AN APPLICATION OF ANALYZING CORRELATED BINARY OUTCOMES IN A STUDY OF TWINS

by

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ABSTRACT

Twin studies have been an important area of epidemiologic research. Traditional analyses of risk use regular linear or logistic models. Regular linear regression and logistic regression assume that all observations are independent of each other. However, there is correlation between the observations in a study of twins that needs to be taken into account. Two ways to handle the correlated binary outcomes include Generalized Estimating Equations (GEE) and mixed models. In this thesis, we used univariate and multivariable GEE models to investigate an association between maternal pre-pregnancy BMI and a binary outcome variable, small for gestational age (SGA) in twins. In addition, we used splines to explore the relationship between SGA and pre-pregnancy BMI. SGA birth outcomes are considered one of the major concerns in public health issues because they could affect infant mortality as well as infant morbidity. Our data is a random sample of birth certificate records of twin births in Pennsylvania from 2003 to 2011 (n=20,072 infants). Our findings suggest that underweight women have higher risk of SGA births compared to normal weight women controlling for other maternal characteristics (OR=1.62, 95% CI (1.33,1.99)). The public health significance of this work is that the results from this paper could be used as a reference for making decisions on interventions to reduce SGA births in twins.

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1.0 INTRODUCTION

1.1 TWINS

Twin births occur when two infants are born during the same birth. There are two type of twins: dizygotic (“fraternal”) and monozygotic (“identical”) twins. Fraternal twins have two different zygotes and only share 50% of their DNA. Identical twins share the same zygotes. Identical twins then could be categorized in dichorionic (each twin has separate placenta) and monochorionic (both twins share the same placenta) [28]

According to the national vital statistics reports in December 2013, the U.S. infant mortality rate for multiple births such as twins is about 5 times the rate for singleton births. The infant mortality rate for twins was four times higher than the infant mortality for singleton (24.03 per 1,000 live births vs. 5.45 per 1,000 live births) in 2010. [2] In 2014, one out of every pair of twins were born preterm or low birthweight. [32]

1.2 SMALL FOR GESTATIONAL AGE (SGA)

Small for gestational age (SGA) births are classified as babies that have birth weights below the tenth percentile for babies of the same gestational age in weeks. [2] According to Altman et al. who performed a retrospective nationwide cohort study in Sweden to investigate the relationship between infant mortality and the cause of death in singletons babies, SGA infants are at a higher risk of neonatal and post-neonatal mortality compared to non-SGA infants. The study sample included 2,152,738 singleton babies who were born at 37 gestational weeks or later. The results showed that the risk of infant mortality for singletons is double for very small gestational age infants (SGA< 3rd percentile) and for moderately SGA births (from 3rd to <10th percentile) is 1.4 times higher compared to infants with normal birth weight for gestational age. [19]

In 2015, Ananth investigated a relationship between risk of infant mortality among twins and placental abruption. The study sample included women who had delivered twins at 22 weeks or older and with the infant weighted 500 grams or more in U.S. from 1989 to 2000. The study found that the risk for infant mortality in presence of abruption for preterm SGA was higher compared with twins of the appropriate growth delivered at term (36.2, 95% CI (28.4, 46.1)). [37]

Multiple pregnancies such as twins and triplets have different growth patterns than singleton babies. The birthweight chart for singletons might not adequate for twin babies Therefore, the SGA standard for singletons standard should not be used as reference for twin babies. SGA for twins should be assessed using their own standard. In 2012, Doom et al did a study based on population birth register for Study Center for Perinatal Epidemiology (the database that included all singleton and multiple births in Flanders and University Hospital of Brussels). The study included all twins with birthweight of 500 grams or greater and were born from 24 to 40 gestational age week. The study showed an association between twin birth weight and gestational age. Birth weight increased as the gestational age increased. The author claimed that there should be specific birth weight curve references for the twin population because twin babies usually have lower birth weight than singletons due to the Intra-uterine growth restriction

(IUGR). The author claimed that the peak for twin growth was from 32 to 36 weeks while peak of growing in singletons was from 36 to 38 weeks. From the study sample, the author mentioned that the average birthweight of the twins increased with 141 grams per week. The peak of growing was at 32 weeks with the maximum growth of 190 grams. The study resulted in developing a birth weight curve by gestational age for the twin population. However, the authors did not take the correlation between the twins into consideration. [3]

In 2012, Liao, Adolfo Wenjaw et al., described the development of a reference chart for twins by gestational age based on the data of 125 uncomplicated twin pregnancies in Brazil. The study included women at less than 21 weeks of gestational age and with twin pregnancy at Twins Clinic, Brazil. The result also confirmed that there is a positive correlation between fetal growth and gestational age. Reference ranges for fetal ultrasound biometry measurements and growth parameters in twin pregnancies were established as a result of the study [4].

In 2015, Shivkumar et al. did a retrospective cohort study of live-born twins who were born at 34 weeks or older in Royal Victoria Hospital, Canada. The result of the study provided an ultrasound-based fetal weight reference chart for twins stratified by chronicity. The chart was developed based on the study population of 642 twin pregnancies. The study showed that monochorionic twins (identical twins that share the same placenta) were lighter than dichorionic twins (each twin has its own placenta). [5]

Some of the potential factors that could influence SGA outcomes in singletons include: maternal race, maternal body mass index (BMI), history of chronic hypertension, maternal age, and tobacco use [20]. SGA is associated with higher mortality risk during the first year of life in singleton babies [24]. Campbell et al confirmed that maternal age of greater or equal than 35, maternal smoking status during pregnancy, and preeclampsia were associated with severe SGA (birthweight <3rd percentile). In addition, maternal underweight pre-pregnancy BMI was associated with moderate SGA (birthweight from 3rd to <10 percentile) for singleton babies. [23] Catov et al showed that chronic hypertension, parity, and underweight status were related to SGA. [25]

In addition, in 2011, Inde et al. did a study to investigate the maternal risk factors for SGA dichorionic twins in Japan. The data were collected from 340 twins who were born from 2003 to 2008 at the Japanese Red Cross Katsushka Maternity Hospital, Tokyo. The study showed some of the maternal risk factors associated with SGA were maternal nulliparity, smoking, pre-pregnancy-induced hypertension. This study only assessed the association between BMI at delivery and SGA. As BMI at delivery increased, probability of SGA births decreased. [33]

Schwendemann did a study in 2005 to evaluate risks factors for adverse fetal growth in twin pregnancies. There were 11,827 twin pregnancies that were included in the study. The results showed that SGA was associated with the following risk factors: tobacco abuse, poor weight gain, lean pre-pregnancy body mass index (BMI), nonmarried, and African American race. [35]

1.3 MATERNAL PRE-PREGNANCY BMI AND SGA

Maternal BMI is calculated using maternal weight before pregnancy (in kilograms) divided by maternal height (in meter squared). In our study, the mothers' pre-pregnancy BMI and height were measured in pounds and inches. Thus, mothers' weights were first converted into kilograms and mothers' heights were converted into meters squared from inches. BMI is typically classified into four groups according to the World Health Organization (WHO): Underweight (BMI<18.5), Normal weight (BMI from 18.5 to less 25), Overweight (BMI from 25 to less 30), Obese (BMI from 30 or greater).

The prevalence of overweight and obese women is increasing in U.S. population especially women of childbearing age. It is important to assess the impact of maternal BMI on adverse birth outcomes. Observational studies have shown that pre-pregnancy BMI is associated with infant birth outcomes. Obese women have increased risk of adverse pregnancy and birth outcomes such as cesarean section deliveries or preterm birth. On the other hand, underweight women also have high risk of preterm birth and small for gestational age [34].

M Nakamura et al. performed a retrospective study of 3046 singleton babies that were born between 2005 and 2007 at Showa University Hospital in Japan. The goal was to investigate the possibility of SGA births and risk factors. In this study, the author categorized maternal BMI into two groups: under 18.5 and 18.5+. The odd ratio of SGA was 1.8 with 99% CI (1.2, 2.6) for maternal BMI that was lower than 18.5 compared to those who have BMI at 18.5 or greater. [8]

Goetzinger et al did a study to assess the relationship between maternal BMI and tobacco use on SGA infants in 2012. The study was based on a retrospective cohort study of 65,104 mothers. The study showed that underweight BMI category (BMI less than 18.5kg/m^2) was significantly associated with SGA controlling for other confounders. This result is from retrospective cohort study of 65,104 patients who were pregnant with singleton babies. The BMI was categorized into underweight, normal weight, overweight, and obese. The results also showed that for singleton births, women in the underweight BMI category were at 1.8 times higher risk of having SGA births than women in the normal BMI category. [20]

In addition, Yu, Zhangbin et al. in 2013 performed a systematic review and meta-analysis. The search strategy for the study was developed using the search terms “pregnancy, pre-pregnancy, body mass index, obesity, overweight, birthweight, childhood, infant, adolescence”. The study showed that women who were underweight had 1.8 times higher to the risk of SGA births compared to pre-pregnancy normal weight women. [22]

Based on the literature from the studies summarized above, it appears that pre-pregnancy BMI has an association with SGA in singletons. Although there are not many studies conducted on the relationship between SGA and infant mortality in multiples pregnancy outcomes such as twins, pre-pregnancy BMI could potentially be associated with SGA in multiple births as well. It possible that reducing SGA outcomes would help to reduce infant mortality in twins as well as in singletons. The studies in singletons showed the risk of SGA decreases as pre-pregnancy BMI increases. Underweight women (BMI<18.5) have a higher risk of SGA births outcomes. On the other hand, obese/overweight women have a higher risk of being large for gestational age (LGA).

1.4 STATEMENT OF PROBLEM

Adverse birth outcomes in twins such as pre-term births and SGA births have raised concerns. According to the national vital statistics report from Centers for Disease Control and Prevention (CDC) in December 2015, the twin birth rate was 33.9 per 1,000 births in 2014, which is considered high for the nation. [32]. It is important to understand which factors influence SGA births in twin babies because the numbers of multiple pregnancies in the U.S. are increasing. Understanding these factors might allow appropriate intervention strategies to be developed and to help improve SGA birth outcomes. We hypothesize that underweight women are more likely to give birth to twins that are small for gestational age.

We decided to use the cut points for 10^{th} percentile of the fetal weight reference for twins based on Shivkumar et al. because we believe that the study population in Canada seems to be more diverse than the Brazilian population. In addition, these data would be more similar with regards to diversity to our dataset. Unfortunately, we are unable to determine the chronicity of the twins in our dataset. Thus, we assumed that all twins in our study population were dichorionic twins and used the reference chart for dichorionic twins to calculate the birth weight percentile.

The goal is to investigate maternal BMI as a potential risk factor for small for gestational age (SGA) babies in twin pregnancies. Using the potential maternal risk factors for SGA births based on the literature reviews such as age, race, educational level, and smoking status [34], we will attempt to construct a multivariable model to assess the relationship between maternal BMI and SGA births controlling for other potentially important covariates.

The paired structure of the data from twin studies, possess certain challenges in terms of data analysis because regular regression models assume independence in observations [12]. We need statistical methods to account for correlation of twins within the mother. We attempt to solve this problem by using Generalized Estimating Equations (GEE) model to allow for clustered data. A non-parametric approach using different types of splines will be fitted to examine the association of the variable pre-pregnancy BMI and SGA.

2.0 MODELS

2.1 CORRELATED DATA

Clustered data (i.e., correlated) occur when observations within a common group (person, hospitals, neighborhood, etc.) are not independent from each other. For example, individuals can be nested within a larger group, such as hospitals or communities. In longitudinal studies, clusters are composed of repeated measurements obtained from a single individual at different time points. In twin studies, outcomes are clustered within mothers. In our study sample, small for gestational age (SGA) birth outcomes might be correlated because each twin pair has the same mother. Observations within a subject tend to be similar. Thus, failure to take into account the correlated data might result in smaller standard errors values for the model which then causes the confidence intervals to be narrower than what they should be.

2.2 BINARY OUTCOMES

For binary data, there are two possible outcomes for each observation: success or failure, typically coded as 0 (failure) or 1(success). Many health outcomes such as mortality or disease prevalence can be characterized with a binary outcome (dead or alive, exposed vs. nonexposed). In the current study case, the outcome variable, SGA (birth weight percentile that is less than or equal to 10^{th} percentile) will be treated as binary (SGA (1) or non-SGA (0)).

2.3 LOGISTIC REGRESSION

A logistic model is used when the outcome is dichotomous (binary), Y_i=0 or 1. In our study sample, Y_i is an indicator of whether the birth is SGA or not, and takes on the value of 0 (non-SGA) or 1 (SGA). We assume that the outcome, Y_i follows binomial distribution. $Y_i \sim B(n_i, p_i)$, so that the

Logistic model has the following form:

$$\text{Logit}(p_i) = \log\left(\frac{pi}{1-pi}\right) = \beta_0+\beta_1 x_{1i}+\ldots+\beta_k x_{ki},$$

where $\beta_{0,\ldots,}$ β_k are unknown parameters, n_i is number of observations, p_i is the probability of being "success" and 1-p_i is the probability of being "failure". In our case, p_i would be the probability of observing an SGA birth and 1-p_i would be the probability of observing a non-SGA birth.

From the logistic model, the expected proportion of being a "success" is given by $p_i=\frac{\exp(\beta 0+\beta 1x1i)}{1+\exp(\beta 0+\beta 1x1i)}$

The odds ratio is the measure of association from a logistic regression and is calculated as:

$$OR=\frac{P(Y=1|X)}{P(Y=0|X)}=\exp(\beta_1)$$

In our case, we are interested in the relationship of mother's pre-pregnancy BMI and the probability of an SGA birth so the independent variable of interest is pre-pregnancy BMI (categorize as underweight vs. normal weight). If we used underweight group as the baseline, the odds ratio can be interpreted as the odds of SGA births of women in the normal weight group are $(\frac{pi}{1-pi})$ times the odds of SGA births for women in the underweight group.

2.4 GEE MODEL

Generalized Estimating Equations (GEE) is a technique that is used to describe the changes in population mean response averaged for a unit change in the predictor taking into account clustering of the data. GEE assumes that the missing observations in the data are missing completely at random. This means that the probability that an observation is missing does not have any relationship with the observed or unobserved measurements in the data. GEE is restricted to only one level of clustering.

The GEE model is given as the follows:

$g(\mu_{ij})=x_{ij}^T\beta$

- $\mu_{ij} = E(Y_{ij}|X_{ij})$ is the marginal mean response for subject i at jth response.
- y_{ij} is the outcome for observation j in cluster i ; i=1,..,n, j=1,…,J.
- x_{ij} is a p x 1 vector of covariates
- β is a p x 1 vector of unknown regression coefficients
- g(.) is the known link function.

In our case, the link function g(.) is logit link because our response, SGA birth, is binary.

The logit link function is $g(.)=\log(\frac{pi}{1-pi})$

GEE assumes that there is independence between subjects. In our dataset, we will assume that each subject (mother) is independent from another mother. Also, GEE requires a common set of correlation parameters for all subjects. There are 5 common types of correlation structures:

- Independent: responses are uncorrelated within a subject.
- Exchangeable: any two responses within a subject have the same correlation. This assumption is appropriate when we cannot really distinguish one member of a cluster from another. For our dataset, this assumption might work best because our observations are twins.
- Autoregressive AR (1) the correlation depends on time between measurement j and k.
- Stationary m-dependent: correlation k occasion apart are the same for k=1,2,..,m whereas correlations more than m occasions apart are zero.
- Unstructured: no assumption about correlations are made.

One of the properties of GEE is that it yields consistent estimates of the regression parameters and their variances even if the working correlation matrix is misspecified. We will fit several models and test if the models are sensitive to misspecification of the correlation matrix.

2.5 LINEAR MIXED MODEL

The linear mixed model is another method to analyze correlated data where the outcome is continuous. The linear mixed model contains both fixed and random effects. Fixed effects have level that are of primary interest and would be used again if the experiment were repeated. The random effects are associated with individual experimental units drawn at random from a population. The random effects have prior distributions whereas fixed effects do not.

The general form for linear mixed model is as follows:

$$\mu_{ij} = x_{ij}^T\beta + Z_i b_i$$

Where Z_i is the random effect, b_i is a vector containing the effect parameter for subject I and $Z_i \sim N(0,\sigma^2_u)$

The linear mixed model assumes that the missing observations in the data are missing at random (MAR) meaning the probability of an observation being missing does not depend on the unobserved measurements. Similar to GEE, there are different types of correlation structures. The following are the common correlation structures:

- Compound Symmetric: observations on the same subject have the same covariance and variance.
- Autoregressive AR (1) covariance between observations on the same subject are not equal.
- Unstructured: Specifies no patterns in the covariance matrix

2.6 GENERALIZED LINEAR MIXED MODEL

The generalized mixed model (GLMM) is an extension of the linear mixed model that allows response variables from different distributions such as a binary response. Unlike GEE, one could have multiple levels of clustering in GLMM. Although, we only have one level of clustering in our dataset that is SGA births outcomes of twins within a mother, one could go further and examine the clustering of mothers between geographical areas or within different hospitals. While the coefficient in GEE represents population average change, GLMM represents subject specific level (i.e. the coefficient in mixed model represents the change within a subject). Though, both GEE and GLMM are used to handle clustered data. For our analysis, we will put our focus on GEE instead of mixed model because the study is cross-sectional. For this type of study, we can compare different population groups at a single time frame. GLMM is not ideal to estimate individual level estimates using cross sectional study.

The general form of generalized mixed model is:

$g(\mu_{ij})=x_{ij}^{T}\beta + Zib_i$

- Where $\mu_{ij}= E(Y_{ij}|x_{ij} , \eta_{ij})$ is the expectation of the conditional distribution of the outcome given the random effects .
- β is p x 1 column vector of the fixed effect regression
- Z_i is the random effect
- b_i is a vector of the random effect.
- g(.) is a known link function

Similar to GEE, the link function for binary outcomes is logistics link function: g(.)=log $(\frac{pi}{1-pi)})$

The logistic regression model with a random effect is as follows:

$\text{logit}(\pi_i)=\beta_0+\beta_1x_{1i}+\ldots+\beta_kx_{ki}+z_i$

where $\pi_i=\frac{p_i}{1-p_i}$

Where $\beta_{0,\ldots,}$ β_k are unknown parameters and u_i is a random effect.

z_i is an observation of a random variable Z_i and we assume that Z_i ~$N(0,\sigma^2{}_u)$

2.7 SPLINES

Spline regression is a nonparametric approach to assess the fit of data taking into account the variation in the relationship between outcome and predictor variable. In a non-parametric approach, we make as few assumptions about the regression function as possible. Instead, we try to learn the shape of the function. The splines are used in our analysis to explore the relationship of pre-pregnancy BMI variable and SGA.

Splines are piecewise polynomials that join smoothly at knots which are where the linear segments connect. A spline function of degree n is a continuous function with n-1 continuous derivatives. We can increase the numbers of knots to obtain a flexible curve. However, adding too many knots in to a spline might result in over fitting. It is recommended to use the smallest amount of knots as possible and use at least 4 or 5 points per segment.

Polynomial spline functions are best to describe polynomial –like behavior of the data. The point $c_1,\ldots,c_k$ are called knots

The spline function is defined by

$$S(x) = \begin{cases} S_0\ (x), \quad x \in [c_0, c_1] \\ S_1(x), \quad x \in [c_1, c_2] \\ \cdot \\ \cdot \\ \cdot \\ S_{n-1}(x), x \in [c_{n-1}, c_n] \end{cases}$$

Where each $S_i(X)$ is a linear polynomial: $S_i(X) = \beta_0 + \beta_i X$

A linear spline is a continuous function formed by connecting linear segments: $f(X)=\beta_0+\beta_1 X+\Sigma\beta_i S_i$

Where β_i is the weight of each linear function and S_i refers to the i^{th} linear function with the knot at c_i

$$S_i = \begin{cases} x - c_i : if\ x - c_i \ > 0 \\ 0 \qquad : if\ x - c_i \ \leq 0 \end{cases}$$

A cubic spline is a cubic function that formed by connecting polynomial segments so that the function is continuous, has 2 continuous derivatives, and 3th derivative is a constant between knots: $f(X)=\beta_0+ \beta_1X+\beta_2X^2 +\beta_3X^3+ \Sigma\beta_iS_i{}^3$. However, cubic splines sometimes perform poorly at the outer range of X. Thus, restricted cubic splines are used to constrain the function to be linear at the tails.

Median splines are a convenient way to see the relationship between outcome and predictor. Median splines divide a scatter plot into vertical bands then calculate bivariate medians for each interval and as a last step uses the median points as knots to fit a cubic splines.

3.0 METHODS

3.1 DATA COLLECTION

The dataset used for this thesis was a random sample of birth certificate records from 2003-2011 twin births in the state of Pennsylvania. Some of the information was self-reported by mothers and some information was collected at the time of birth by Department of Health representatives. These representatives were responsible for filling out and filing birth certificates to be submitted to the Pennsylvania Department of Health, specifically the Bureau of Health Statistics and Research. The records included data for each mother of twins along with the birth weights and other infant characteristics such as sex and infant morbidity. In addition, the mother’s characteristics such as morbidity, education, geographical information, race, income status, age, education level, smoking status, insurance type, BMI, and number of prenatal visits were included. These data also included some risk factors such as pre-pregnancy hypertension, gestational diabetes, vaginal bleeding, and STD infections such as syphilis, hepatitis B, and Hepatitis C. There was also information on the fathers’ characteristics as well, such as age, race, level of education, and infant death status. There were some observations that did not align such as twins babies that did not have the same gestational age and some mothers of a set of twins did not have the same characteristics. We fixed this problem by modifying the information from the second twin (according to their delivery time) to be the same as the first twin.

The original sample size was 22,618 infants. There were 7.37% of the observations missing BMI. We decided to exclude the observations with missing pre-pregnancy BMI because we could not assess the association with SGA and pre-pregnancy BMI was the variable of interest. There were 0.73% of the observations missing birth weight and 1.15% missing gestational age which were excluded because we could not calculate SGA. (Note that we removed the pairs of twins meaning that if only one twin in the pair has missing gestational age, we still excluded both of them). We only included infants that were alive at the time of report and were born at 22 weeks or older. In total, 2,546 observations were excluded, resulting in a sample size of 20,072 infants (10,036 mothers). The majority of women in our study sample are Non-Hispanic and White, married, college graduates, age 30 years or older, have never smoked, and have private insurance.

3.2 VARIABLE SELECTION

Outcome variable: We categorized birth weight into two groups: SGA (birth weight that is below the tenth birth weight percentile) and non-SGA (birth weight that is equal or greater than the birth weight tenth percentile). The outcome variable was coded as SGA (1=yes, 0=no). Our study sample size contained 20,072 live infants' births that were born at 22 weeks or older. SGA (less than 10^{th} percentile) variable was calculated using reference for dichorionic for twins in Shivkumar study.

For example, an infant who was born at 27 weeks with the birthweight of 797 grams would be considered as SGA based on the chart in the article. Because the reference chart from the Shivkumar article does not refer to twins after 37 weeks of gestational age, we used the baseline reference for SGA at 37 weeks of gestational age in the article for the twins in our sample that were born at 37 weeks or older. In our sample, almost 22% of the twins were born at 38 weeks or older.

Independent variables: Based on the literature, we decided to include the following maternal variables: prior number of deliveries, marital status, maternal race, age, education, maternal BMI, smoking status, and pre-pregnancy hypertension. We also included insurance to provide an estimate for income level of the mothers in our sample. Table 1 is the list of independent variables and their definitions. We included the categorical pre-pregnancy BMI variable which was divided into 4 groups: Underweight (BMI <18.5 kg/m^2), Normal Weight (BMI>18.5 kg/m^2 and <25 kg/m^2), Overweight (BMI>25 kg/m^2 but <30 kg/m^2), and obese (BMI>30 kg/m^2) based on WHO classification.

Table 1 Variable List

Variable	Description
Prior number of deliveries	0= 0 live births 1=1 or 2 live births 2=3+ live births
Marital status	0=unmarried 1=married
Mother's age at time of delivery	0=30 years or greater 1=20-29 years 2=<20 years
Mother's education	0=<HS 1=HS or GED 2=Some college/associates 3=College graduate
Mother's race	1=NH White 2=NH Black 3= Hispanic 4= NH Other
Pattern of smoking	1=No smoking during pregnancy 2=Smoke during pregnancy
Insurance	1=Private Insurance 2=Public (Medicaid) 3=Other
Pre-pregnancy hypertension	1=Yes 0=no
Pre-pregnancy BMI category	1 = Underweight <18.5 2 =Normal weight 18.5-<25 3 =Overweight 25-<30 4 =Obese 30+
Pre-pregnancy BMI	Continuous variable

3.3 STATISTICAL ANALYSIS

In our dataset, there were missing data. In order to perform GEE and mixed model analysis, the missing data assumptions must hold. Thus, the assumptions of missing at completely random (MCAR) for GEE and missing at random (MAR) for mixed model were assessed for the variables with the highest percentage of missing values in our data. The Little's Missing Completely at Random (MCAR) test was performed to test for MCAR assumption. In addition, the probability of unobserved and observed observations for pre-pregnancy BMI and insurance types, which were the two variables with highest percentage of missing values were tested with other independent variables. We attempted to assess the MAR assumption using a table of missing pattern table for our data.

Descriptive statistics for the independent variables (prior number of deliveries, education level, race, marital status, age, smoking pattern, pre-pregnancy hypertension, and insurance) were computed by maternal pre-pregnancy BMI (categorical variable). Variance inflation factors (VIF) were calculated for the independent variables to assess the muticollinearity between the independent variables. We decided to use GEE instead of mixed model because our dataset is cross sectional study. A mixed model is not ideal for analyzing cross sectional studies.

Univariate GEE and generalized linear mixed models for binary outcomes were fitted for the covariates of interest to determine their relationship to the probability of SGA. Quasilikelihood under the independence model criterion (QIC) was used to assess the goodness of fit of GEE models. QIC values were obtained for univariate GEE for different correlation matrices. The correlation matrix that gave the smallest QIC was selected as correlation matrix for multivariable GEE. A multivariable GEE model was fitted for the independent variables that show statistical significance (p value <0.05) in the univariable models.

We compared the beta coefficients as well as their 95 percent confidence intervals for different multivariable GEE models to determine which model has the best fit. QICu (a simplified version of QIC which is used to compare models that have the same working correlation matrix) was also used as the goodness of fit for the models. The model with smaller QICu was selected as the best model.

In addition, there are some extreme observations such as twins born at 47 weeks of gestation and a mother with a pre-pregnancy BMI equals to 76 that we are unable to verify. Thus, after finding the best model, we fitted another model with these points removed to assess the sensitivity of the model to these unusual points.

Splines were added for better understanding of the association between pre-pregnancy BMI and the probability of SGA in the univariate. Model median spline was fitted for a convenient way to assess the relationship between pre-pregnancy BMI and SGA. Linear and restricted cubic spline graphs were also fitted. We decided to use 5 knots. The 5 knots for linear and restricted cubic spline were placed using percentiles of pre-pregnancy BMI at 10th, 20th, 50th, 75th, and 90th. We chose to equally space out the knots using the percentiles of BMI because we wanted the spline curve to not be influenced by extreme observations. All of the analyses were done using Stata version 14.0.

4.0 RESULTS

4.1 DESCRIPTIVE

Figure 1 shows the correlation between the twins' birthweights. There appears to be a linear relationship between the twins' birthweight (correlation coefficient equals to 0.8). In addition, there are a couple of pairs of twins that have big differences in birthweight. The differences between birthweights of twin A and twin B were computed. The average difference between the birthweight of the twin pairs is 280 grams with a standard deviation of 251 grams. We noticed that there were 3 extreme pairs where the difference between birthweight was greater than 2000 grams. After the exclusion of these 3 extreme pairs, the average difference between the birthweight of the twins from the same mother is about 279 grams with a standard deviation of 245 grams (note that we did not exclude these 3 extreme pairs when building the models). There were 18% of the twin pairs in the sample where the birthweights were discordant by more than 20% in birthweight.

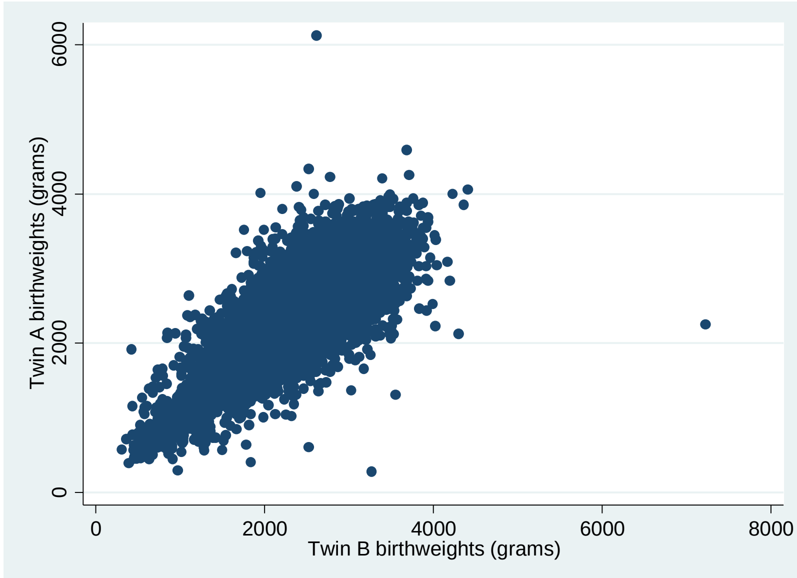

Figure 1 Correlation between the twins' birthweights

Table 2 shows the descriptive statistics of pre-pregnancy BMI of the mothers in our study sample. The range for maternal pre-pregnancy BMI in our sample ranged from 13.7 kg/m^2 to 65.5 kg/m^2 .The gestational age of the twins ranged from 22 to 47 weeks. The maximum values for BMI, gestational age, and birthweight appear to be extreme. The average pre-pregnancy BMI in our sample was about 26 kg/m^2 with a standard deviation of 6.7 kg/m^2. The average gestational age of the twins was about 35 weeks with a standard deviation of 3 weeks. The average birthweight was about 2,389 grams with a standard deviation of 599.2 grams.

Table 2 Descriptive Statistics of Pre-pregnancy BMI, Birthweight, and Gestational Age

Variable	Mean	Standard Deviation	Min	Max	N
pre-pregnancy BMI	26.41	6.66	13.76	65.52	10,036
Gestational Age (weeks)	35.39	2.88	22	47	20,072
Birthweight (grams)	2388.78	599.18	281	7229	20,072

Table 3 provides preliminary descriptive statistics for mother's race, marital status, age, level of education, smoking patterns, and insurance type. The variables that have the highest missing percentages are insurance and smoking patterns.

Table 3 Descriptive statistics of categorical variables

Variable	n	Percent
Mother's race		
1=NH White	7,537	75.10
NH Black	1,451	14.46
Hispanic	616	6.14
Other	422	4.20
Missing	10	0.10
Marital status		
0=unmarried	3,017	30.06
1=married	7,001	69.76
Missing	18	0.18
Mother's age at time of delivery		
0=>30 years	5,408	53.89
1=20-29 years	4,239	42.24
2=<20 years	381	3.80
Missing	8	0.08
Mother's education		
0=<HS	1,009	10.05
1=HS or GED	2,310	23.02
2=Some college/associates	2,626	26.17
3=College graduate	4,048	40.33
Missing	43	0.43
Insurance		
1=Private insurance	6,896	68.71
2=Public (Medicaid)	2,224	22.16
3=Other	333	3.32
Missing	585	5.81
Pattern of smoking		
0=No Smoking during pregnancy	8,620	85.89
1=Smoked during pregnancy	1,239	12.35
Missing	177	1.76

**NH: Non-Hispanic

Figure 2 shows the distribution of infants' birth weight in our study sample. Weights ranged from 281 to 7,229 grams. There are two extreme values that were above 6,000 grams.

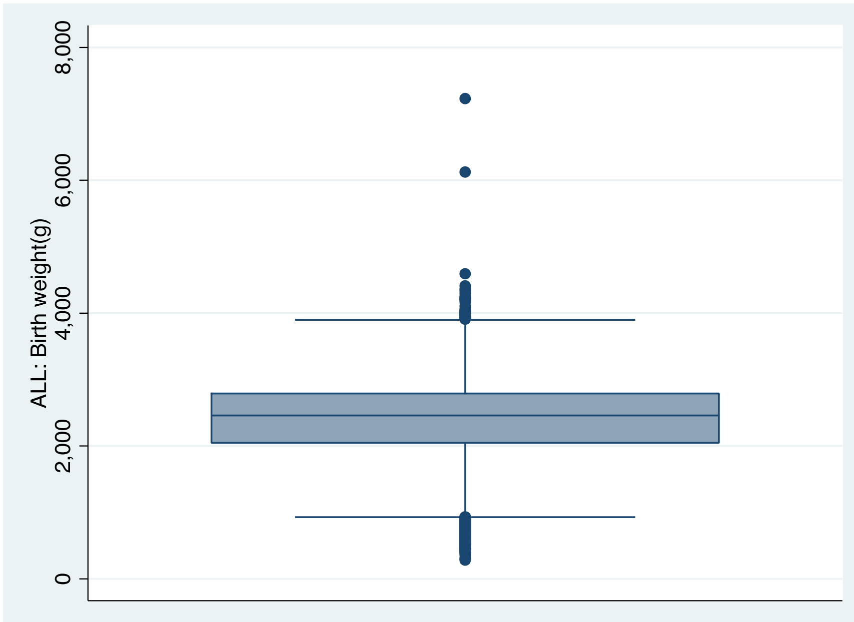

Figure 2 Birth weight Distribution

Figure 3 shows that birth weight of infants increased as gestational age increased. However, there is a case where the gestational age is 47 weeks but the birth weight is only about 2,000 grams. There are also several extreme points that seem to be outliers.

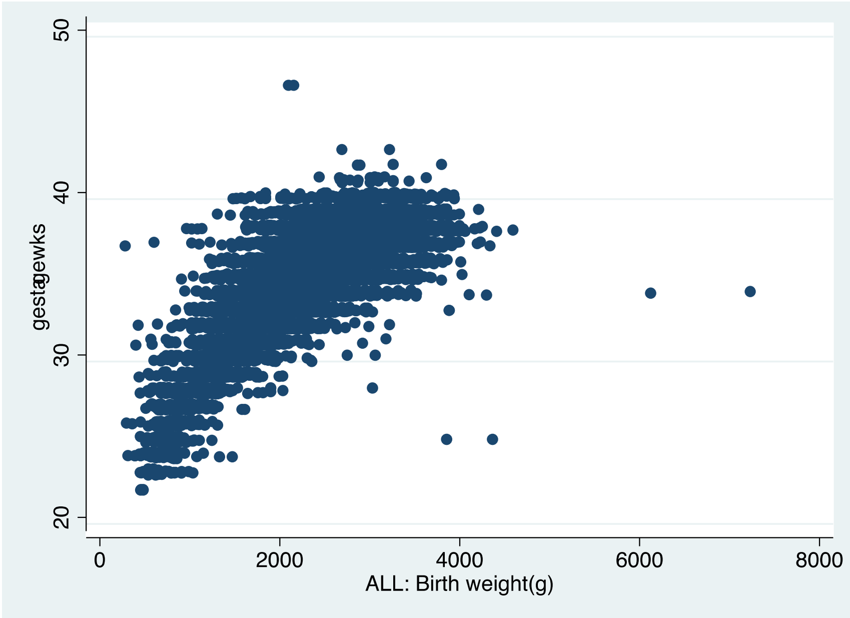

Figure 3 Scatter plots of Gestational Age (weeks) and Birth weight

In Figure 4, the boxplot pre-pregnancy BMI shows that most of women in the study are in the normal weight group (BMI of >18.5 to 25). There is also an extreme case where BMI goes up to 65.5 kg/m^2.

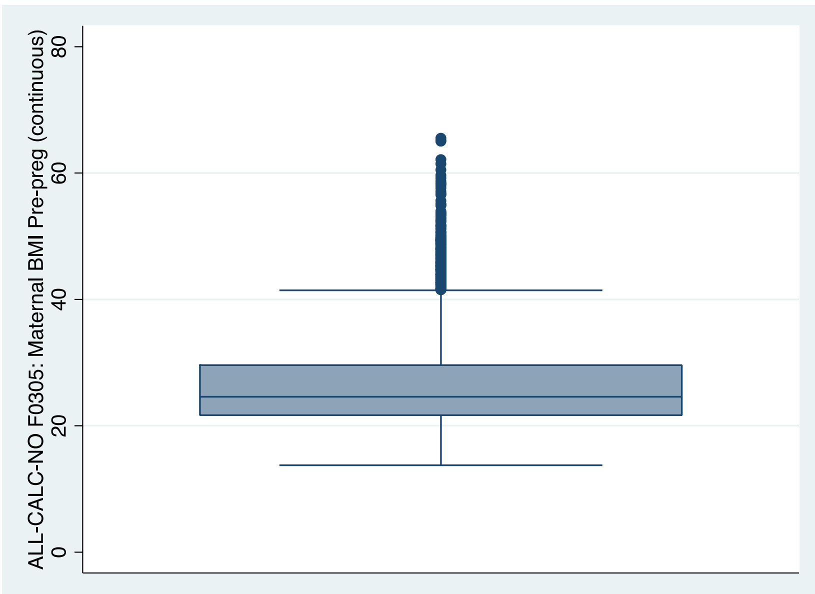

Figure 4 Boxplot of Pre-pregnancy BMI

Table 4 shows the mean of gestational age of babies between the SGA groups. The means appear to be similar in each group. Table 5 shows the percentages of non-SGA births by BMI categories. Percentage of non-SGA and SGA are similar for all pre-pregnancy BMI groups. In our sample, the women in underweight group have the highest SGA birth outcomes compared to women in the other groups. These preliminary statistics support for our hypothesis that the underweight women would be at a higher risk for SGA births.

Table 4 Gestational age by SGA groups

	SGA			Non-SGA		
Variable	Mean (SD)	Max/Min	N (total)	Mean (SD)	Max/Min	N (total)
Gestational age (wks)	35.52 (2.89)	47/23	15,619	34.90 (2.86)	43/22	4,453

Table 5 Descriptive of pre-pregnancy BMI by SGA groups

Variable	Non-SGA(N=15,619)	SGA(N=4,453)	N
Underweight (BMI<18.5)	434 (2.78%)	230(5.17%)	664
Normal weight (BMI=18.5 to <25)	7,599(48.65%)	2,263(50.80%)	9,862
Overweight (BMI=25 to less than 30)	3,774 (24.16%)	1,010(22.68%)	4,784
Obese (BMI=30+)	3,812(24.41%)	950(21.30%)	4,762

We also assessed the missing completely at random (MCAR) and missing data assumption required for the GEE modeling. The results from the Little's test for MCAR assumption show this assumption is violated. In addition, the probability test between unobserved and observed factors between insurance types and smoking patterns (two variables with highest percentage of missing observations) with other independent variables have shown that data is not MCAR. Some of the missing patterns of several variables including insurance, prior number of deliveries, education level, and smoking pattern showed that data were MAR.

Thus, the assumption of GEE is violated. However the missing percentage is small, we think that it would not be problematic to use GEE model. To assess collinearity between our predictor of interest, we computed VIFs. The VIF values were all smaller than 10 which indicate that multicollinearity is not likely an issue.

Most of the mothers were in the normal weight category. Furthermore, there are more mothers were classified as obese (pre-pregnancy BMI greater than 30) compared to those who classified as underweight (pre-pregnancy BMI less than 18.5). There are only a small portion of mothers were classified as underweight in our study population (about 3.3 percent). Data represented in Table 6, illustrates that 49.7 percent of the mothers in our study sample who are college graduates are normal weight. Additionally, about 68.7 percent of the mothers had private insurance.

Table 6 Descriptive Statistics stratified by BMI

Pre-pregnancy BMI					
Variable	Underweight (BMI<18.5) N=332	Normal weight (BMI>18.5 and <25) N=4,932	Overweight (BMI>25 and <30) N=2,390	Obese (BMI >30) N=2,382	N 10,036
Prior number of deliveries					
0= 0 live births	64(2.9%)	1,207(55.1%)	497(22.7%)	422(19.3%)	2,190
1=1 or 2 live births	217(3.6%)	3,002(49.4%)	1,425(23.5%)	1,428(23.5%)	6,072
2=3+ live births	45(2.6%)	694(40.5%)	453(26.5%)	520(30.4%)	1,712
Marital status					
0=unmarried	122(4.4%)	1,213(40.2%)	775(25.7%)	907(30.1%)	3,017
1=married	210(3.0%)	3,709(53.0%)	1,613(23.0%)	1,469(21.0%)	7,001
Mother’s education					
0=<HS	39(3.9%)	418(41.4%)	285(28.2%)	267(26.5%)	1,009
1=HS or GED	90(3.9%)	917(39.7%)	558(24.2%)	745(32.3%)	2,310
2=Some college/associates	73(2.8%)	1,121(42.7%)	699(26.6%)	733(27.9%)	2,626
3=College graduate	129(3.2%)	2,452(60.6%)	842(20.8%)	625(15.4%)	4,048
Mother’s age at time of delivery					
0=<20 years	20(5.2%)	198(52.0%)	100(2.5%)	63(16.5%)	381
1=20-29 years	167(3.9%)	1,883(44.4%)	1,034(24.4%)	1,155(27.3%)	4,239
2=>=30 years	145(2.7%)	2,845(52.6%)	1,255(23.2%)	1,163(21.5%)	5,408
Pattern of smoking					
1=No smoking during pregnancy	274(3.2%)	4,340(50.3%)	2,031(23.6%)	1,975(22.9%)	8,620
2=Smoked during pregnancy	55(4.4%)	509(41.1%)	312(25.2%)	363(29.3%)	1,239

Table 6. Continued

Pre-pregnancy BMI					
Variable	Underweight (BMI<18.5)	Normal weight (BMI>18.5 and <25)	Overweight (BMI>25 and <30)	Obese (BMI >30)	N
Pre-pregnancy hypertension					
0=No	331(3.4%)	4,889(49.6%)	2,351(23.9%)	2,277(23.1%)	9,848
1=Yes	1(0.5%)	43(22.9%)	39(20.7%)	105(55.9%)	188
Insurance					
1=Private insurance	199(2.9%)	3,623(52.5%)	1,598(23.2%)	1,476(21.4%)	6,896
2=Public (Medicaid)	101(4.5%)	867(39.0%)	583(26.2%)	673(30.3%)	2,224
3=Other	11(3.3%)	157(47.2%)	82(24.6%)	83(24.9%)	333
Mother's race					
1=NH White	259(3.4%)	3,937(52.2%)	1,747(23.2%)	1,594(21.2%)	7,537
2=NH Black	28(1.9%)	467(32.2%)	391(27%)	565(38.9%)	1,451
3=Hispanic	19(3.1%)	267(43.3%)	170(27.6%)	160(26%)	616
4=NH Other	26(6.2%)	255(60.4%)	79(18.7%)	62(16.7%)	422

4.2 UNIVARIATE MODELS

In Table 7, we could see that all of the variables are significantly associated with SGA (global p values<0.05). We showed the results from GEE, mixed, and logistic model. Compared to GEE, mixed model yield similar results. Logistic models yield similar ORs compared to GEE. However, the 95% CIs are narrower for the variables compared to GEE models which is what we expect. For the logistic model we did not take into account the cluster. Thus, the standard errors will usually be smaller because the observations are assumed to be independent which produce lower variance between them. Smaller standard error will cause narrower confident interval for logistic models.

Table 7 P values for univarite GEE, mixed, and logistic model

Variables in the model	GEE model OR (95% CI)	GEE model(global p values)	Mixed model OR(95% CI)	Mixed Model (global p values)	Logistic Model	Logistic Model (global p values)
Prior number of deliveries		<0.001		<0.001		0.001
0 live	1 (ref)		1 (ref)		1(ref)	
1 or 2 live	1.06 (0.98,1.15)		1.08 (0.98,1.21)		0.93 (0.84,1.01)	
3+live	0.89 (0.79,0.99)		0.84 (0.72,0.98)		0.77 (0.69,0.86)	
Marital status		<0.001		<0.001		0.007
unmarried	1(ref)		1(ref)		1(ref)	
married	0.64 (0.59,0.69)		0.54 (0.48,0.60)		0.64 (0.59,0.68)	
Age		<0.001		<0.001		0.005
>=30 years	1(ref)		1(ref)		1(ref)	
20-29 years	1.13 (1.05,1.22)		1.18 (1.06,1.32)		1.13 (1.06,1.21)	
<20 years	2.24 (1.87,2.68)		3.09 (2.38,4.03)		2.24 (1.92,2.61)	
Education		<0.001		<0.001	1(ref)	0.004
Less than high school	1 (ref)		1(ref)			
High School/GED	0.84 (0.74,0.96)		0.79 (0.66,0.96)		0.84 (0.75,0.95)	
Some College	0.72 (0.63,0.82)		0.63 (0.53,0.77)		0.72 (0.64,0.81)	
College Graduate	0.64 (0.35,0.72)		0.54 (0.45,0.64)		0.64 (0.57,0.71)	
Race		<0.001		<0.001		0.007
NH White	1 (ref)		1(ref)		1(ref)	
NH Black	1.69 (1.53,1.86)		2.05 (1.77,2.36)		1.69 (1.54,1.84)	
Hispanic	1.19 (1.02,1.39)		1.27 (1.02,1.57)		1.19 (1.04,1.37)	
NH Other	1.57 (1.33,1.88)		1.88 (1.47,2.40)		1.56 (1.35,1.84)	
Pattern of smoking		<0.001		<0.001		0.008
No smoking during pregnancy	1(ref)		1(ref)		1(ref)	
Smoked during pregnancy	1.87 (1.69,2.07)		2.4 (2.07,2.78)		1.87 (1.71,2.05)	

Table 7. Continued

Insurance Private Public (Medicaid) Other	 1 (ref) 1.45 (1.33,1.59) 1.14 (0.92,1.42)	<0.001	 1 (ref) 1.66 (1.47,1.88) 1.29 (0.88,1.59)	<0.001	 1 (ref) 1.45 (1.34,1.57) 1.14 (0.95,1.38)	0.004
Pre-pregnancy hypertension No Yes	 1 (ref) 1.31 (1.01,1.72)	0.0459	 1 (ref) 1.45 (1.00,2.12)	0.052	 1 (ref) 1.31 (1.04,1.65)	<0.001
Pre- pregnancy BMI	0.98(0.98,0. 99)	<0.001	0.97(0.97,0. 98)	<0.001	0.98(0.98,0.9)	<0.001

Figure 5 and Figure 6 show that the marginal probability of SGA decreases as pre-pregnancy BMI increases using univariate GEE and mixed model. The conditional predicted probability of SGA values in the mixed model seem to be categorized into three main groups. Though it looks like that every woman with the same BMI would have 3 different probabilities of having an SGA births according to Figure 7, each subject our sample has exactly one predicted value for probability of SGA. Some BMI values were similar with a few decimal places difference but had big difference in the probability of SGA values because of the random effect coefficient. Thus, this might cause the graph looks like it was categorized into 3 different clusters. When we calculated the average probability of SGA (Figure 6) for assessing whether we had any diagnostic issues with the mixed model we saw in Figure 6, the same pattern as the univariate GEE model.

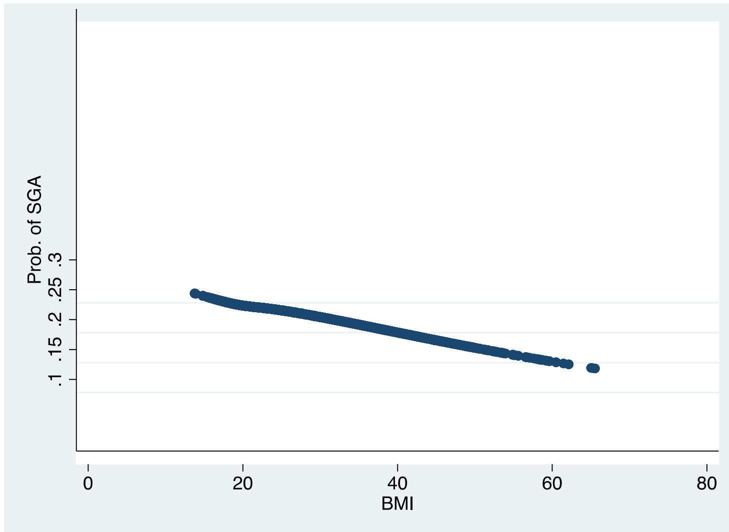

Figure 5 Predicted values of SGA vs BMI (GEE model)

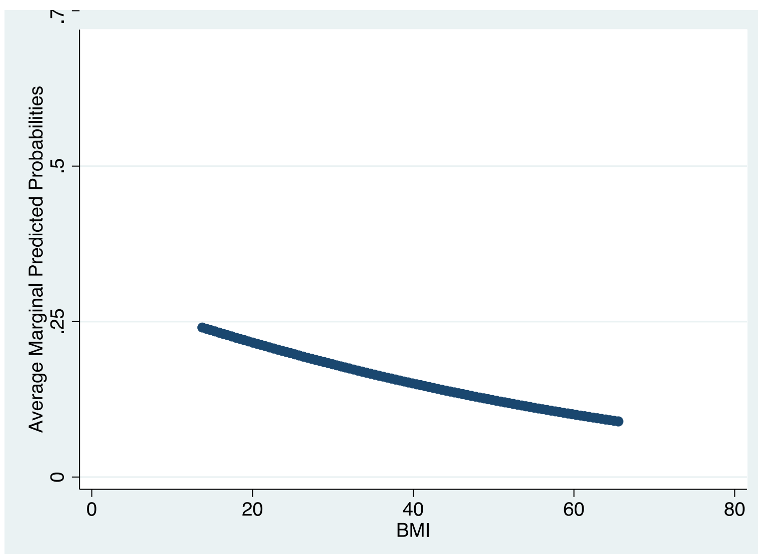

Figure 6 Marginal Predicted values of SGA vs BMI (mixed model)

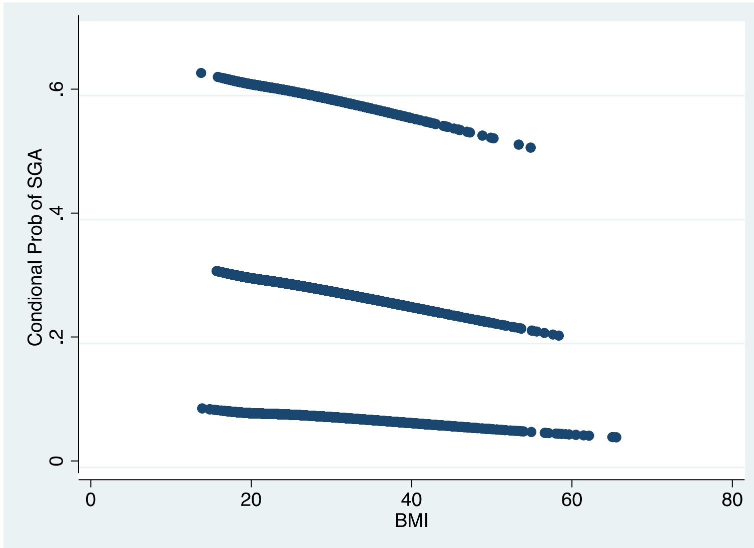

Figure 7 Conditional Predicted values of SGA vs BMI (mixed model)

Some explorations using splines on continuous pre-pregnancy BMI variable were performed. For Figure 6, the linear spline was used. It seems that there is a departure from linearity for BMI as the linear spline graph has some curvature. It appears that probability of SGA decrease as BMI increases. The wide confidence interval at BMI less than 20 might due to the small sample size.

The median spline (Figure 10) showed a negative linear relationship between pre-pregnancy BMI and predicted values of SGA. However, the linear spline and restricted cubic spline show that predicted values of SGA become stable at pre-pregnancy BMI equal to 20 kg/m^2. After pre-pregnancy BMI at 30 kg/m^2, the predicted values seem to decrease again. The restricted cubic spline seems to have a smoother curve at the points where BMI equals to 20 kg/m^2 to BMI equals to 40 kg/m^2compared to linear spline. It seems that the non-linearity part of BMI at 20 kg/m^2 follows cubic function rather than linear.

For linear spline model, the non-linearity was only statistically significant at the first knot (pvalue<0.05). The restricted cubic spline model shows that the non-linearity was statistically significant at first, second, and third knot (pvalues<0.05). However, when we fitted another model where we added the linear spline and restricted cubic spline covariates in one model, the restricted cubic spline were not statistically significant (pvalue>0.05)

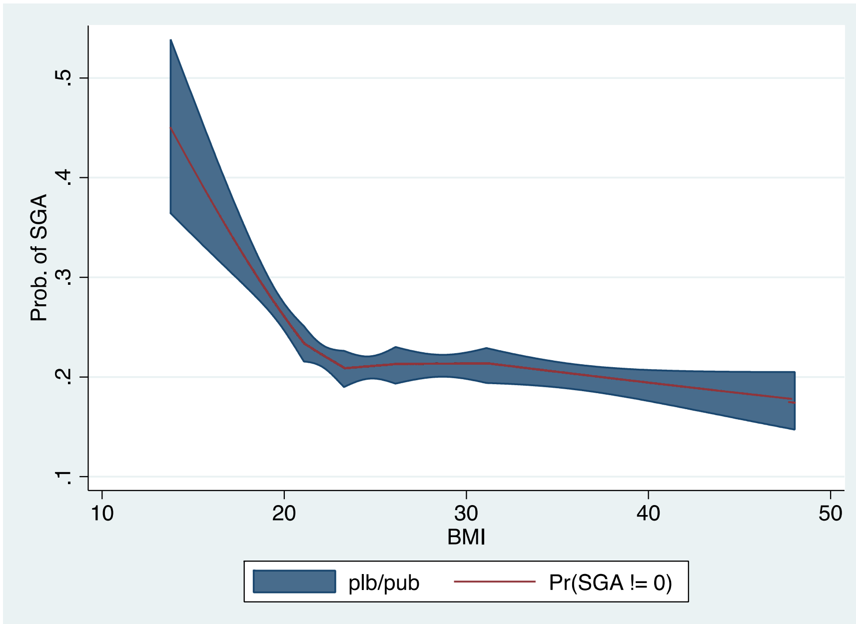

Figure 8 Linear Spline and 95% CI

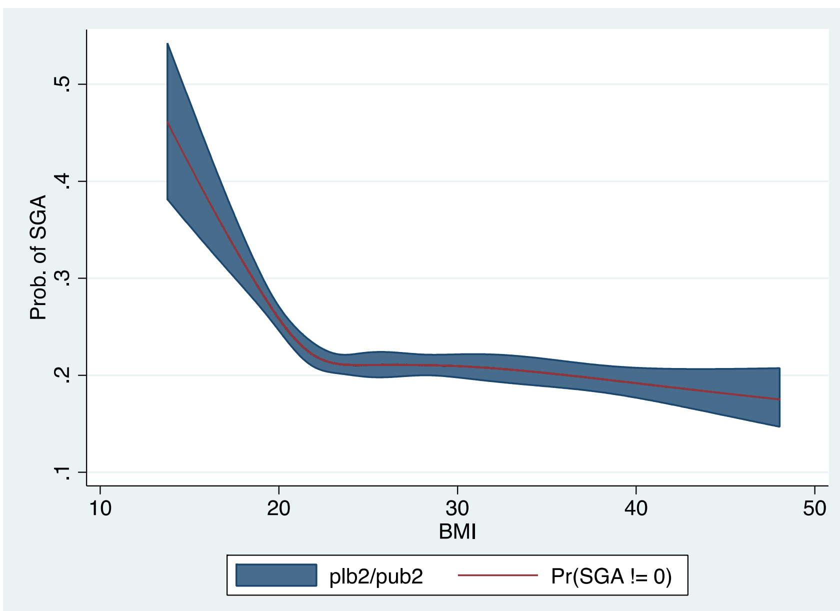

Figure 9 Restricted Cubic Spline with 95% CI

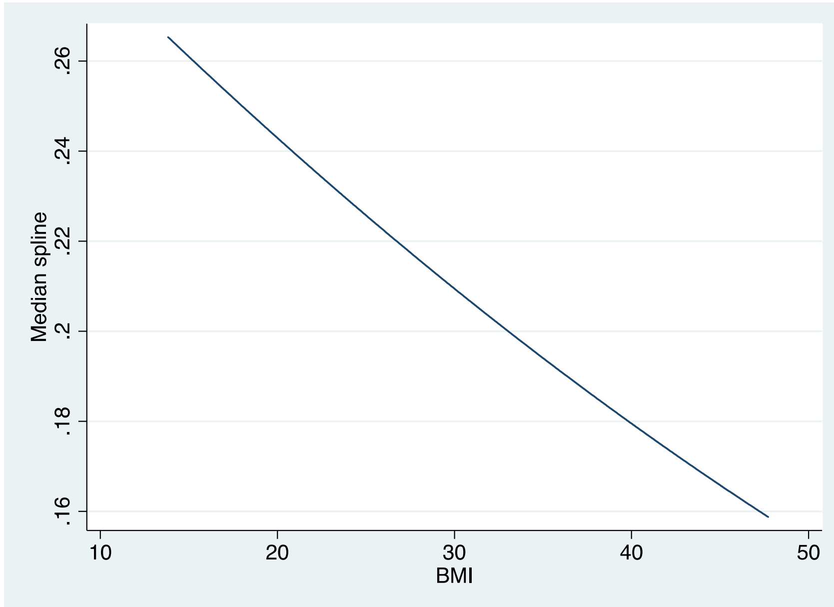

Figure 10 Median Spline

4.3 MULTIVARIATE MODELS

The multivariable mixed model (Model 1) was fitted with all the variables that were statistically significance from the univariate models (prior number of deliveries, education level, race, marital status, age, smoking pattern, pre-pregnancy hypertension, and insurance, and categorical pre-pregnancy BMI). Another multivariable GEE (Model 2) was fitted removing the not statistical significance predictors (p values> 0.5). The second model removed education level, and insurance. We compared the changes in the ORs and their 95 percent confidence interval (CI) of pre-pregnancy BMI variables from the two models. The coefficient of BMI and its 95% CI did not change dramatically. However, the QICu value for the second model was much larger than the first one. Thus, the full model (Model 1) was the best model.

4.4 FINAL MODEL

We re-fit Model 1 after removing the observations of gestational age equal to 47 weeks and pre-pregnancy BMI equal to 65.5 kg/m^2 (Model 3). However, the ORs of pre-pregnancy BMI variable did not change much between Model 1 and Model 3. Thus, we decided to leave these observations in the data as they are not outliers.

As a final model (Table 8), the multivariable GEE for SGA was fitted including the following independent variables: prior number of deliveries, categorical pre-pregnancy BMI, marital status, age, education, race, pattern of smoking, insurance, and pre-pregnancy hypertension. The categorical pre-pregnancy BMI was used for the final model instead of the continuous variable in order to obtain the odds of SGA for different BMI groups. The following table showed the ORs of BMI for different groups.

Table 8 Final Model

Variables in the model	ORs (95% CI)
Prior number of deliveries	
0 live	1 (ref)
1 or 2 live	1.02 (0.94,1.11)
3+live	0.77(0.68,0.87)
Marital status	
unmarried	1 (ref)
married	0.87(0.77,0.97)
Age	
<20 years	1.67(1.15,1.81)
20-29 years	0.94(0.86,1.04)
>=30 years	1 (ref)
Education	
Less than high school	1 (ref)
High School/GED	1.01(0.86,1.18)
Some College	0.98(0.83,1.16)
College Graduate	0.94(0.79,1.12)
Race	
NH White	1 (ref)
NH Black	1.56(1.38,1.77)
Hispanic	1.08(0.90,1.29)
NH Other	1.66(1.38,1.99)
Pattern of smoking	
No smoking during pregnancy	1 (ref)
Smoked during pregnancy	1.81(1.61,2.04)
Insurance	
Private	1 (ref)
Public (Medicaid)	1.05(0.93,1.18)
Other	1.04(0.82,1.31)
Pre-pregnancy hypertension	
No	1 (ref)
Yes	1.33(1.00,1.77)
Pre- pregnancy BMI	
Underweight<18.5	1.62(1.33,1.99)
Normal Weight 18.5-<25	1 (ref)
Overweight 25-<30	0.86 (0.77,0.95)
Obese 30+	0.74(0.67,0.82)

From the results, underweight women would have higher risk of SGA (OR=1.62, 95% CI (1.33,1.99)) compared to normal weight women controlling for priority number of deliveries, education, marital status, age, race, smoking status, insurance type, and pre-pregnancy hypertension.

Table 9 shows the comparison between univariate GEE and multivariate GEE model for pre-pregnancy BMI. For the univariate GEE, we removed all missing observation for priority number of deliveries, education, marital status, age, race, smoking status, insurance type, and pre-pregnancy hypertension variables to make sure that the sample size is the same for both univariate and multivariate GEE models. Compared to the multivariable, the ORs in the univarite model are a little bit higher. The 95% CIs are a little bit wider for univariate comparing to multivariate model. However, there are no huge differences between the ORs and CIs comparing the two models. Thus, there might not be the issue of confounders.

Table 9 Univariate and Multivariate GEE for BMI variable

Variables in the model	ORs (95% CI) (Univariate)	ORs (95% CI) (Multivariate)
Pre-pregnancy BMI		
Underweight<18.5	1.76 (1.45,2.14)	1.62 (1.33,1.99)
Normal Weight 18.5-<25	1 (ref)	1 (ref)
Overweight 25-<30	0.9 (0.82,1.00)	0.86(0.77,0.95)
Obese 30+	0.82 (0.74,0.91)	0.74 (0.67,0.82)

5.0 DISCUSSION

The results from the final model, multivariable GEE, show women with the following characteristics show statistically significant for higher risk having SGA twins birth outcomes: underweight, Non-Hispanic Black, unmarried, less than 20 years old, smoked during pregnancy, have pre-pregnancy hypertension, underweight, and receiving Medicaid.

Compared to the observational studies in the literatures on SGA and pre-pregnancy BMI for singletons, our results confirmed that association in twins. From the final model, the marginal odds of having SGA births in obese women would be 26 percent lower than normal weight women. The findings indicates that underweight women have higher odds of having SGA births compared to normal weight, controlling for prior number of deliveries, marital status, education level, age, race, smoking pattern, insurance, and pre-pregnancy hypertension. The OR for underweight compared to normal weight was 1.62 (1.33,1.99) in our findings. This confirmed which other observational studies in singletons that were mentioned in this paper.

It has been shown in recent studies that pre-pregnancy BMI is associated with infant birth weight. Inadequate gestational weight gain is associated with the increase of SGA. Li did a study in 2013 to evaluate maternal pre-pregnancy BMI and gestational weight gain with pregnancy outcomes in singletons. The study showed that maternal inadequate gestational weight gain is associated with increased risks of SGA [9]. Underweight women might be used to their dieting behaviors that might lead to inadequate gestational weight gain during pregnancy and therefore lead to SGA birth outcomes.

The marginal odds of having SGA births in twins of Non-Hispanic Black mothers is 1.56 times higher compared to Non-Hispanic White. In singleton, Asian women were shown to have higher risk of SGA compared to U.S. born White women. [31] From our results, the marginal odds of having SGA births of women in the other race group is 1.66 times higher than Non-Hispanic White women. The “other” group for maternal race consisted of women who are Non-Hispanic Asian, Native Hawaiian, Guamanian/Chamarro, Samoan, and Other Pacific Islander. Sixty-five percent of the women in this category are Non-Hispanic Asian. We think that Non-Hispanic Asian women might have significantly higher marginal odds of having SGA births in twins.

Campbell MK et al showed that the odd of having SGA births in singletons would be higher for mothers age 35 or older and who smoked during pregnancy [23]. From our results, the marginal odds of having SGA births in twins of women who are from 20 to 29 years old is less than women who are 30 years old or older. The odds of having GA births in twins of women who are less than 20 years old is 1.67 times higher compared to women who are 30 years or older. The marginal odds of having SGA births is 1.81 times higher for women who smoked during pregnancy compared to women who did not smoked during pregnancy.

Mothers with pre-pregnancy hypertension have 1.33 times higher the marginal odds of having SGA births compared to mothers without pre-pregnancy hypertension. Our findings showed that mother education levels and insurance type have no association with SGA births in twins. Raum et al showed that women with lowest educational level had a higher risk than women with highest educational level [27]. However, in their study, the lowest education level is from less than or equal to 8 years in school and the highest education level is a university degree. In our findings, the marginal risks of SGA births of women with a college degree is 6% lower compared to women who did not have a high school degree.

Table 10 shows the results when the new cutoff point was used for BMI instead of the WHO categories of BMI variable. Compared to the WHO cut points, the new cut point at BMI equals 20 kg/m^2 yields a smaller OR compared to the cutoff at 18. From the spline graphs, the risk of SGA decreases rapidly as BMI increases before BMI equals to 20 kg/m^2. After the cut point of BMI equal to 20 kg/m^2, the risk of SGA still decreases but not that extreme like before. Because of this, the OR of women who have pre-pregnancy below 20 kg/m^2 should be higher compared to women who have BMI equals to 20 kg/m^2 or higher. Therefore, the new cutoff point at 20 kg/m^2 might be more helpful in study related to pre-pregnancy BMI and SGA.

Table 10 Comparison of WHO categories of BMI and new categories of BMI variable

Variables in the model	OR (95% CI)
Pre-pregnancy BMI	
Underweight<18.5	1.78 (1.48,2.15)
Normal Weight 18.5-<25	1 (ref)
Overweight 25-<30	0.90 (0.82,0.99)
Obese 30+	0.84 (0.80,0.92)
Pre-pregnancy BMI	
BMI<18.5	1.91 (1.59,2.29)
BMI>18.5	1 (ref)
Pre-pregnancy BMI	
BMI<20	1.46 (1.31,1.64)
BMI=20+	1 (ref)

In our data, we have 22% of SGA births which is much higher than what expected comparing to the study of Shivkumar in Canada. Though comparing to other available birthweight reference charts for twins, we think that women in Canadian population of Shivkumar study would be more diverse. We assumed that the population is Canada would be closer to our dataset in term of racial diversity. However, we have over 20% of the women are Black and Hispanic in our study sample. In the study of Shivkumar, there were no Black or Hispanic mothers. Thus, we think the higher percentage of SGA births in our sample might due to the racial difference. In addition, the weight of the babies in the Shivkumar chart was done using ultrasound method. The infants in our sample were weighted after birth which might also cause percentage of SGA to be higher in our study.

6.0 LIMITATION

As one of the limitations, ultrasound based fetal weight references for twins were used to determine the percentile of SGA births outcomes in our data. However, we used the reference chart for dichorionic twins to calculate the birth weight percentile since we are unable to determine the chronicity of the twins in our statewide dataset. In addition, we used the weight cut off point for twins who were born at 37 gestational age weeks for twins who were born at gestational age weeks of 37 or older. There were 4,403 (22%) babies were born at 38 weeks or older. Thus, we might detect less number of SGA births.

In addition, there are not many twin birthweight percentile charts available for calculating SGA. In 2012, Doom published an article with the birth weight curves reference for twin among Flemish population. The author did not take into account the correlation between the twins. Another twin birthweight percentile was constructed by Liao based on a study in Brazil. In this study, the author took into account of correlated data However, we think that the racial diversity from the study is not adequate to our study sample. The most recent one that we could use is the chart from Shikumar study. However, the study only consisted of While, Middle Eastern, and East Asian women. We used the chart from Shikumar article because the mothers' race diversity was the closest to our data compared to other studies. Compared to birthweight charts for singletons, the chart from Shikumar shows similar results for the gestational age week before 32 weeks. At 32 weeks, the estimated fetal weight between twins and singletons are completely different [5]. Salomon did a study for singletons in French to develop a fetal weight reference chart. Comparing the chart from this study to Shikumar chart, the estimate of fetal weight for babies from 22 weeks to 31 weeks were similar. The 10th percentile estimated of fetal weight at 31 weeks for singletons was 1506 grams [36] compared to 1463 grams for Shikumar chart [5]. At 32, 33, and 34 gestational age weeks, Salomon chart suggested a fetal weight of 1680, 1847, and 1997 grams for 10th percentile [36] while Shikumar char suggested a fetal weight of 1631, 1785, and 1944 grams respectively [5]. It appears that after 32 weeks, twin babies have different pattern growth than singletons. Therefore, singletons birth weight reference chart cannot be used in our analysis.

Also, another limitation is the inaccuracy of birth certificate data. All of the information for our dataset is based on birth certificate data. Maternal weight data is poorly reported on birth certificates. The agreement of pre-pregnancy BMI records on birth certificate with medical records BMI varied from 52% to 100%. [26].

In addition, we could not account for hospital in our dataset. Different hospitals might have different ways to record the data as well as ways to measure the mothers' heights and weights. These differences might create bias for the data in our study sample. We were not able to control for the hospital variable because there was no record in the data that indicates which hospital the observations come from.

Recording errors are an issue in our dataset. We saw some inaccuracy of gestational age and birthweight in our sample. For example, a baby weighted 1,150 grams and was born at 24 weeks old. There was no way to verify whether this information were accurate. .Also, we discovered recording errors for some twin pairs in our dataset. Some twins did not have the same mothers' characteristics. There was no way to check for the errors. Thus, we have to match the information of second twin based on the data of the first twin. By doing this, we might accidentally misclassify some of the women from underweight group to be normal weight or overweight category. However, the percentage of these recording errors was very small comparing to the sample size we had. Therefore, we do not think that the misaligned values would be problematic.

7.0 FUTURE WORK

As mentioned earlier, the MCAR assumption did not hold for our data based on the Little's test. One could try data imputation to adjust for what is missing and then fit the GEE model.

Also, we did not consider interaction terms between the independent variables in our analysis. Possible future work could be done on assessing the interaction terms to test whether there is a need for interaction in the model. One could try to assess the interaction between maternal race and pre-pregnancy BMI.

More exploration with spline is needed as we only included some general types of splines in our analysis. In addition, the linear and cubic spline for BMI variable suggests that mothers' BMI has a peak change at BMI equal 20 instead of 18.5. One could try to categorize BMI variable that less than or equal to 20 instead of 18.5 to explore more about the association between mother pre-pregnancy BMI and SGA twin births outcomes.

8.0 PUBLIC HEALTH SIGNIFICANCE

Higher SGA births in twins will lead to higher infant mortality and morbidity. Sicker babies will consume more public resources. Therefore, reducing numbers of SGA births would help to lower infant morbidity in twins causing less public spending. From our findings, underweight women are at a higher risk of SGA births compared to women in other groups. Percentage of underweight women in U.S. is not a huge problem at this moment. However, the OR for SGA overweight and obese women groups is reduced in our results. As of now, obesity is raising a flag and causes many problems for public health issues in U.S. Based on our findings, the focus for preventing SGAs births in twins would be underweight women. Overweight and obese women were being protected from SGA births according to our result. Inadequate interpretation of this result such as inappropriately improving the weight of women prior getting pregnant would lead to higher percentage of overweight and obese women in the nation.

APPENDIX: TABLES

Table 11 Model 2

Variables in the model	ORs (95% CI)
Prior number of deliveries	
0 live	1 (ref)
1 or 2 live	1.04 (0.96,1.13)
3+live	0.80(0.71,0.90)
Marital status	
unmarried	1(ref)
married	0.83(0.75,0.92)
Age	
<20 years	1.53(1.25,1.88)
20-29 years	0.94(0.86,1.03)
>=30 years	1(ref)
Race	
NH White	1(ref)
NH Black	1.63(1.45,1.84)
Hispanic	1.16(0.99,1.37)
NH Other	1.65(1.38,1.97)
Pattern of smoking	
No smoking during pregnancy	1(ref)
Smoked during pregnancy	1.84(1.65,2.06)
Pre-pregnancy hypertension	
No	1(ref)
Yes	1.39(1.05,1.84)
Pre-pregnancy BMI	
Underweight<18.5	1.65(1.36,2.01)
Normal Weight 18.5-<25	1(ref)
Overweight 25-<30	0.86(0.78,0.95)
Obese 30+	0.75(0.68,0.83)

Table 12 Model 3

Variables in the model	ORs (95% CI)
Prior number of deliveries 0 live 1 or 2 live 3+live	 1 (ref) 1.02 (0.94,1.11) 0.77(0.68,0.87)
Marital status unmarried married	 1(ref) 0.87(0.77,0.97)
Age <20 years 20-29 years >=30 years	 1.44(1.15,1.81) 1(ref) 0.94(0.86,1.04)
Education Less than high school High School/GED Some College College Graduate	 1(ref) 1.01(0.87,1.19) 0.98(0.83,1.16) 0.94(0.79,1.12)
Race NH White NH Black Hispanic NH Other	 1 1.56(1.37,1.77) 1.08(0.90,1.29) 1.66(1.38,2.00)
Pattern of smoking No smoking during pregnancy Smoked during pregnancy	 1(ref) 1.81(1.61,2.04)
Insurance Private Public (Medicaid) Other	 1(ref) 1.05(0.93,1.18) 1.04(0.82,1.31)
Pre-pregnancy hypertension No Yes	 1(ref) 1.33(1.00,1.77)
Pre-pregnancy BMI Underweight<18.5 Normal Weight 18.5-<25 Overweight 25-<30 Obese 30+	 1.62(1.33,1.99) 1(ref) 0.86(0.78,0.95) 0.74(0.67,0.83)

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