The median interpregnancy interval was roughly 23 months (interquartile range: 24). Those mothers with incident prepregnancy overweight or obesity were more likely than women who remained normal weight to be Non-Hispanic Black, younger, without college education, with prepregnancy diabetes and hypertension, smokers, and living in neighborhoods with higher percentage of Blacks. They also had larger percentages of having non-private insurance, were unmarried, and had shorter interpregnancy intervals (Table 4 and Table 9). During their previous pregnancy, these women had experienced more adverse pregnancy outcomes including infant death, stillbirth, large for gestational age birth, and infants with low APGAR score as well as higher gestational weight gain and lower prevalence of breast feeding (Table 10 and 11.).

The confounder adjusted association between BMI category change and the risk of stillbirth is provided in Table 5. Compared to women who remained normal weight in their second pregnancy, those who became overweight had 1.4 (95% confidence interval (CI): 0.6, 2.2) excess stillbirths per 1,000 pregnancies. The mothers who became obese had 4.0 (95% CI: 1.4, 6.6) excess stillbirth per 1,000 pregnancies. Becoming underweight at the second pregnancy also increased risk of stillbirth by 2.4 (95% CI: -0.1, 4.9) excess stillbirths per 1,000 pregnancies. We did not find strong associations between different prepregnancy BMI categories and infant mortality. After dividing infant mortality into neonatal and post-neonatal categories, women with new-onset obesity had 2.3 (95% CI: 0.1, 4.5) excess neonatal mortality events per 1,000 births (Table 5) compared to those women who maintained normal weight. A similar pattern was observed for risk ratios (Tables 5).

The adjusted dose response curve between interpregnancy BMI change and risk of stillbirth resembled a J-shape, with the lowest risks at BMI change of 0 to 2 units (Figure 5A). Stillbirth risk rose sharply as BMI increased beyond 2-kg/m2 (equivalent to an average weight gain of 5 kg for women with 160 cm height). In terms of infant mortality, the U-shaped dose-response curve identified the lowest risks at BMI values that were similar to previous pregnancy. The risk of infant mortality rose with increasing or decreasing BMI changes (Figure 5B). The dose-response curve for stillbirth did not vary according to interpregnancy interval (Figure 5C). However, the association between BMI change and risk of infant death was stronger for women with short interpregnancy interval than those with a longer interpregnancy interval (Figure 5D). The curves for neonatal mortality showed similar patterns to infant mortality, but no association was observed between interpregnancy BMI changes and postneonatal mortality (Figure 8).

5.5 DISCUSSION

Our study found that women who were normal weight at conception of the initial pregnancy and became overweight or obese at conception of the subsequent pregnancy had higher stillbirth and neonatal mortality rates than women who remained normal weight. We identified a dose-response relationship between interpregnancy BMI changes and risk of stillbirth and infant mortality. This association between BMI changes and infant mortality was stronger among the subgroup of women with a short interpregnancy interval than those with a longer interval. Taken together, our results suggest that becoming obese within average of 2 years of a given pregnancy is associated with a higher risk of adverse pregnancy outcomes.

One way to differentiate between the effects of recently-developed obesity versus long-standing obesity is to measure BMI status repeatedly over the course of a woman's reproductive history. Only three studies[162,175,176] have examined maternal BMI status in relation to stillbirth and infant mortality across multiple pregnancies. One study using Missouri vital records[162] found that compared with mothers who stayed at normal weight, normal weight mothers becoming overweight or obese had risks of stillbirth that were 20% (hazard ratio 1.2; 95% CI:1.0, 1.4) and 50% (hazard ratio: 1.5; 95% CI: 1.1, 2.1) greater, respectively. The magnitude of these effects are smaller than those in our study. This difference may be explained by these authors adjustment for several variables (including preeclampsia and gestational diabetes in the second pregnancy) that may be impacted by pre-pregnancy obesity. It is increasingly recognized that controlling for such intermediates can result in overadjustment bias[177], resulting in potentially misleading estimates.

Two other studies using a Swedish population-based cohort attempted to answer questions about interpregnancy weight change. Villamor et al.,[175] did not find an association between BMI changes and stillbirth in the subgroup of women without overweight. While Cnattingius et al.,[176]

found that among women whose BMI were less than 25 kg/m^2 in the first pregnancy, gaining more than 2 units of BMI increased risk of stillbirth, infant mortality, neonatal mortality as well as postneonatal mortality. Our results were similar to their findings except for postneonatal mortality. Compared to their study, we adjusted for additional characteristics from the prior pregnancy which may explain away the association.

Our findings should be interpreted in light of some key limitations. BMI values calculated from self-reported height and weight may result in misclassification of BMI categories[178]. However, our previous studies analyzing this cohort showed that after accounting for misclassification, the relations between prepregnancy obesity and infant mortality were not meaningfully different[117]. We are also aware that BMI measurements were only available at the start of each pregnancy. Women who were normal weight in their first pregnancy may have had a history of overweight or obesity, and we could not account for this. Furthermore, in order to identify newly-developed overweight/obesity, we restricted our analysis to those who had two pregnancies and were normal weight before the first pregnancy. We need to be mindful of generalizing our results to different populations.

Studies have shown reproductive history plays an important role in subsequent pregnancies[179]. Therefore, we adopted a reproductive life-based approach[180] which considers potential impacts from prior pregnancies (Appendix A). Unlike previous studies that restricted analyses to women without experiencing events in the first pregnancy[162,175,176], we adjusted for pregnancy outcome as well as other characteristics of the prior pregnancy. By doing so, we were able to account for confounding effects of reproductive history without introducing selection bias [177]. In addition, we avoided adjusting for obstetric complications or any variables on the pathway from prepregnancy BMI to stillbirth or infant mortality of second pregnancy.

Women of childbearing age experience a weight gain trajectory and may develop into obesity due their pregnancy[181–183]. Postpartum weight retention is one of the common reasons for women to transiting into overweight/obese; around 13-20% of women retain 5 kg or more of their prepregnancy weight at 1-year after delivery[181]. Health care providers should provide consultation of weight maintenance (e.g. adequate gestational weight gain[184] or postpartum weight lost before next pregnancy) to pregnant women. The efforts should especially apply for those at the upper limits of normal weight categories[185]. In order to develop effective interventions for weight maintenance for the purposes of preventing stillbirth and infant mortality, future studies focusing on the cause of becoming obese are warranted.

5.6 FIGURES AND TABLES

Table 4. Characteristics of normal weight, incident overweight, and incident obese pregnancies for infant mortality analysis (2003-2013)

	Normal weight N (%) (n=160,001)		Overweight N (%) (n=39,011)		Obesity N (%) (n=8,426)	
Maternal race						
NH White	125,246	(78.3)	27,068	(69.4)	5,288	(62.8)
NH Black	15,527	(9.7)	6,163	(15.8)	1,834	(21.8)
Hispanic	11,089	(6.9)	4,151	(10.6)	1,051	(12.5)
Others	8,139	(5.1)	1,629	(4.2)	250	(3.0)
Maternal age (year)						
<= 20	6,024	(3.8)	1,772	(4.5)	461	(5.5)
20-29	74,788	(46.7)	21,379	(54.8)	5,303	(62.9)
>= 30	79,189	(49.5)	15,860	(40.7)	2,662	(31.6)
Maternal education						
Less than high school	19,750	(12.3)	5,996	(15.4)	1,739	(20.6)
High school or equivalent	35,196	(22.0)	11,428	(29.3)	3,027	(35.9)
Some college	37,649	(23.5)	10,934	(28.0)	2,421	(28.7)
College graduate	67,406	(42.1)	10,653	(27.3)	1,239	(14.7)
Metropolitan area						
>= 1mile	85,355	(53.4)	20,246	(51.9)	4,296	(51.0)
250,000- 1 mile	46,115	(28.8)	11,406	(29.2)	2,454	(29.1)
< 250,000	28,531	(17.8)	7,359	(18.9)	1,676	(19.9)
Neighborhood (% of Black)						
Lowest	57,283	(35.8)	12,728	(32.6)	2,459	(29.2)
Middle	59,299	(37.1)	12,668	(32.5)	2,376	(28.2)
Highest	43,419	(27.1)	13,615	(34.9)	3,591	(42.6)
Prepregnancy DM						
No	159,547	(99.7)	38,828	(99.5)	8,373	(99.4)
Yes	454	(0.3)	183	(0.5)	53	(0.6)
Prepregnancy HTN						
No	159,187	(99.5)	38,653	(99.1)	8,234	(97.7)
Yes	814	(0.5)	358	(0.9)	192	(2.3)
Prepregnancy smoking						
Non-smoker	131,100	(81.8)	30,592	(78.4)	6,282	(74.6)
Very light	7,852	(4.9)	2,495	(6.4)	612	(7.3)
10-<20	8,639	(5.4)	2,505	(6.4)	616	(7.3)
>=20	12,510	(7.8)	3,419	(8.8)	916	(10.9)
Insurance						
Non-private	53,279	(33.3)	16,849	(43.2)	4,734	(56.2)
Private	106,722	(66.7)	22,162	(56.8)	3,692	(43.8)
Marital status						
Unmarried	45,542	(28.5)	15,342	(39.3)	4,349	(51.6)
Married	114,459	(71.5)	23,669	(60.7)	4,077	(48.4)
Inter-pregnancy interval						
< 18 months	101,450	(63.4)	26,480	(67.9)	6,145	(72.9)
>= 18 months	58,551	(36.6)	12,531	(32.1)	2,281	(27.1)

Table 5. Risk difference and ratios of stillbirth and infant mortality by prepregnancy BMI category

BMI category	Event	Population at risk	Risk difference (95% CI)[a]	Risk ratio (95% CI)
Stillbirth				
Under weight	28	4891	2.4 (-0.1, 4.9)	1.86 (1.15, 3.03)
Normal weight	388	144,366	reference	reference
Overweight	160	35,834	1.4 (0.6, 2.2)	1.48 (1.21, 1.82)
Obesity	60	7,850	4.0 (1.4, 6.6)	2.40 (1.62, 3.56)
Infant mortality				
Under weight	30	5,451	-0.2 (-2.2, 2.2)	1.00 (0.62, 1.60)
Normal weight	719	160,001	reference	reference
Overweight	189	39,011	-0.1 (-0.9, 0.7)	0.97 (0.82, 1.16)
Obesity	64	8,426	2.0 (-0.4, 4.5)	1.43 (0.99, 2.06)
Neonatal mortality				
Under weight	19	5451	0.4 (-1.5, 2.2)	1.13 (0.63, 2.02)
Normal weight	436	160,001	reference	reference
Overweight	115	39,011	-0.1 (-0.7, 0.6)	0.97 (0.77, 1.22)
Obesity	48	8,426	2.3 (0.1, 4.5)	1.81 (1.18, 2.77)
Postneonatal mortality				
Under weight	11	5,432	-0.3 (-1.6, 1.0)	0.84 (0.38, 1.87)
Normal weight	283	159.565	reference	reference
Overweight	74	38,896	-0.1 (-0.6, 0.4)	0.96 (0.73, 1.28)
Obesity	16	8,378	-0.2 (-0.0, 0.9)	0.85 (0.40, 1.79)

[a.] Risk difference: per 1000 live births (or pregnancies)

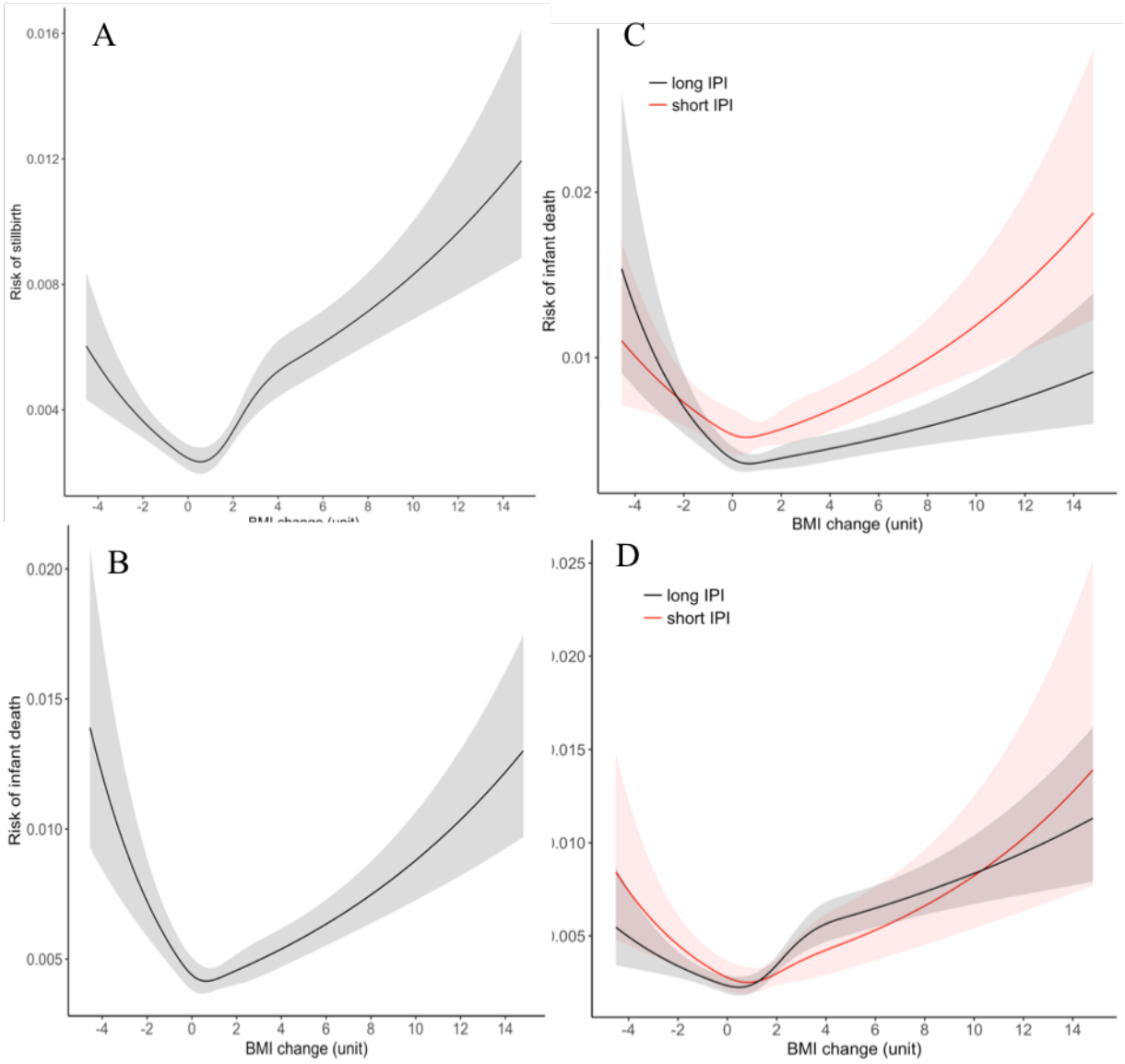


Figure 5. Interpregnancy BMI changes and risk of stillbirth and infant mortality

6.0 SYNTHESIS

6.1 SUMMARY OF FINDINGS

The main objective of this dissertation is to advance our understanding and address methodological challenges in estimating this association of newly-developed obesity prior pregnancy on the risk of stillbirth and infant mortality. Our analytic cohort was constructed from a population-based cohort study linking birth and infant/fetal death records in Pennsylvania from 2003-2013 (n=1,551,919 singleton pregnancies). All the analyses were performed in a cohort of multiparous women who were non-obese in their first pregnancy.

Our findings for each specific aim were summarized as follows:

Aim 1. To develop an algorithm to visualize the impact of the bias-variance tradeoff for each confounder, and the effect on the estimate of interest and propensity score overlap

By applying our SAS macro to an empirical study examining the association of incident prepregnancy obesity and stillbirth, among 36 confounders, we identified two confounders (prior prepregnancy BMI and prior gestation weight gain) that had high impact on the MSE of the risk ratio of stillbirth. After removing these two high-impact confounders, MSE decreased and propensity score overlap was improved. Our results suggest careful consideration of the analytic impact of all confounders should be made when fitting inverse probability weighting estimators.

Aim 2. To explore the extent to which parametric models may have different estimates of the association of incident prepregnancy obesity with stillbirth and infant mortality when compared to more nonparametric methods.

We applied several methods with difference reliance on parametric assumptions (non-parametric, semiparametric, and parametric) to estimate the relationship between incident obesity with stillbirth and infant mortality. We identified consistently increased risk of stillbirth among women who became obese compared to those who stayed non-obese. Discrepancies between methods in terms of magnitude were found: Risk differences from IPW and nonparametric TMLE were larger than those from parametric g computation method and parametric TMLE. Our results suggest incident obesity increased risk of stillbirth, while parametric assumptions can play an important role in influencing estimates of this relationship.

Aim 3. To evaluate the relation of newly-developed pre-pregnancy overweight and obesity with stillbirth and infant mortality of second pregnancies.

We applied nonparametric TMLE to estimate the relationship of newly-developed overweight/obese with stillbirth and infant mortality of second pregnancies among a cohort of women who were normal weight at their first pregnancies. Our results showed women becoming overweight had increased risks of stillbirth while those became obese had increased risk of both stillbirth and neonatal mortality at the second pregnancy. A dose-response relationship showed that at values greater than 2 units of BMI change, increasing BMI change was associated with

increased risk of stillbirth and infant mortality. In addition, short interpregnancy interval and greater BMI changes between pregnancies synergistically increased risk of infant mortality.

6.2 STRENGTHS AND LIMITATIONS

Given all of the careful considerations in our approach, we were also aware that the findings should be interpreted with respect to the following limitations.

6.2.1 Aim 1

Our visualization tool was designed to only exclude one confounder at a time; we also did not impose a functional form on these covariates or include interaction terms in the propensity score models. We cannot guarantee that this simplified algorithm can reflect the true relationships between confounders and the exposure in the model. Furthermore, our assessment of the impact of each confounder on the point estimate might conflict with the purpose of the propensity score as a "design" phase tool[15]. However, our tool addressing the issue of selection of variables for propensity scores plays important roles in obtaining unbiased and efficient estimates[16]. Our tool is user-friendly for visually detecting the impact of each confounder on the point estimates as well as propensity score distributions. It is especially useful for identifying extreme violations of the positivity assumption.

6.2.2 Aim 2 and 3

BMI measurements in our study were calculated from self-reported weight and height which may subject to misclassification. However, a previous study using the same cohort showed that after accounting for misclassification, the association between prepregnancy BMI and infant mortality did not have a meaningful difference. In addition, BMI were only available at the start of each pregnancy. Women who were normal weight in their first pregnancy may have had a history of obesity, for which could not be accounted.

In order to estimate the effect of newly-developed obesity and bounded onset of obesity in a known interval, we restricted women who had at least two pregnancies and were normal weight at their first pregnancy. By doing so, we clearly defined our exposure of interest at the price of decreasing generalizability. Since obesity is associated with suboptimal fertility, women who became infertile due to obesity cannot be identified by our study design. Also, the risk factors for developing obesity after experiencing pregnancy may be different from those who became obese without experiencing pregnancy. We need to be mindful of generalizing our results to these different populations.

Although we addressed two important challenges encountered when estimating the effect of obesity, the relationships identified in our study still may not be interpreted as causal effect. There are several approaches can alter women's BMI status, such as diet, physical activity or bariatric surgery. Each of these methods may have different impacts on stillbirth and infant mortality. Our dataset did not have sufficient information in determining the cause of developing obesity, therefore, it limited our ability to interpret results as causation.

Nevertheless, PennMOMs study provided a unique opportunity for us to explore this complex relationship of developing obesity with stillbirth and infant mortality. Using a 10-year

study period, we were able to study these rare outcomes. Linkage of women across pregnancies allowed us to observe BMI status changes over time and account for the potential confounding effects from prior pregnancies. Our utilization of causal diagrams in depicting our conceptual framework enabled us to identify sufficient confounders in estimating less-biased relationships. Our findings that becoming obese increased risk of stillbirth were based on robust estimates from different analytic approaches and generated consistent results.

6.3 PUBLIC HEALTH IMPLICATIONS

6.3.1 Clinical Application

Relatively high stillbirth rate and infant mortality are still of public health concern in the United States, compared to other similar countries. Experiencing perinatal death casts substantial impacts on the well-being of families as well as increased risk of recurrent adverse pregnancy outcomes for mothers. It is essential to identify modifiable risk factors, such as maternal obesity, to explain excess stillbirth and infant mortality in the U.S. With the obesity epidemic among women of childbearing age in the U.S, this is an important and logical area of study.

Our findings contribute to this important field by providing the further evidence that transitioning from normal weight to overweight or obese increases risk of stillbirth and infant mortality. The risk increased with average interpregnancy weight gain of, for example, 5 kg or more for women with a height of 160 cm. Based on our findings, health care providers can communicate and emphasize the importance of weight maintenance with women at prepregnancy normal weight, especially for those who were on the upper limit of normal weight category. These

are great and effective opportunities for preventing the onset of obesity, and particularly since women access health care more often during pregnancy, in addition to the added incentive for seeking healthy lifestyle at this time.

6.3.2 Research application

The perfect study for quantifying the effect of exposure would be a randomized trial with full compliance of participants. We would simply contrast the event rates between two groups as the effect of exposure. However, when randomizing an exposure is implausible, such as the case of obesity, several barriers need to be addressed in observational studies in order to estimate the effect of exposure. The study results demonstrated that using nonparametric approaches for controlling confounding generated different magnitude of associations, when compared to universally practiced parametric approaches. Providing unbiased effect estimates are crucial to inform clinical practice of health care providers, and which have overarching implications on policy development. The demonstration of our nonparametric results may contribute to the evidence for the importance of careful consideration of analytic method selections, and to show future investigations that the conventional method is not always most appropriate

6.4 FUTURE RESEARCH

The mechanisms of how prepregnancy obesity increases risks of stillbirth and infant mortality remain largely unknown. Therefore, more efforts are needed to identify potential pathways between prepregnancy obesity and both of these outcomes. Mediation analysis can be utilized to

examine the contributions from each potential mediator (e.g. fetal growth, gestational age) on explaining the association of prepregnancy obesity with stillbirth and infant mortality. Clarifying this mechanism will help us to develop effective interventions for preventing stillbirth and infant mortality among women with prepregnancy obesity.

Studies focusing on the causes for transitioning from normal weight to overweight or obesity are needed for better preventing the onset of maternal obesity. Several plausible reasons can be examined, such as parity, excess gestational weight gain, or postpartum weight retention. Analyzing these factors would be especially beneficial in the long run since literature showed children born to mothers with obesity are at risk of developing future obesity. Preventing the onset of maternal obesity can break the intergenerational pattern of obesity.

Our study focused on quantifying the association of newly-developed prepregnancy obesity with stillbirth and infant mortality among multiparous women. However, the causes of becoming obese may be different between nulliparous and multiparous women. In this case, future studies can further examine the impact of newly-developed prepregnancy obesity on pregnancy outcomes among nulliparous women. In addition, studies using longitudinal BMI measurements throughout reproductive age are needed for better definition and answering the impact of obesity duration on pregnancy outcomes.

Finally, our research demonstrated the application of a complex machine learning algorithm with the purpose of minimizing residual confounding. With the increasing popularity of utilizing machine learning algorithms in the epidemiology field, we need to enhance our understanding on how these algorithms work. For example, there is a need for evaluation of the importance of each covariate to the prediction of an outcome; it is also crucial to diagnose whether

the algorithms perform well. It is of utmost importance to have more published studies focusing on the translating the knowledges between statistics, computer science with epidemiology.

APPENDIX A: CONCEPTUAL FRAMEWORK

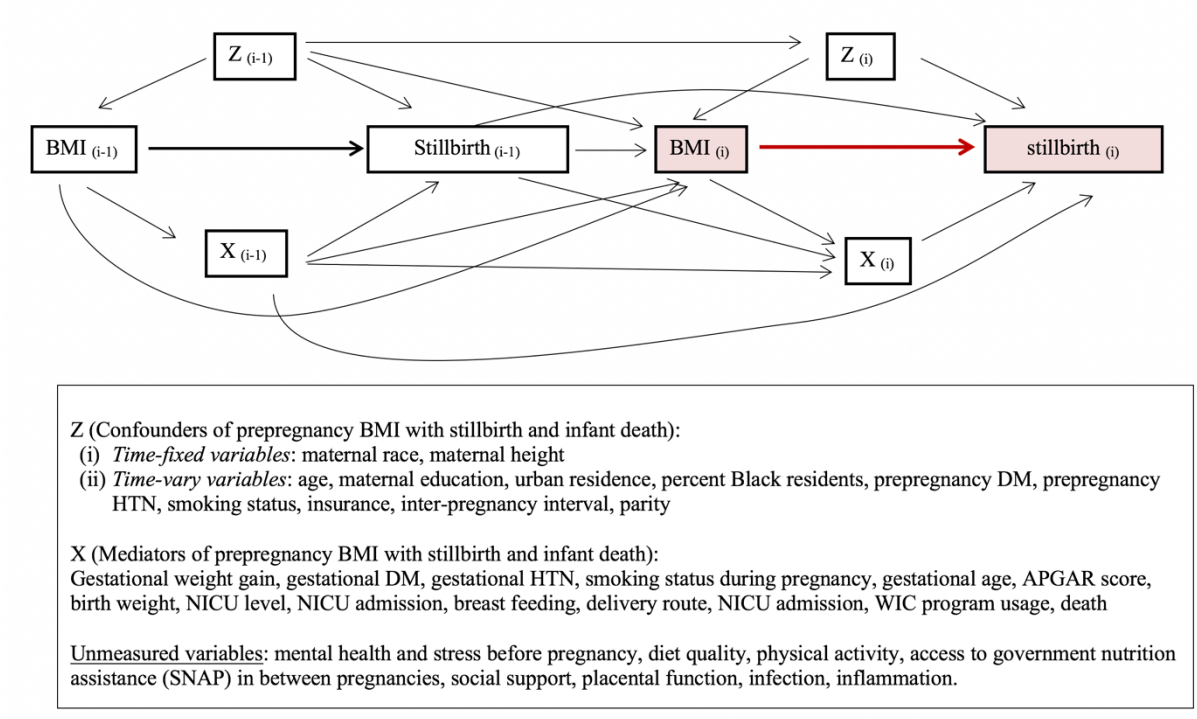


Figure 5. Causal diagram representing the relationship of prepregnancy BMI with stillbirth and infant death at the ith pregnancy

APPENDIX B: PAPER 1 SUPPLEMENTARY MATERIALS

Process of data linkage

We extensively cleaned the data to eliminate duplicate records and to identify and correctly match up twins and higher order gestations from the same pregnancy. When potential duplicate records matched on several mother characteristics (including baby's date of birth, mother's name, mother's date of birth, etc.) but had discrepant baby information (birthweight, sex, etc.), they were recoded as twins. We also created a unique maternal ID to identify repeat pregnancies from the same mother over time using a sequential, deterministic linkage strategy (Blakely & Salmond 2002; Herman et al. 1997). The records were separated into batches by delivery year and then further into sub-groups by year of last live birth. These subgroups were then merged with birth records from the year indicated as the year of the last live birth. For instance, the 2011 batch of delivery records with 2010 listed as year of last live birth could potentially link with the 2010 delivery records to identify the sibling. Special consideration was given to the potential for two babies delivered to the same mother in the same calendar year, either due to multiple births, or one sibling delivered early in the calendar year and one at the end. Several attempts at linking with maternal identifiers took place for each batch, and additional maternal variables were used to validate the matches, with discrepancies manually checked and corrected. Any false positive matches identified through discrepant validation variables were recoded as unmatched. At the end of the process, 57% of the birth and fetal death records were linked with at least one sibling. Among those who could not be linked, 58% were the first birth for the woman or were missing information on year of previous last live birth and 38% had a last live birth from prior to 2003, and thus could not be linked.

Blakely, T. and C. Salmond (2002). Probabilistic record linkage and a method to calculate the positive predictive value. Int J Epidemiol 31(6): 1246-1252.

Herman, A. A., et al. (1997). "Data linkage methods used in maternally-linked birth and infant death surveillance data sets from the United States (Georgia, Missouri, Utah and Washington State), Israel, Norway, Scotland and Western Australia." Paediatr Perinat Epidemiol 11 Suppl 1: 5-22.

Example of output from SuperLearner algorithm

Initial estimation of Q

Procedure: SuperLearner

Model:

Y ~ SL.mean_All + SL.nnet_All + SL.earth_All + SL.ranger_All + SL.xgboost_All + SL.glmnet_0_All + SL.glmnet_0.25_All + SL.glmnet_0.5_All + SL.glmnet_0.75_All + SL.glmnet_1_All + SL.gam_3_All + SL.gam_4_All + SL.xgb.1_All + SL.xgb.2_All + SL.xgb.3_All + SL.xgb.4_All + SL.xgb.5_All + SL.xgb.6_All + SL.xgb.7_All + SL.xgb.8_All + SL.xgb.9_All + SL.xgb.10_All + SL.xgb.11_All + SL.xgb.12_All + SL.ranger_500_2_All + SL.ranger_1000_2_All + SL.ranger_500_5_All + SL.ranger_1000_5_All + SL.ranger_500_11_All + SL.ranger_1000_11_All + SL.glm.interaction_All

Coefficients:

SL.mean_All 0

SL.nnet_All 0

SL.earth_All 0

SL.ranger_All 0

SL.xgboost_All 0.2937091

SL.glmnet_0_All 0.1466514

SL.glmnet_0.25_All 0

SL.glmnet_0.5_All 0

SL.glmnet_0.75_All 0

SL.glmnet_1_All 0

SL.gam_3_All 0

SL.gam_4_All 0

SL.xgb.1_All 0

SL.xgb.2_All 0

SL.xgb.3_All 0.1847042

SL.xgb.4_All 0.125794

SL.xgb.5_All 0

SL.xgb.6_All 0

SL.xgb.7_All 0

SL.xgb.8_All 0

SL.xgb.9_All 0

SL.xgb.10_All 0

SL.xgb.11_All 0

SL.xgb.12_All 0

SL.ranger_500_2_All 0.1219778

SL.ranger_1000_2_All 0

SL.ranger_500_5_All 0

SL.ranger_1000_5_All 0

SL.ranger_500_11_All 0.1113301

SL.ranger_1000_11_All 0

SL.glm.interaction_All 0.0158334

Estimation of g (treatment mechanism)

Procedure: SuperLearner

Model:

A ~ SL.mean_All + SL.nnet_All + SL.earth_All + SL.ranger_All + SL.xgboost_All + SL.glmnet_0_All + SL.glmnet_0.25_All + SL.glmnet_0.5_All + SL.glmnet_0.75_All + SL.glmnet_1_All + SL.gam_3_All + SL.gam_4_All + SL.xgb.1_All + SL.xgb.2_All + SL.xgb.3_All + SL.xgb.4_All + SL.xgb.5_All + SL.xgb.6_All + SL.xgb.7_All + SL.xgb.8_All + SL.xgb.9_All + SL.xgb.10_All + SL.xgb.11_All + SL.xgb.12_All + SL.ranger_500_2_All + SL.ranger_1000_2_All + SL.ranger_500_5_All + SL.ranger_1000_5_All + SL.ranger_500_11_All + SL.ranger_1000_11_All + SL.glm.interaction_All

Coefficients:

SL.mean_All 0

SL.nnet_All 0

SL.earth_All 0

SL.ranger_All 0

SL.xgboost_All 1

SL.glmnet_0_All 0

SL.glmnet_0.25_All 0

SL.glmnet_0.5_All 0

SL.glmnet_0.75_All 0

SL.glmnet_1_All 0

SL.gam_3_All 0

SL.gam_4_All 0

SL.xgb.1_All 0

SL.xgb.2_All 0

SL.xgb.3_All 0

SL.xgb.4_All 0

SL.xgb.5_All 0

SL.xgb.6_All 0

SL.xgb.7_All 0

SL.xgb.8_All 0

SL.xgb.9_All 0

SL.xgb.10_All 0

SL.xgb.11_All 0

SL.xgb.12_All 0

SL.ranger_500_2_All 0

SL.ranger_1000_2_All 0

SL.ranger_500_5_All 0

SL.ranger_1000_5_All 0

SL.ranger_500_11_All 0

SL.ranger_1000_11_All 0

SL.glm.interaction_All 0

Estimation of g.Z (intermediate variable assignment mechanism)

Procedure: No intermediate variable

Estimation of g.Delta (missingness mechanism)

Procedure: No missingness

Bounds on g: (0.025 0.975)

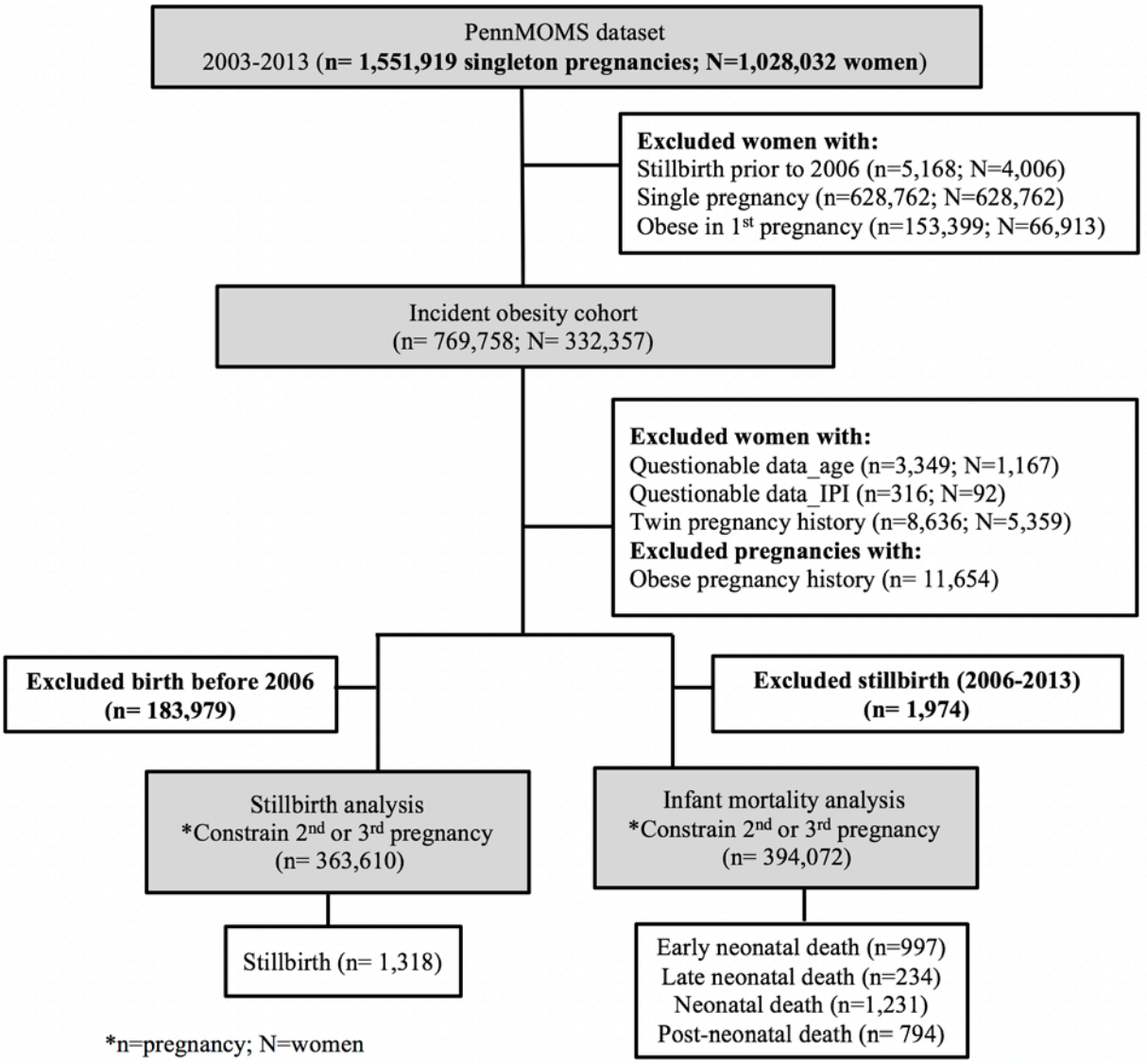


Figure 6. Flow chart of analytic sample selection for paper 1

Table 6. Characteristics of Last Pregnancy in Non-obese vs. Obese, Infant Mortality Analysis (2003-2013)

	Non-obese N (%) (n=354,079)		Obese N (%) (n=39,993)	
Gestational weight gain z-score (percentile)				
<= 20th	60,691	(17.1)	4,451	(11.1)
20th -80th	247,309	(69.9)	25,256	(63.2)
>= 80th	46,079	(13.0)	10,286	(25.7)
Gestational diabetes				
No	345,581	(97.6)	38,471	(96.2)
Yes	8,498	(2.4)	1,522	(3.8)
Gestational hypertension				
No	342,726	(96.8)	37,646	(94.1)
Yes	11,353	(3.2)	2,347	(5.9)
Smoke during pregnancy				
No	298,101	(84.2)	32,411	(81.1)
Yes	55,978	(15.8)	7,582	(19.0)
Birth facility level of neonatal care				
Level 1	67,735	(19.1)	8,908	(22.3)
Level 2 or 2A	57,769	(16.3)	5,923	(14.8)
Level 3 or 3A/3B/3C	228,575	(64.6)	25,162	(62.9)
Women, Infants, and Children program usage				
No	230,962	(65.2)	20,020	(50.1)
Yes	123,117	(34.8)	19,973	(49.9)
Death				
Live birth	350,464	(99.0)	39,411	(98.5)
Infant death	2,571	(0.7)	417	(1.0)
Fetal death	1,044	(0.3)	167	(0.4)
Preterm birth				
No	301,624	(85.2)	33,890	(84.7)
Yes	52,455	(14.8)	6,103	(15.3)
Small for gestational age				
No	332,438	(93.9)	37,890	(94.7)
Yes	21,641	(6.1)	2,103	(5.3)
Large for gestational age				
No	302,333	(85.4)	32,156	(80.4)
Yes	51,746	(14.6)	7,837	(19.6)
Prepregnancy BMI				
Underweight	23,905	(6.8)	523	(1.3)
Normal weight	251,501	(71.0)	9,732	(24.4)
Overweight	78,673	(22.2)	29,738	(74.4)
Breastfeeding				
No	113,725	(32.1)	15,915	(39.8)
Yes	240,354	(67.9)	24,078	(60.2)
Delivery route				
Vaginal	279,457	(78.9)	29,054	(72.7)
Planned cesarean	38,018	(10.7)	5,097	(12.7)
Unplanned cesarean	36,604	(10.3)	5,842	(14.6)

Table 7. Characteristics of Non-obese vs. Incident Obese Pregnancies for Stillbirth Analysis (2006-2013)

	Non-obese N (%) (n=326,179)		Obese N (%) (n=37,432)	
Maternal race				
Non-Hispanic White	244,918	(75.1)	24,837	(66.4)
Non-Hispanic Black	39,912	(12.2)	7,643	(20.4)
Hispanic	26,171	(8.0)	4,012	(10.7)
Others	15,177	(4.7)	940	(2.5)
Maternal age (year)				
<= 20	10,531	(3.2)	1,270	(3.4)
20-29	160,717	(49.3)	21,615	(57.7)
>= 30	154,930	(47.5)	14,547	(38.9)
Maternal education				
Less than high school	47,574	(14.6)	6,179	(16.5)
High school or equivalent	80,504	(24.7)	12,456	(33.3)
Some college	80,448	(24.7)	11,273	(30.1)
College graduate	117,652	(36.1)	7,524	(20.1)
Metropolitan area				
>= 1mile	169,994	(52.1)	18,729	(50.0)
250,000- 1 mile	95,344	(29.2)	10,899	(29.1)
< 250,000	60,840	(18.7)	7,804	(20.9)
Neighborhood (% of Black)				
Lowest	111,964	(34.3)	11,470	(30.6)
Middle	115,208	(35.3)	11,076	(29.6)
Highest	99,006	(30.4)	14,886	(39.8)
Prepregnancy diabetes				
No	324,933	(99.6)	37,078	(99.1)
Yes	1,245	(0.4)	354	(0.9)
Prepregnancy hypertension				
No	323,724	(99.3)	36,548	(97.6)
Yes	2,454	(0.7)	884	(2.4)
Prepregnancy smoking				
Non-smoker	259,755	(79.6)	28,674	(76.6)
Very light	18,023	(5.5)	2,565	(6.9)
10-<20	19,591	(6.0)	2,510	(6.7)
>=20	28,809	(8.8)	3,683	(9.8)
Insurance				
Non-private	127,233	(39.0)	18,653	(49.8)
Private	198,945	(61.0)	18,779	(50.2)
Marital status				
Unmarried	106,304	(32.6)	16,625	(44.4)
Married	219,874	(67.4)	20,807	(55.6)
Inter-pregnancy interval				
< 18 months	217,048	(66.5)	27,178	(72.6)
>= 18 months	109,130	(33.5)	10,254	(27.4)

Table 8. Characteristics of Last Pregnancy Among Non-obese vs. Obese for Stillbirth Analysis (2006-2013)

	Non-obese N (%) (n=326,178)		Obese N (%) (n=37,432)	
Gestational weight gain z-score (percentile)				
<= 20th	55,694	(17.1)	4,176	(11.2)
20th -80th	228,027	(69.9)	23,681	(63.3)
>= 80th	42,457	(13.0)	9,575	(25.6)
Gestational diabetes				
No	318,319	(97.6)	36,007	(96.2)
Yes	7,859	(2.4)	1,425	(3.8)
Gestational hypertension				
No	315,613	(96.8)	35,217	(94.1)
Yes	10,565	(3.2)	2,215	(5.9)
Smoke during pregnancy				
No	247,937	(84.3)	30,370	(81.1)
Yes	51,241	(15.7)	7,062	(18.9)
Birth facility level of neonatal care				
Level 1	61,729	(18.9)	8,287	(22.1)
Level 2 or 2A	53,379	(16.4)	5,535	(14.8)
Level 3 or 3A/3B/3C	211,070	(64.7)	23,610	(63.1)
Women, Infants, and Children program usage				
No	211,911	(65.0)	18,575	(49.6)
Yes	114,267	(35.0)	18,857	(50.4)
Death				
Live birth	322,881	(99.0)	36,893	(98.6)
Infant death	2,224	(0.7)	368	(1.0)
Fetal death	1,073	(0.3)	171	(0.5)
Preterm birth				
No	276,990	(84.9)	31,598	(84.4)
Yes	49,188	(15.1)	5,834	(15.6)
Small for gestational age				
No	297,932	(91.3)	34,256	(91.5)
Yes	28,246	(8.7)	3,176	(8.5)
Large for gestational age				
No	291,942	(89.5)	32,323	(86.4)
Yes	34,236	(10.5)	5,109	(13.7)
Prepregnancy BMI				
Underweight	21,942	(6.7)	479	(1.3)
Normal weight	232,006	(71.1)	9,166	(24.5)
Overweight	72,230	(22.1)	27,787	(74.2)
Breastfeeding				
No	103,311	(31.7)	14,747	(39.4)
Yes	222,867	(68.3)	22,685	(60.6)
Delivery route				
Vaginal	256,401	(78.6)	27,087	(72.4)
Planned cesarean	35,609	(10.9)	4,826	(12.9)
Unplanned cesarean	34,168	(10.5)	5,519	(14.7)

APPENDIX C: PAPER 2 SUPPLEMENTAL MATERIALS

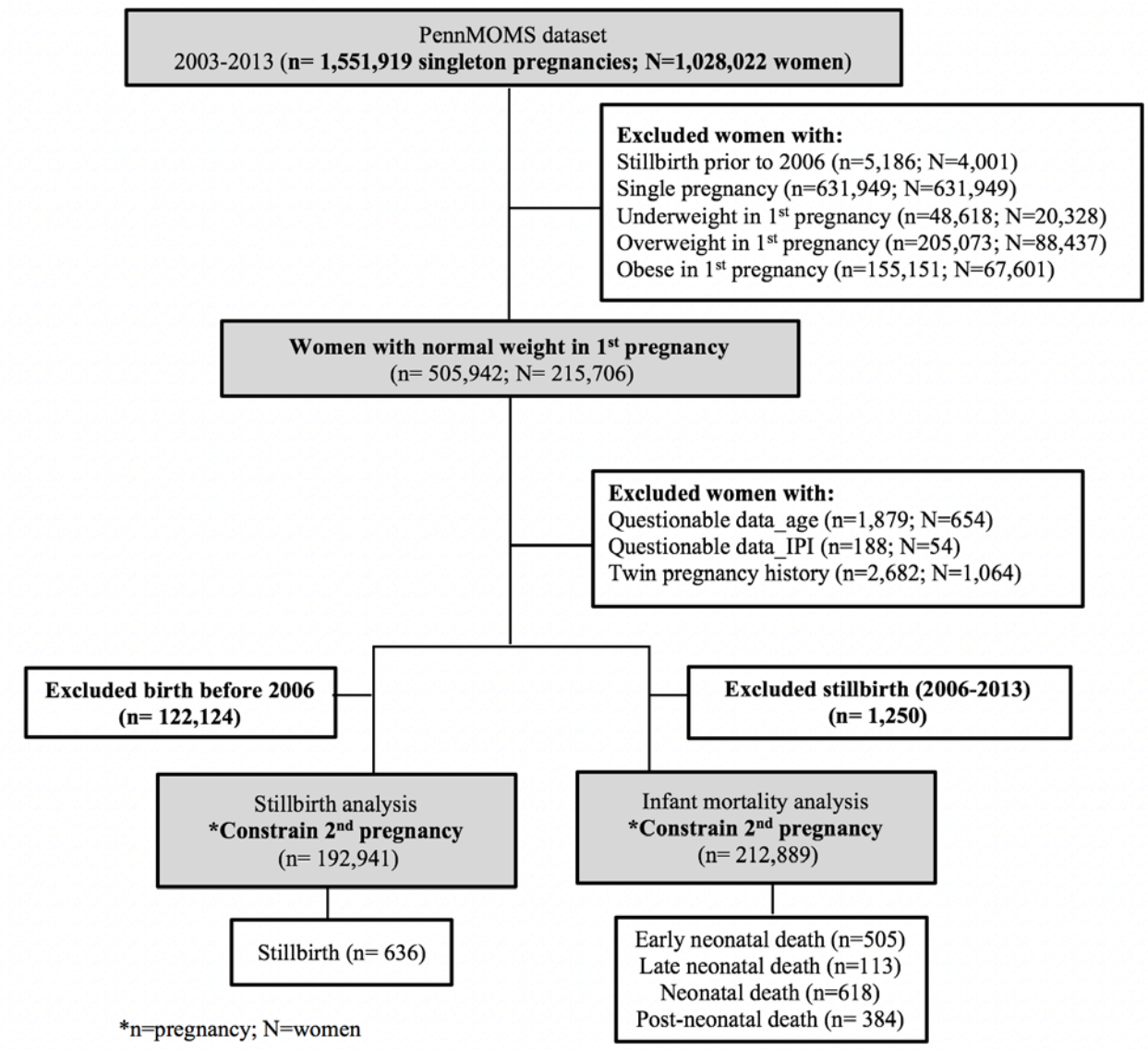


Figure 7. Flow chart of analytic sample selection for paper2

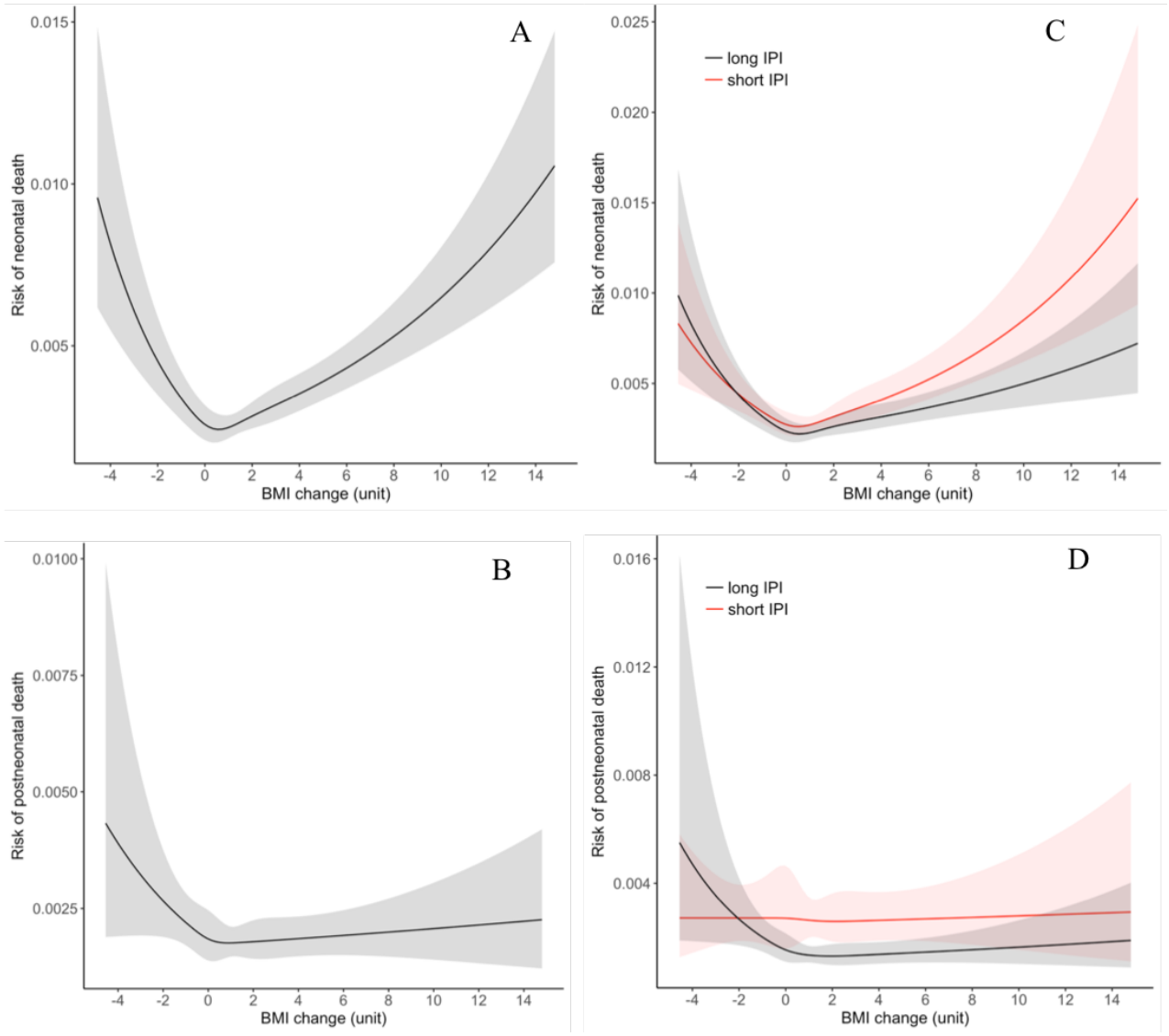


Figure 8. Interpregnancy BMI changes and risk of neonatal and postneonatal death

Table 9. Characteristics of last pregnancy among normal weight, incident overweight and incident obese pregnancies for infant mortality analysis (2003-2013)

	Normal weight N (%) (n=160,001)		Overweight N (%) (n=39,011)		Obesity N (%) (n=8,426)	
GWG z-score (percentile)						
<= 20th	26,525	(16.6)	4,612	(11.8)	977	(11.6)
20th -80th	114,056	(71.3)	24,098	(61,8)	4,296	(51.0)
>= 80th	19,420	(12.1)	10,301	(26.4)	3,153	(37.4)
Gestational DM						
No	156,733	(98.0)	37,960	(97.3)	8,205	(97.4)
Yes	3,268	(2.0)	1,051	(2.7)	221	(2.6)
Gestational HTN						
No	155,161	(97.0)	37,312	(95.6)	7,969	(94.6)
Yes	4,840	(3.0)	1,699	(4.4)	457	(5.4)
Smoke during pregnancy						
No	137,745	(86.1)	32,536	(83.4)	6,648	(78.9)
Yes	22,256	(13.9)	6,475	(16.6)	1,778	(21.1)
NICU level						
Level 1	29,667	(18.5)	7,994	(20.5)	1,863	(22.1)
Level 2 or 2A	27,204	(17.0)	6,126	(15.7)	1,200	(14.2)
Level 3 or 3A/3B/3C	103,130	(64.5)	24,891	(63.8)	5,363	(63.6)
WIC usage						
No	111,481	(69.7)	22,153	(56.8)	3,682	(43.7)
Yes	48,520	(30.3)	16,858	(43.2)	4,744	(56.3)
Death						
Live birth	158,810	(99.1)	38,642	(99.1)	8,278	(98.3)
Infant death	951	(0.6)	285	(0.7)	105	(1.3)
Fetal death	240	(0.2)	84	(0.2)	43	(0.5)
Preterm birth						
No	136,979	(85.6)	33,206	(85.1)	7,108	(84.4)
Yes	23,022	(14.4)	5,805	(14.9)	1,318	(15.6)
SGA						
No	145,798	(91.1)	35,708	(91.5)	7,592	(90.1)
Yes	14,203	(8.9)	3,303	(8.5)	834	(9.9)
LGA						
No	145,232	(90.8)	34,771	(89.1)	7,489	(88.9)
Yes	14,769	(9.2)	4,240	(10.9)	937	(11.1)
Breastfeeding						
No	46,243	(28.9)	13,854	(35.5)	3,758	(44.6)
Yes	113,758	(71.1)	25,157	(64.5)	4,668	(55.4)
Delivery route						
Vaginal	127,135	(79.5)	29,835	(76.5)	6,331	(75.1)
Planned cesarean	14,760	(9.2)	3,835	(9.8)	892	(10.6)
Unplanned cesarean	18,106	(11.3)	5,341	(13.7)	1,203	(14.3)
Low APGAR score						
No	158,550	(99.1)	38,571	(98.9)	8,264	(98.1)
Yes	1,451	(0.9)	440	(1.13)	162	(1.9)

Table 10. Characteristics of normal weight, incident overweight and incident obese pregnancies for stillbirth analysis (2006-2013)

	Normal weight N (%) (n=144,366)		Overweight N (%) (n=35,834)		Obesity N (%) (n=7,850)	
Maternal race						
NH White	112,806	(78.1)	24,762	(69.1)	4,899	(62.4)
NH Black	13,958	(9.7)	5,737	(16.0)	1,720	(21.9)
Hispanic	10,063	(7.0)	3,800	(10.6)	990	(12.6)
Others	7,539	(5.2)	1,535	(4.3)	241	(3.1)
Maternal age (year)						
<= 20	5,087	(3.5)	1,500	(4.2)	405	(5.2)
20-29	67,211	(46.6)	19,562	(54.6)	4,940	(62.9)
>= 30	72,068	(49.9)	14,772	(41.2)	2,505	(31.9)
Maternal education						
Less than high school	16,828	(11.7)	5,194	(14.5)	1,538	(19.6)
High school or equivalent	31,726	(22.0)	10,560	(29.5)	2,857	(36.4)
Some college	34,493	(23.9)	10,190	(28.4)	2,294	(29.2)
College graduate	61,319	(42.5)	9,890	(27.6)	1,161	(14.8)
Metropolitan area						
>= 1mile	76,988	(53.3)	18,658	(52.1)	4,011	(51.1)
250,000- 1 mile	41,645	(28.9)	10,479	(29.4)	2,285	(29.1)
< 250,000	25,733	(17.8)	6,697	(18.7)	1,154	(19.8)
Neighborhood (% of Black)						
Lowest	50,885	(35.3)	11,476	(32.0)	2,247	(28.6)
Middle	54,060	(37.5)	11,745	(32.8)	2,219	(28.3)
Highest	39,421	(27.3)	12,613	(35.2)	3,384	(43.1)
Prepregnancy DM						
No	143,945	(99.7)	35,662	(99.5)	7,797	(99.3)
Yes	421	(0.3)	172	(0.5)	53	(0.7)
Prepregnancy HTN						
No	143,594	(99.5)	35,493	(99.1)	7,666	(97.7)
Yes	772	(0.5)	341	(0.9)	184	(2.3)
Prepregnancy smoking						
Non-smoker	118,285	(81.9)	28,093	(78.4)	5,863	(74.7)
Very light	7,114	(4.9)	2,305	(6.4)	574	(7.3)
10-<20	7,822	(5.4)	2,310	(6.5)	564	(7.2)
>=20	11,145	(7.7)	3,126	(8.7)	849	(10.8)
Insurance						
Non-private	47,795	(33.1)	15,391	(43.0)	4,400	(56.0)
Private	96,571	(66.9)	20,443	(57.1)	3,450	(44.0)
Marital status						
Unmarried	41,519	(28.8)	14,232	(39.7)	4,088	(52.1)
Married	102,847	(71.2)	21,602	(60.3)	3,762	(47.9)
Inter-pregnancy interval						
< 18 months	97,857	(67.8)	25,898	(72.7)	6,053	(77.1)
>= 18 months	46,509	(32.2)	9,936	(27.7)	1,797	(22.9)

Table 11. Characteristics of last pregnancy among normal weight, incident overweight and incident obese pregnancies for stillbirth analysis (2006-2013)

	Normal weight N (%) (n=144,366)		Overweight N (%) (n=35,834)		Obesity N (%) (n=7,850)	
GWG z-score (percentile)						
<= 20th	23,672	(16.4)	4,241	(11.8)	897	(11.4)
20th -80th	103,037	(71.4)	22,163	(61.9)	4,033	(51.4)
>= 80th	17,657	(12.2)	9,430	(26.3)	2,920	(37.2)
Gestational DM						
No	141,387	(97.9)	34,857	(97.3)	7,645	(97.4)
Yes	2,979	(2.1)	977	(2.7)	205	(2.6)
Gestational HTN						
No	139,923	(96.9)	34,224	(95.5)	7,416	(94.5)
Yes	4,443	(3.1)	1,610	(4.5)	434	(5.5)
Smoke during pregnancy						
No	124,466	(86.2)	29,950	(83.6)	6,196	(78.9)
Yes	19,900	(13.8)	5,884	(16.4)	1,654	(21.1)
NICU level						
Level 1	26,483	(18.3)	7,271	(20.3)	1,722	(21.9)
Level 2 or 2A	24,699	(17.1)	5,622	(15.7)	1,130	(14.4)
Level 3 or 3A/3B/3C	93,184	(64.6)	22,941	(64.0)	4,998	(63.7)
WIC usage						
No	100,130	(69.4)	20,191	(56.4)	3,363	(42.8)
Yes	44,236	(30.6)	15,643	(43.6)	4,487	(57.2)
Death						
Live birth	143,339	(99.3)	35,504	(99.1)	7,714	(98.3)
Infant death	778	(0.5)	243	(0.7)	92	(1.2)
Fetal death	249	(0.2)	87	(0.2)	44	(0.6)
Preterm birth						
No	123,732	(85.7)	30,462	(85.0)	6,620	(84.3)
Yes	20,634	(14.3)	5,372	(15.0)	1,230	(15.7)
SGA						
No	131,479	(91.1)	32,787	(91.5)	7,072	(90.1)
Yes	12,887	(8.9)	3,047	(8.5)	778	(9.9)
LGA						
No	131,197	(90.9)	31,961	(89.2)	6,996	(89.1)
Yes	13,169	(9.1)	3,873	(10.8)	854	(10.9)
Breastfeeding						
No	40,973	(28.4)	12,557	(35.0)	3,446	(43.9)
Yes	103,393	(71.6)	23,277	(65.0)	4,404	(56.1)
Delivery route						
Vaginal	114,145	(79.1)	27,258	(76.1)	5,861	(74.7)
Planned cesarean	13,418	(9.3)	3,573	(10.0)	849	(10.8)
Unplanned cesarean	16,803	(11.6)	5,003	(14.0)	1,140	(14.5)
Low APGAR score						
No	143,060	(99.1)	35,429	(98.9)	7,699	(98.1)
Yes	1,306	(0.9)	405	(1.1)	151	(1.9)

APPENDIX D: PAPER 3 SUPPLEMENTARY MATERIALS

SAS Macro

```
*******bias and variance trade-off for binary variabls (stablized weight and
single time point)*********;

%macro bias_var(data= ,catevar= ,convar= , exp= , outcome= ,id= );
************************STAGE 1: Exclude one categorical variable per
time**************************
*STEP 1: Create macro variables for model;
/*Keep this output and merge back to the final result by varnum, later we can
add label too*/
data &data.pre ;set &data;
      keep &catevar;
run;

proc contents data=&data.pre
      out = vars (keep = varnum name)
      noprint;
run;

proc sort data=vars; by varnum; run;

/*calculate the total number of categorical variables and save it as a global
macro variable*/
/*symputx can convert variable to string before assigning macro variable*/
/*when assigning file name, we need to use string*/
data _null_;
  set vars; by varnum;
  if last.varnum;
  call symput('number_cate',varnum);
  call symputx('number_cate2',varnum);
run;

%do i= 0 %to &number_cate;
%global var&i.;
Proc SQL noprint ;
      select distinct name into:var&i. separated by " "
      from vars
      where varnum^= &i;
Quit;

*STEP 2: IPW model (stablized weight for binary exposure and single time
point);
/*Marginal probability of being exposed*/
proc logistic data= &data desc noprint;
      model &exp= / maxiter=100;
      output out=&data.1 prob=m;run;
run;quit;run;
```

```
/*Propensity score*/
proc logistic data= &data.1 desc noprint;
      class &&var&i;
      model &exp= &&var&i &convar/ maxiter=100;
      output out=&data.1 prob=p;run;
run;quit;run;

/*Calculated stablized weights*/
data &data.1; set &data.1;
      if &exp=0 then do;
            weight=1/(1-p);
            sw=(1-m)/(1-p);
      end;
      else if &exp=1 then do ;
      weight=1/p;
    sw=m/p;
      end;
run;

*STEP 3: Creat dataset for PS overlapped plots (weight dataset: swvar&i, ps
dataset: pvar&i);
data swvar&i ;set &data.1;
      varnum=&i.;
      keep &exp p sw varnum;
run;

proc univariate data= &data.1 noprint;
      class &exp;
      var p;
      output out=psvar&i mean=mean median=median Q1=q1 Q3=q3 max=max min=min;
run;

data psvar&i ;set psvar&i;
      varnum=&i.;
run;

*STEP 4: outcome model;
*Outcome model (RD);
ods select none;
proc genmod data= &data.1 desc;
      ods output Estimates=RDvar&i;
      class &outcome &exp(ref="0")  &id ;
      model &outcome=  &exp / dist=bin link=identity;
      weight sw;
      repeated subject = &id / type=ind;
      estimate "overall"  &exp 1 -1  ;
run;
ods output close;

data RDvar&i; set RDvar&i;
      where Label="overall";
      Varname="var&i";
      keep Varname LBetaEstimate LBetaLowerCL LBetaUpperCL;
      rename LBetaEstimate=RD;
      rename LBetaLowerCL=LCI;
      rename LBetaUpperCL=UCI;
run;
```

```
*Outcome model (RR);
ods select none;
proc genmod data=&data.1 desc;
      ods output Estimates=RRvar&i;
      class &outcome  &exp(ref="0")  &id ;
      model &outcome= &exp / dist=bin link=logit;
      weight sw;
      repeated subject = &id / type=ind;
      estimate "overall"    &exp 1 -1 /EXP ;
run;
ods output close;

data RRvar&i; set RRvar&i;
      where Label="Exp(overall)";
      Varname="var&i";
      keep Varname LBetaEstimate LBetaLowerCL LBetaUpperCL StdErr ;
      rename LBetaEstimate=RR;
      rename LBetaLowerCL=LCI;
      rename LBetaUpperCL=UCI;
      rename StdErr=SE;
run;

%end;

*Step 5: Generate a dataset of combined estimates for plots;
*For outcome models;
data &outcome._RR;
      format varname $32.;
      set RRvar0-RRvar&number_cate2.;
run;
data &outcome._RD;
      format varname $32.;
      set RDvar0-RDvar&number_cate2.;
run;

*For IPW distribution;
data &outcome._SW;
      set swvar0-swvar&number_cate2.;
      varname=cats('var',varnum);
run;

*For PS distribution;
data &outcome._PS;
      set psvar0-psvar&number_cate2.;
      varname=cats('var',varnum);
run;

*Merge with variable names;
data vars1;set vars;
   length varname $32;
   varname=cats('var',varnum);
   drop varnum;
run;

proc sort data=vars1;by varname; run;
proc sort data= &outcome._rd;by varname;run;
```

```
proc sort data= &outcome._rr;by varname;run;
proc sort data= &outcome._sw;by varname;run;
proc sort data= &outcome._ps;by varname;run;

data &outcome._rd; merge vars1 &outcome._rd; by varname;if varname="var0"
then name="full";run;
data &outcome._rr; merge vars1 &outcome._rr; by varname;if varname="var0"
then name="full";run;
data &outcome._sw; merge vars1 &outcome._sw; by varname;if varname="var0"
then name="full";run;
data &outcome._ps; merge vars1 &outcome._ps; by varname;if varname="var0"
then name="full";run;


**********STAGE 2: Exclude one continuous variable per
time******************
*STEP 1: Create macro variables for model;
/*Keep this output and merge back to the final result by varnum, later we can
add label too*/
data &data.pre2 ;set &data;
      keep &convar;
run;

proc contents data=&data.pre2
      out = cvars (keep = varnum name)
      noprint;
run;

proc sort data=cvars; by varnum; run;

/*calculate the total number of categorical variables and save it as a global
macro variable*/
data _null_;
  set cvars; by varnum;
  if last.varnum;
  call symput('number_con',varnum);
  call symputx('number_con2',varnum);
run;

%do m=1 %to &number_con;
%global cvar&m.;
Proc SQL noprint ;
      select distinct name into:cvar&m. separated by " "
      from cvars
      where varnum^= &m.;
Quit;

*STEP 2: IPW model (stablized weight for binary exposure and single time
point);
/*Marginal probability of being exposed*/
proc logistic data= &data desc noprint;
      model &exp= / maxiter=100;
      output out= &data.2 prob=m;run;
run;quit;run;

/*Propensity score*/
proc logistic data= &data.2 desc noprint;
```

```
      class &catevar.;
      model &exp= &&cvar&m. &catevar./ maxiter=100;
      output out= &data.2 prob=p;run;
run;quit;run;

/*Calculated stablized weights*/
data &data.2; set &data.2;
      if &exp=0 then do;
            weight=1/(1-p);
            sw=(1-m)/(1-p);
      end;
      else if &exp=1 then do ;
      weight=1/p;
    sw=m/p;
      end;
run;

*STEP 3: Creat dataset for PS overlapped plots;
data swcvar&m ;set &data.2;
      varnum=&m.;
      keep &exp p sw varnum;
run;

proc univariate data= &data.2 ;
      class &exp;
      var p;
      output out=pscvar&m mean=mean median=median Q1=q1 Q3=q3 max=max
min=min;
run;

data pscvar&m ;set pscvar&m;
      varnum=&m.;
run;

*STEP 4: outcome model;
*Outcome model (RD);
ods select none;
proc genmod data= &data.2 desc;
      ods output Estimates=RDcvar&m.;
      class &outcome &exp(ref="0")  &id ;
      model &outcome= &exp/ dist=bin link=identity;
      weight sw;
      repeated subject = &id / type=ind;
      estimate "overall"  &exp 1 -1  ;
run;
ods output close;

data RDcvar&m.; set RDcvar&m.;
      where Label="overall";
      Varname="cvar&m";
      keep Varname LBetaEstimate LBetaLowerCL LBetaUpperCL ;
      rename LBetaEstimate=RD;
      rename LBetaLowerCL=LCI;
      rename LBetaUpperCL=UCI;
run;
```

```
*Outcome model (RR);
proc genmod data=&data.2 desc;
      ods output Estimates=RRcvar&m;
      class &outcome  &exp(ref="0")  &id ;
      model &outcome= &exp / dist=bin link=logit;
      weight sw;
      repeated subject = &id / type=ind;
      estimate "overall"    &exp 1 -1 /EXP ;
run;
ods output close;

data RRcvar&m; set RRcvar&m;
      where Label="Exp(overall)";
      Varname="cvar&m";
      keep Varname LBetaEstimate LBetaLowerCL LBetaUpperCL StdErr;
      rename LBetaEstimate=RR;
      rename LBetaLowerCL=LCI;
      rename LBetaUpperCL=UCI;
      rename StdErr=SE;
run;
%end;

*Step 5: Generate a dataset of combined estimates for plots;
*For outcome models;
data &outcome._cRR;
      format varname $32.;
      set RRcvar1-RRcvar&number_con2;
run;
data &outcome._cRD;
      format varname $32.;
      set RDcvar1-RDcvar&number_con2;
run;

*For IPW distribution;
data &outcome._cSW;
      set swcvar1-swcvar&number_con2;
      varname=cats('cvar',varnum);
run;

*For PS distribution;
data &outcome._cPS;
      set pscvar1-pscvar&number_con2;
      varname=cats('cvar',varnum);
run;


*Merge with variable names;
data cvars1;set cvars;
   length varname $32;
   varname=cats('cvar',varnum);
   drop varnum;
run;

proc sort data=cvars1;by varname; run;
proc sort data= &outcome._crd;by varname;run;
proc sort data= &outcome._crr;by varname;run;
proc sort data= &outcome._csw;by varname;run;
```

```
proc sort data= &outcome._cps;by varname;run;

data &outcome._crd; merge cvars1 &outcome._crd; by varname;run;
data &outcome._crr; merge cvars1 &outcome._crr; by varname;run;
data &outcome._csw; merge cvars1 &outcome._csw; by varname;run;
data &outcome._cps; merge cvars1 &outcome._cps; by varname;run;

*****************STAGE 3: Truncated weight based on percentiles
***************;
/*Default: we show results of truncated 1% and 5%, as well as customized
percentlile if present*/
/*NOTE: do we need to add the features of customized percentiles? also how to
present truncated weight in
PS overlap model? present weight or PS? */
/*Obtain weight from full model*/
proc logistic data= &data desc noprint;
      model &exp= / maxiter=100;
      output out= &data.3 prob=m;run;
run;quit;run;

/*Propensity score*/
proc logistic data= &data.3 desc noprint;
      class &catevar.;
      model &exp= &catevar. &catevar./ maxiter=100;
      output out= &data.3 prob=p;run;
run;quit;run;

/*Calculated stablized weights*/
data &data.3; set &data.3;
      if &exp=0 then do;
            weight=1/(1-p);
            sw=(1-m)/(1-p);
      end;
      else if &exp=1 then do ;
      weight=1/p;
    sw=m/p;
      end;
run;

/*Truncate weight*/
proc univariate data=&data.3 noprint;
      var sw;
      output out=pt pctlpts=1 5 95 99 pctlpre=sw
run;

data &data.3;
 set &data.3;
      if _n_ eq 1 then do;
 set pt;
 end;
run;

data &data.3;set &data.3;
 if sw > sw99 then tsw1 = sw99;
 else if . < sw < sw1 then tsw1 =sw1;
 else tsw1=sw;
```

```
 if sw > sw95 then tsw2 = sw95;
 else if . < sw < sw5 then tsw2 =sw5;
 else tsw2=sw;

run;

/*Outcome models*/
*Outcome model (RD);
%do i= 1 %to 2;
ods select none;
proc genmod data= &data.3 desc;
      ods output Estimates=RDtsw&i;
      class &outcome &exp(ref="0")  &id ;
      model &outcome=  &exp / dist=bin link=identity;
      weight tsw&i;
      repeated subject = &id / type=ind;
      estimate "overall"  &exp 1 -1  ;
      run;
ods output close;

data RDtsw&i; set RDtsw&i;
      where Label="overall";
      Varname="tsw&i";
      keep Varname LBetaEstimate LBetaLowerCL LBetaUpperCL;
      rename LBetaEstimate=RD;
      rename LBetaLowerCL=LCI;
      rename LBetaUpperCL=UCI;
run;

*Outcome model (RR);
ods select none;
proc genmod data=&data.3 desc;
      ods output Estimates=RRtsw&i;
      class &outcome  &exp(ref="0") &id ;
      model &outcome= &exp / dist=bin link=logit;
      weight tsw&i;
      repeated subject = &id / type=ind;
      estimate "overall" &exp 1 -1 /EXP ;
run;
ods output close;

data RRtsw&i; set RRtsw&i;
      where Label="Exp(overall)";
      Varname="tsw&i";
      keep Varname LBetaEstimate LBetaLowerCL LBetaUpperCL StdErr ;
      rename LBetaEstimate=RR;
      rename LBetaLowerCL=LCI;
      rename LBetaUpperCL=UCI;
      rename StdErr=SE;
run;

%end;

/*Generate a dataset of combined estimates for plots*/
*For outcome models;
data &outcome._tRR;
      format varname $32.;
```

```
      set RRtsw1-RRtsw2;
      if varname='tsw1' then name='Truncated 1 %';
      if varname='tsw2' then name='Truncated 5 %';
run;
data &outcome._tRD;
      format varname $32.;
      set RDtsw1-RDtsw2;
      if varname='tsw1' then name='Truncated 1 %';
      if varname='tsw2' then name='Truncated 5 %';
run;

*****************STAGE 4: merge output from stage 1-3 and calculated
MSE***************;
*Count number of obeservation in the dataset (for calculating MSE);
%global obscount;
proc sql noprint;
      select count(*)
      into :obscount
      from out2.sample;
quit;

*Save point estimates from full model as the true value of point estimate;
data _null_;
  set RRvar0;
  call symput("RR_FULL",RR);
run;

data _null_;
  set RDvar0;
  call symput("RD_FULL",RD);
run;

data &outcome._SW_F;
set &outcome._csw &outcome._sw;
run;

data &outcome._PS_F;
set &outcome._cps &outcome._ps;
run;

/*MSE:calculated from logRR????*/
data &outcome._RR_F;
      set &outcome._cRR &outcome._RR &outcome._tRR;
      lnRR=log(RR);
      lnRR_full=log(&&RR_FULL);
      lnuci=log(uci);
      lnlci=log(lci);
      variance=(((lnuci-lnlci)/2*1.96)*sqrt(&obscount))**2;
      MSE=(lnRR-lnRR_full)**2+variance;
run;

data &outcome._RD_F;
      set &outcome._cRD &outcome._RD &outcome._tRD;
      variance=(((uci-lci)/2*1.96)*sqrt(&obscount))**2;
      MSE=(RD-&&RD_FULL)**2+variance;
run;
```

```
*delete dataset;
proc datasets lib=work nolist;
 delete
      swvar0-swvar&number_cate2
      psvar0-psvar&number_cate2
      rrvar0-rrvar&number_cate2
      rdvar0-rdvar&number_cate2
      swcvar1-swcvar&number_con2
      pscvar1-pscvar&number_con2
      rrcvar1-rrcvar&number_con2
      rdcvar1-rdcvar&number_con2
      rdtsw1-rdtsw2
      rrtsw1-rrtsw2
      &outcome._SW
      &outcome._cSW
      &outcome._ps
      &outcome._cps
      &outcome._rr
      &outcome._crr
      &outcome._trr
      &outcome._rd
      &outcome._crd
      &outcome._trd
      vars vars1
      cvars cvars1
      pt
;
quit;
run;

/*Prepare dataset for bias variance tradeoff plot*/
data &outcome._RR_F1;set &outcome._RR_F;
 if name="full" then name2="overall";
 if name^="full" then name1=name;
 if name="full" then MSE=.;
 RRCI = put(RR, 6.4) || " (" || put(LCI, 6.4) || ", "|| put(UCI, 6.4) || ")";
 RR_n="RR(95%CI)";
 LCI_n="LCI";
 UCI_n="UCI";
 MSE_n="MSE";
run;

proc sort data=&outcome._RR_F1;
by descending mse;
run;

ods graphics on / width=8in height=8.5in;
title "Impact of excluding variables on bias and variance";
title2 h=10pt 'Risk Ratio and 95% CI';
proc sgplot data=&outcome._RR_F1 noautolegend;
 scatter y=name2 x=rr / xerrorupper=uci xerrorlower=lci
markerattrs=(symbol=squarefilled size=8);
 scatter y=name2 x=rr_n / markerchar=rrci x2axis;
 scatter y=name1 x=rr/ xerrorupper=uci xerrorlower=lci;
 scatter y=name1 x=rr / markerattrs=(symbol=diamondfilled size=6);
 scatter y=name1 x=rr_n / markerchar=rrci x2axis;
 scatter y=name1 x=MSE_n / markerchar=MSE x2axis;
```

```
 refline 1 / axis=x;
 refline 0.01 0.1 10  / axis=x lineattrs=(pattern=shortdash)
 transparency=0.5;
 xaxis type=log offsetmin=0 offsetmax=0.35 min=0.0 max=10 minor
display=(nolabel) ;
 x2axis offsetmin=0.70 display=(noticks nolabel) valueattrs=(size=8pt)
labelattrs=(size=8pt);
 yaxis display=(noticks nolabel)offsetmin=0.05 offsetmax=0.05
valueattrs=(size=8pt) ;
run;
ods graphics off;

/*Propensity score overlapped plots*/
proc sort data=&outcome._RR_F1;by varname;run;
proc sort data=&outcome._PS_F;by varname;run;
data =&outcome._PS_F1;
      merge &outcome._RR_F1 (keep=varname mse)&outcome._PS_F;
by varname;
if varname in ("tsw1","tsw2") then delete;
if name= "full" then mse=99999999;
run;
proc sort data=&outcome._PS_F1;by descending mse; run;

ods graphics on / width=8in height=8.5in;
title "Impact of excluding variables on propensity score overlap  ";
proc sgplot data=&outcome._PS_F1 nocycleattrs;
  highlow y=name high=max low=min / group=obesity groupdisplay=cluster
clusterwidth=0.7;
  highlow y=name high=q3 low=median / group=obesity type=bar
groupdisplay=cluster grouporder=ascending clusterwidth=0.7 barwidth=0.7
name='a';
  highlow y=name high=median low=q1 / group=obesity type=bar
groupdisplay=cluster grouporder=ascending clusterwidth=0.7 barwidth=0.7;
  scatter y=name x=mean / group=obesity groupdisplay=cluster
grouporder=ascending clusterwidth=0.7 markerattrs=(size=9);
  keylegend 'a'/TITLE= "Exposure";
  yaxis grid LABEL="Excluded variable";
  xaxis min=0.0 max=1 LABEL="Propensity score";
  run;
ods graphics off;
```

%mend bias_var;

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