

The Effects of Pre-Pregnancy BMI on the Relationship Between Maternal Smoking and Low Birth Weight

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Summary

1. Introduction

The relationship between maternal prenatal smoking and low birth weight (LBW) is a topic that has long been of interest to investigators, due to the association of LBW with poor health outcomes (Blencowe et al. 2019). An infant is considered to be LBW when they are born weighing less than 2500 grams, or less than about 5.5 lbs (“WHO Global Nutrition Targets 2025: Low Birth Weight Policy Brief” n.d.). LBW has been associated with many adverse effects, such as a higher mortality rate (Martin et al. 2015); various psychiatric and neurological problems (Hack et al. 2005); and even poor academic achievement (Hack et

al. 2002). LBW has also been implicated as an economic impact, with Kowlessar, Jiang, and Steiner (2006) reporting an increased cost of hospital stays at \$27,200 for LBW infants compared to \$3,200 for all newborns. Maternal smoking during pregnancy has been of intense interest for decades because it has been implicated in LBW (Zhang and Yang 2019; Parascandola 2014; J. Yerushalmy 2014).

However, although the association of maternal smoking with LBW is well-documented and consistent (Ventura et al. 2003), the mechanism by which it contributes to LBW and how this mechanism might be affected by other factors are not well understood. For example, the risk of LBW from prenatal smoking has been demonstrated to be significantly reduced among overweight and obese mothers (La Merrill et al. 2011). But it is unclear how these mechanisms interact with one another, as maternal pre-pregnancy BMI is itself implicated as a predictor for birth-weight (Gul et al. 2020). This relationship is further complicated by the fact that one of the primary outcomes that makes LBW a topic of interest for researchers, perinatal death, is not always associated with LBW in the way that it might seem that it should — it was demonstrated by J. Yerushalmy (2014) that among LBW infants, maternal smoking was actually associated with a decreased risk of perinatal death. Ebrahim (2014) proposed that these seemingly contradictory findings, often referred to as the “Birth weight Paradox” (Tyler J. VanderWeele 2014). This would reasonably explain Yerushalmy’s finding if the association of this phenotype with maternal smoking were strong enough such that LBW infants with smoking mothers were much more likely to have this phenotype compared to others.

The mechanisms that might contribute to these “other” phenotypes of LBW are not entirely clear, although existing work does point toward some reasonable candidates to start with. Tyler J. VanderWeele (2014) proposes that the increase in mortality for LBW infants with non-smoking mothers compared to smoking mothers may be that there is a much more insidious root cause for LBW in non-smoking mothers, such as malnutrition. There is some support for malnutrition as a potential cause for LBW, as it has been demonstrated there is a higher risk of pregnancies resulting in LBW in situations of inadequate social support, such as in low-income households (Gould, Davey, and LeRoy 1989) and in teenage pregnancies (Fraser, Brockert, and Ward 1995). As noted above, low pre-pregnancy BMI has been noted to be associated with LBW (Gul et al. 2020), as well. These findings suggest that evaluating the effects that BMI has on the relationship between maternal smoking and LBW may help to clarify potential directions for future work related to the mechanisms underlying LBW and infant mortality.

2. Study Background

The sample used for this analysis was taken from the Child Health and Development Studies (CHDS), a data set used by J. Yerushalmy (2014). Below is Yerushalmy’s description of this data set:

The information is derived from our Child Health and Development Studies (CHDS)—a comprehensive investigation of all pregnancies that occurred between 1960-1967, among women in the Kaiser Foundation Health Plan in the San Francisco-East Bay area. The Kaiser Health Plan is a prepaid medical care program.

The members represent a broadly based group which is not atypical of an employed population. It is deficient only in the two extremes: the very affluent and the very indigent portions of the population. The women were interviewed on a variety of medical, genetic, and environmental subjects, including behavior variables, such as smoking, drinking, use of contraceptive methods and the like. The interview took place early in pregnancy. The information was thus derived prospectively before the woman knew the outcome of the pregnancy. The child was followed to evaluate his physical and mental development including survival and the development of congenital anomalies.

The interviewed group comprised some 15,000 pregnancies. This study is based on single live born infants among the whites and the blacks. The numbers of members in the other ethnic groups in the sample were too small and were therefore left out. The study is based on 9,793 pregnancies among the whites and 3,290 among the blacks

A key point to note from the description above is that the majority of pregnancies from the data set involve middle-class women who have established healthcare. This will be an important limitation going forward, because low social status has been shown to be associated with both LBW (Gould, Davey, and LeRoy 1989) and, to some extent, with BMI (Basto-Abreu et al. 2018). There is the possibility that there are aspects of the relationship between maternal smoking and LBW that would not be apparent from this sample simply because it has poor representation of women with low socio-economic status or women who are not established with a regular medical provider. With that being said, however, this analysis is still expected to provide some value in the sense that it may provide insight into potential avenues that might be taken. Potentially, this analysis could reveal important attributes of the relationship between maternal smoking and factors such as pre-pregnancy BMI, maternal height, or maternal age, which could then be evaluated further in future work.

Due to limitations of scope, this analysis was performed with a reduced sample of 680 white women from the source data set. Many of the variables described by Yerushalmy in the quote above, such as alcohol use or contraceptive methods, were not examined. Instead, the focus of this analysis is on 6 variables from the J. Yerushalmy (2014) study: birth-weight as the response variable; and gestational age, maternal age, mean number of cigarettes smoked per day by the mother, maternal height, and maternal pre-pregnancy weight as the predictors. Additionally, pre-pregnancy BMI was derived from maternal height and pre-pregnancy weight and examined as well. Each of these variables is discussed briefly below:

Birth weight This is the the weight of the infant at the time of birth, in pounds. This is the response variable for this analysis and, as noted previously, this is of interest because LBW has been associated with poor health outcomes, such as infant mortality (Martin et al. 2015).

Mean number of cigarettes smoked per day is split into four categories, for levels of smoking: light (< 10 cigarettes per day), moderate (10 - 20 cigarettes per day), and heavy (> 20 cigarettes per day) smokers. This is the primary predictor of interest in this analysis, since, as described above, it has been demonstrated in multiple studies in the past that maternal smoking is associated with LBW (Zhang and Yang 2019; Parascandola 2014; J. Yerushalmy 2014). These category thresholds were chosen somewhat arbitrarily, although it should be noted that consistency in definitions for smoking severity has been poor. For example, Husten (2009) reports that measures such as thresholds of <4 , <10 , <15 , and <20 have all been used to classify “light” smoking. husten_how_2009 further points out that cigarettes smoked per day may not necessarily be the best proxy for toxin exposure levels, due to reasons such as the differences in toxin levels in different tobacco products and the nonlinear relationship of cigarette consumption with disease risk in some cases, among others. For these reasons, levels of smoking severity were chosen out of convenience in providing separation of smoking groups, with the intention of potentially identifying general trends and without interpreting too heavily in what significant differences between these levels might mean. It should be noted that the effects of other potential exposures, such as paternal smoking during the pregnancy, were not assessed in this analysis.

Gestational age is a continuous variable, measured in weeks. This is a secondary predictor variable for this analysis and is of interest in the study because, as noted by Engle (2006), birth weight is often associated with gestational age but can differ in clinically-significant ways. This suggests that controlling for gestational age may reveal more about the biological mechanisms underlying the relationships of birth weight with the other variables in this study than if birth weight were examined without gestational age.

Maternal age is a continuous variable, measured in years. This is also a secondary predictor of interest in this analysis, although the relationship that maternal age has with birth weight is more complex. Dennis and Mollborn (2013) discuss how pregnancies at both ends of the spectrum for maternal age are associated with an increased risk for LBW. However, they also report that there are a variety of other non-biological factors involved and that “LBW disparities by maternal age are a complex product of socioeconomic disadvantage and current social and behavioral factors, such that LBW risk does not operate uniformly by race/ethnicity or maternal age.” (Dennis and Mollborn 2013) Similarly, Wang et al. (2020) found that the relationship between maternal age and birthweight is non-linear and that the risk of LBW increased both with very young and very old maternal age. For these reasons, including maternal age in the analysis can serve to verify past results and also provide another means for observing how relationships with the response variable change when other predictors are present.

Maternal height is a continuous variable, measured in inches. This is a secondary variable of interest for this analysis because maternal height has been shown to have a direct association with LBW, with increasing risk for LBW as height decreases, even in cases where socio-economic status is thought not to be a factor (Inoue et al. 2016). This would suggest that there could be a biological component in LBW independent of malnutrition or social status. Including this variable in the study is useful because it serves to motivate the biological argument for LBW not explained by maternal smoking.

Maternal pre-pregnancy weight is a continuous variable, measured in pounds. Similar to maternal height, this is a secondary predictor of interest in this analysis due to the biological implications it might have about the mechanism for LBW. Also like maternal height, pre-pregnancy weight has been shown to have a direct association with LBW, with increasing risk of LBW as pre-pregnancy weight decreases (Zhang and Yang 2019). Pre-pregnancy weight is useful to include in the analysis because it has been postulated that the association between pre-pregnancy weight and LBW can be explained by poor nutrition or malnutrition (Inoue et al. 2016), suggesting that pre-pregnancy weight might be a good proxy for the mother’s pre-pregnancy nutritional status.

Maternal pre-pregnancy BMI is a continuous variable, derived from maternal height and pre-pregnancy maternal weight data from the study. This is another secondary predictor that is of interest for this analysis because it provides for a slightly different way to examine the relationship between maternal height and pre-pregnancy weight, since BMI is a measure of weight relative to height. This may make pre-pregnancy BMI a better proxy for nutritional status than pre-pregnancy weight alone.

There is a strong likelihood that the small size and relative uniformity of the sample used for this analysis will result in issues of generalization, particularly when the original data set the sample was itself fairly homogeneous. The purpose of this analysis for this reason is not to make generalizable conclusions about the population but instead to identify general trends towards significance that may inform future work.

3. Statistical Analysis

This analysis has two primary aims: (1) to evaluate the effects of BMI on the relationship between maternal smoking and birth weight; and (2) to develop a model to predict birth weight based on factors such as smoking status, maternal BMI, and age. The primary hypothesis that will be evaluated during this analysis is that pre-pregnancy BMI is a confounder for the relationship between birthweight and smoking status. A major reason BMI is of interest in this analysis is due to its usefulness as a diagnostic tool for evaluating malnutrition, which can be otherwise difficult to assess (Cederholm et al. 2015). If a high BMI were to significantly mitigate the risk of LBW from maternal smoking compared to low BMI, this may highlight a potential biological mechanism for LBW and infant mortality that could be evaluated in future work. The motivation behind the second aim in this analysis would be to provide validation for existing methods of predicting LBW based on maternal characteristics, such as maternal pre-pregnancy BMI (Gul et al. 2020), maternal height (Inoue et al. 2016), and smoking status (Knopik et al. 2016).

The analysis was accomplished in three major steps:

- A preliminary exploratory analysis was performed, in order to identify any basic relationships between the variables in the sample.
- An association model was built using birth weight as the primary response variable and cigarettes smoking as the primary predictor. Multiple relationships were examined during this step, and specifically the role of BMI as a confounder for the relationship between maternal smoking and birth weight was examined.
- A prediction model was then built, again with birth weight as the primary response variable and maternal smoking as the primary predictor.
- Last, a mediation analysis was performed to determine whether any of the secondary predictors might have a mediating effect on the relationship between birth weight and maternal smoking.

Table 1: Descriptive statistics from sample of 680 pregnancies

Variable	Mean	Standard deviation	Min	Q1	Median	Q3	Max
Birth weight (lbs)	7.52	1.09	3.30	6.80	7.60	8.20	11.4
Gestation age (weeks)	39.77	1.88	29.00	39.00	40.00	41.00	48.0
Maternal age (years)	25.86	5.46	15.00	21.00	25.00	29.00	42.0
Number of cigarettes smoked daily	7.43	11.27	0.00	0.00	0.00	12.00	50.0
Maternal height (inches)	64.43	2.48	57.00	63.00	64.00	66.00	71.0
Maternal pre-pregnancy weight (lbs)	126.90	17.88	85.00	115.00	125.00	135.00	246.0
Maternal pre-pregnancy BMI	21.47	2.63	15.55	19.74	21.12	22.59	39.7

3.1 Exploratory Analysis

For this section of the analysis, the primary goal was to gain a basic understanding of the characteristics of the variables used in this analysis. A summary of descriptive statistics is presented in Table 1. A brief analysis of each of the variables shown in Table 1 is described below:

Birth weight is a continuous ratio variable that is measured in lbs. From Figure B.2, it can be seen that the distribution of Birth weight is very symmetric and approximately normal as the response variable. There would be no indication for transformation of this distribution, since the shape is already very reasonably normal and adding transformations to the analysis would therefore be of questionable benefit.

Gestation age is a continuous ratio variable that is measured in weeks. From Figure B.2, it can be seen that this variable is also approximately normal and fairly symmetric.

Maternal age is a continuous ratio variable that is measured in years. Figure B.2 shows that this variable is skewed to the right.

Cigarettes smoked per day is a continuous ratio variable (since it is an average). From Figure B.2, it can be seen that the distribution of this variable is very asymmetric and there appear to be multiple regions around which the data points tend to be concentrated. The most salient of these is around 0 cigarettes per day, which represents non-smokers. This was one of the primary reasons that cigarette-smoking was turned into a categorical variable, as there would be good reason to believe that there are significant differences between the very large non-smoker group and all of the other data points in the sample, particularly when considering the response variable, birth weight. As noted in the previous section, the thresholds chosen for this variable were 0-10, 10-20, and >20 cigarettes per day. These thresholds were chosen partially out of convenience, although Husten (2009) notes that both <10 and <20 cigarettes per day have been used to designate “light” smoking by researchers in the past (it may be helpful to think of the 0-10 and 10-20 thresholds as “light” and “medium-light” for this reason).

Maternal height is a continuous ratio variable, measured in inches. Figure B.2 shows that this variable is reasonably symmetric and approximately normal.

Maternal pre-pregnancy weight is a continuous ratio variable, measured in lbs. Figure B.2 shows that this variable is skewed to the right.

Figure B.1 shows a scatter-plot matrix for each of the variables described in this analysis. This representation shows no obvious departure from linearity for any of the variables in this sample. Some of the variables appear to lack any obvious association at all, such as between BMI and age. Other pairs do seem to more clearly show a possible association, such as birth weight vs gestation age or pre-pregnancy weight and BMI. However, neither of these findings are surprising, as it has been noted by authors such as Engle (2006) that

birth weight and gestational age are associated with one another and BMI was calculated directly from pre-pregnancy weight. These findings suggest that if any associations are found in this analysis, they are likely to be weak.

The correlation matrix from Output A.1 shows similar findings: there are a few pairs, such as birth weight vs gestation age (0.4212) and pre-pregnancy weight vs maternal height (0.9925), that are highly correlated with one another, but otherwise the correlations are much weaker. Other notable associations outside of these more clear associations would be birth weight vs mean cigarettes per day (-0.1707) followed by birth weight vs pre-pregnancy weight (0.0340), although these associations are much weaker.

3.2 Method

A simple linear regression analysis was performed to establish the association between birth weight as the primary response variable and cigarette use as the primary predictor. This is appropriate because the birth weight is a quantitative variable. Simple regression analysis was used to develop an association model and a prediction model with birth weight as the response variables and the remaining variables in this sample as the predictors, namely: gestation age, maternal age, average cigarettes smoked per day, maternal height, and maternal pre-pregnancy weight. Additionally, a new variable BMI was derived from existing maternal height and pre-pregnancy weight data and was included in the analysis, as well. The association model was developed using the “backward-elimination” method for efficiency purposes. The prediction model was developed using the parsimonious framework.

The advantages of this strategy is that simple regression analysis is relatively easy to perform and is not hardware intensive. The findings from this analysis should also be easier to communicate and easier for the reader to interpret, compared to some methods. One potential limitation of this method would be that if the relationships between the variables in this sample are truly non-linear, this would diminish the value of the models produced by this analysis greatly.

BMI and categorical variables for maternal smoking were derived according to the following equations:

$$BMI = 703 * mppwt / mheight^2$$

$$SMK_1 = \begin{cases} 1 & \text{if } 0 < mnocig \leq 10 \\ 0 & \text{otherwise} \end{cases}$$

$$SMK_2 = \begin{cases} 1 & \text{if } 10 < mnocig \leq 20 \\ 0 & \text{otherwise} \end{cases}$$

$$SMK_3 = \begin{cases} 1 & \text{if } mnocig > 20 \\ 0 & \text{otherwise} \end{cases}$$

where *mmpwt* is mean pre-pregnancy weight, *mheight* is maternal height, and *mnocig* is the mean number of cigarettes smoked per day.

3.3 Association Model

First, a crude association model was developed for the response variable birth weight and the primary predictor mean number of cigarettes per day. There was highly statistically significant evidence ($P < 0.001$,

see Output A.2) that this model provides for a better fit of the data compared to the mean value for birth weight alone. These findings suggest that a crude model such as this one would be appropriate for this sample.

Next, an analysis was performed for the remaining variables to determine if any qualify as effect modifiers or confounders. This process was conducted step-by-step with each variable evaluated against the crude model, shown below for each variable.

Gestational Age There was no significant evidence to support the inclusion of gestational age as an effect modifier for the relationship between birth weight and maternal smoking ($p > 0.10$ for all three interaction terms; see Output A.3), but there was sufficient support to include gestational age as a confounder ($>10\%$ change in slope for all three smoking terms; see Output A.4).

Maternal Age There was no evidence supporting the inclusion of maternal age as an effect modifier for the relationship between birth weight and maternal smoking ($p > 0.10$ for all three interaction terms; see Output A.5) and insufficient support to include it as a confounder ($<10\%$ change in slope for all smoking terms, see Output A.6).

Maternal Height There was no evidence to support the inclusion of maternal age as an effect modifier ($p > 0.10$ for all three interaction terms; see Output A.7) and no support for maternal age as a confounder in the model ($<10\%$ change in slope for all smoking terms; see Output A.8).

Maternal Pre-Pregnancy BMI There was no evidence to support the inclusion of maternal age as an effect modifier ($P > 0.10$ for all three interaction terms; see Output A.9), but there was support for the inclusion of BMI as a confounder for the relationship between maternal smoking and birth weight ($>10\%$ change in one slope term for smoking with inclusion of BMI; see Output A.10).

Therefore, the full association model can be described by the following equation:

$$\hat{BWT} = -2.90 - 0.21 * \hat{SMK1} - 0.61 * \hat{SMK2} - 0.39 * \hat{SMK3} + 0.25 * \hat{gestwks} + 0.04 * \hat{BMI}$$

This model satisfies all of the assumptions for regression. Examination of model diagnostic Figures C.1 and C.2 reveals no overt change in variance with increasing \hat{Y} , suggesting that the homoscedasticity assumption is met. Furthermore, the residuals do not seem to be asymmetrically distributed, skewed, or multi-modal in any way, suggesting that the normality assumption is also met. Examination of Q-Q plots shown in Figures C.3, C.4, and C.5 also support the normality assumption, with the majority of points consistent with a straight line and only a handful of points at the extremes possibly signaling a deviation from normality (Shapiro-Wilk testing would not be appropriate in this situation because of the large sample size). The reference cell coding approach for creating dummy variables for smoking category ensures that the linearity assumption is met.

Outliers An assessment of potential outliers was assessed using Cook's Distance, which is shown in Output C.6. None of the data is implausible, with the exception of a 48 week gestational age. According to Hoffman et al. (2008), a gestational age of 48 weeks is in the 99.9th percentile of births. A new data set with this outlier removed was created. In comparison of Output A.12 with A.11, it can be seen that there is only slight changes to the slope coefficients after this was performed.

Colinearity Colinearity was then checked for using a variance inflation factor (VIF) assessment, which is shown in Output C.7. This revealed no factors over 10, which does not suggest there is any significant colinearity in the model.

Confidence Intervals Output A.13 shows confidence intervals for the full vs reduced association models produced by this analysis. These findings show that the confidence intervals for slightly narrower for the full model compared to the reduced model.

From comparison of the crude model in Output A.2 and the adjusted full model from Output A.11, it can be seen that the adjusted R^2 has increased from 0.05432 for the crude model to 0.234 for the full model. This suggests there was improvement in the fit of the regression of birth weight on maternal smoking when

gestational age and pre-pregnancy BMI are included as confounders. These findings provide evidence for a confounding effect from both BMI and gestational age, which suggests that at least some of the association between maternal smoking and birth weight is distorted by maternal smoking and gestational age. This could be due to some causal relationship between these variables or it could be due to some other combination of factors not examined here.

This model was built by starting with a crude model and then separately assessing whether additional predictors should be considered as effect modifiers or confounders. The main advantage of this method was that it is simple and is not time-consuming. A potential drawback from this, however, is that it neglects many of the possible interactions and relationships between the different variables in the study that might not be apparent when only checked against the crude model. However, such an analysis would require extensive examination of interactions between variables and would likely be too cumbersome for the scope of this project.

3.4 Prediction Model

A prediction model was built using a backward-elimination procedure, starting with a complete model containing all variables from the study (except for maternal pre-pregnancy weight, again due to concerns about colinearity with BMI). This model was built over two iterations, shown in Outputs A.14 and A.15. Maternal age was removed during the first step, since it was the least significant term in the model and had an insignificant slope coefficient ($P > 0.10$). During the second step, no variables were removed since all slope coefficients were significant ($P < 0.10$). Although the coefficient for the first smoking term had the highest P-value during this step, it is still considered significant ($0.01 < P < 0.10$). Additionally, this variable will be left in the model due to its role as a primary predictor variable.

This resulted the following model:

$$B\hat{W}T = -8.16 - 0.18 * S\hat{M}K1 - 0.55 * S\hat{M}K2 - 0.41 * S\hat{M}K3 + 0.24 * gest\hat{w}ks + 0.04 * B\hat{M}I + 0.08m\hat{h}eight$$

By inspection, it can be seen that this procedure has produced almost the same model as that produced from the association model-building method. Analysis of residuals in Figures C.8 and C.9 shows that there is no clear change in variance as the value of birth weight changes, suggesting that this model meets the assumption of homoscedasticity. There is also no clear departure from normality in either of these plots. Again, since smoking status was split into dummy variables, the linearity assumption has also been met. VIF assessment does not suggest there is any significant degree of colinearity (output C.7). Confidence intervals for this model are shown in Output A.15 — the confidence intervals for this model appear to be about the same width as those for the association model.

These findings suggest that a baby born at the average gestation time to a non-smoking mother of average height and weight is predicted to be $-8.16 + 39.77 * 0.24 + 0.04 * 21.47 + 0.08 * 64.43 = 7.36$ lbs. Gestation age has by far the most profound effect on this factor, with a coefficient of 0.24 lbs per week gestation, which is reasonable since it has been well established that premature babies have a higher risk of LBW. Smaller effects are seen from pre-pregnancy BMI and maternal height, which result in a change of 0.08 lbs per unit of pre-pregnancy BMI and 0.08 lbs per inch in the mother's height. When the mother smokes, this model predicts a loss of about 0.18 lbs birth weight if the mother is a light smoker (< 10 cigarettes per day) or a loss of 0.41 - 0.55 lbs birth weight if the mother smokes more than that. Since the threshold for LBW is about 5.5 lbs, this suggests that the mother would have to have some combination of smoking and either short stature or low BMI to explain how a newborn might have a weight at this threshold.

The R^2 value for this prediction model is 0.2675 (Output A.15), which is very slightly higher than the R^2 of 0.234 produced by the association model process. This suggests that this prediction model explains slightly more of the variance in the response variable birth weight compared to the association model produced previously. However, these differences are not large enough to be of particular concern that the association model would make for an inferior fit of the data compared to this model, and since the association model

is made up of one fewer variable, it may be reasonable to choose that model over this one for ease of interpretation. It may be that the effect of maternal height is just not significant enough that it would be noticeable in the stepwise procedure used in the association section to check for confounding/effect modification but was significant enough not to be removed from the backward elimination procedure used to create the prediction model. This is reasonable from a logical standpoint, as well, since the association model already includes BMI, which does account for height to some degree. The slight increase in R^2 value in the prediction model compared to the association model could then be explained by the small degree of variance that is explained better by the direct relationship with height rather than the indirect relationship accounted for by BMI.

3.5 Mediation Analysis

Based on preliminary research, the possible relations between the variables in the dataset are depicted below:

[DAG of possible mediators by BMI or gestational age](mediation_dag2.svg “DAG of possible mediators by BMI or gestational age”

Regression of gestational age on BMI provides no significant evidence for an association ($p > 0.10$; Output D.1), suggesting that “intertwined” mediation can be ignored for this analysis (e.g. propensity matching) and that mediation analysis can be performed separately for each of the two potential mediators (gestational age and BMI). The following DAGs depict the hypothesized relations:

Mediation by BMI:

[DAG of possible mediator by BMI](BMI_mediation.svg “DAG of possible mediator by BMI”

Mediation by Gestational Age:

[DAG of possible mediator by gestational age](gestational_age_mediation.svg “DAG of possible mediator by gestational age”

Pre-Pregnancy BMI Linear regression of maternal smoking on pre-pregnancy BMI and of birth weight on pre-pregnancy BMI shows significant relationships ($p < 0.01$ in all cases, see Outputs D.2 and D.3), suggesting the mediation of the smoking-gestational weight relation by BMI is plausible.

Simulations from Outputs D.4, D.5, and D.6 show evidence that ~23%, ~6%, and ~5% of the effect on birth weight from light smoking, moderate smoking, and heavy smoking, respectively, is mediated by pre-pregnancy BMI (slightly different values may be obtained upon subsequent simulations). Estimates for mediated effect and proportion mediated met significance thresholds ($P > 0.10$).

Gestational Age Output D.7 shows evidence that light and moderate smoking categories have a significant association with gestational age ($P < 0.10$) and Output D.8 shows evidence for a significant association between birth weight and gestational age. These findings suggest that the mediation of the smoking-gestational weight relation by BMI is plausible.

Simulations from D.9, D.10, and D.11 show evidence that ~34%, ~18%, and ~13% of the effect on birth weight from light smoking, moderate smoking, and heavy smoking, respectively, is mediated by gestational age (slightly different values may be obtained upon subsequent simulations). Estimates for mediated effect size met the significance threshold ($P < 0.10$) for light and moderate smokers, but not for heavy smokers. Estimates for proportion mediated met significance thresholds ($P < 0.10$) for moderate smokers only.

These findings provide evidence that both BMI and gestational age are independent mediators for the relationship between maternal smoking and birth weight.

4. Discussion

The purpose of this analysis was to build association models and prediction models for the relationship of birth weight with maternal smoking, as well as other predictor variables. It was found that there was a significant linear relationship between birth weight and maternal smoking, at all three designated smoking severity levels. It was also found that pre-pregnancy BMI and gestational age could both qualify as confounders for the relationship between maternal smoking and birth weight. The parsimonious prediction model for birth weight contained one more variable than the association model, maternal height, suggesting that maternal height does have predictive power for birth weight, although there was not evidence to support maternal height as either an effect modifier or a confounder for this relationship. Mediation analysis provided support for both pre-pregnancy BMI and gestational age as mediators for the relationship between maternal smoking and birth weight, suggesting that these variables could partially explain the relationship between birth weight and maternal smoking.

These findings provide support for the hypothesis that BMI is a confounder (and possibly a mediator) for the relationship between maternal smoking and birthweight. These findings may imply that there is some facet of the biological mechanism for low birth weight that smoking mothers are more vulnerable to but mothers with high BMI are more resistant to.

This analysis had some fairly substantial limitations for evaluation of this hypothesis, as discussed earlier. Previous work has discussed how malnutrition may be a significant component in LBW and that the relationship that low pre-pregnancy BMI has with LBW is because BMI can serve as a reasonable proxy for nutritional status in situations of inadequate social support. However, the sample for this analysis contained primarily middle-class white women who all had insurance and regular healthcare. This sample would have very poor representation of individuals with poor nutrition that would be of interest in testing the hypothesis that malnutrition has a significant effect on birth weight that might meaningfully have a connection with the relationship between LBW and infant mortality.

Another potential issue with the sample data used in this analysis, likely due to the age of the study it was taken from, is that there is a large amount of medical data that was missing from this sample that might have been useful for evaluating the relationships in the study. For example, it may have been helpful to know which of the LBW infants in the study had adverse outcomes such as mortality in first year of life, as this may also have resulted in some useful relationships in the model. Other information that might have been useful for the analysis would have been the mother's health status, such as whether she had chronic diseases like diabetes or heart disease; and other social habits, such as alcohol use or use. This information could have helped to broaden the picture more and inform whether the relationships seen in this study were extraneous associations only seen because of how little was known about the sample.

There were also limitations in the procedure used for this analysis, as well. A limited method of association-model building was performed where only the crude model was used to check each variable for effect modification and confounding. Although this method still produced statistically significant findings, it is possible that a more rigorous method for model-building could have produced more appropriate results and possibly helped to identify relationships that were not obvious from this relatively basic approach. Similarly, although a conventional backwards-elimination procedure was performed for the prediction model, the model was not verified against test data. Performing more rigorous model-building procedures in future work would likely provide some improvement for the conclusions made in this analysis.

For these reasons, this analysis should be interpreted with caution and is instead meant to identify trends that might be of interest for future studies. This analysis has identified some trends that may be apparent in more generalized populations and could be of value in future work. Conversely, however, there may be general trends present in the population that were not apparent in this sample but may have become apparent if a more representative sample were used. Overall, these findings are promising in the sense that they show that it might be possible to understand LBW and infant mortality better as more information about the factors surrounding these outcomes becomes available. Future work could examine whether these relationships are changed when mothers in situations of poor social support are included in the study.

Appendices

Appendix A: R Output

Output A.1: Correlation Matrix

```
##           bwt gestwks      age mnocig mheight  mppwt      BMI
## bwt      1.0000  0.4212 -0.0132 -0.1707 -0.0070  0.0340 -0.0235
## gestwks  0.4212  1.0000  0.0074  0.0096  0.0407 -0.0467  0.0444
## age      -0.0132  0.0074  1.0000  0.0476 -0.0035  0.0068  0.0029
## mnocig   -0.1707  0.0096  0.0476  1.0000 -0.0240  0.0318 -0.0337
## mheight  -0.0070  0.0407 -0.0035 -0.0240  1.0000  0.9925 -0.9904
## mppwt     0.0340 -0.0467  0.0068  0.0318  0.9925  1.0000  0.9970
## BMI      -0.0235  0.0444  0.0029 -0.0337 -0.9904  0.9970  1.0000
```

Output A.2: Crude Model (Birth Weight and Maternal Smoking)

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3, data = CHDS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -4.4328 -0.7328 -0.0328  0.7214  3.6672
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)   7.73281     0.05442 142.091 < 2e-16 ***
## SMK1          -0.35223     0.11797  -2.986  0.00293 **
## SMK2          -0.76008     0.14163  -5.367  1.10e-07 ***
## SMK3          -0.46665     0.10790  -4.325  1.76e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.062 on 676 degrees of freedom
## Multiple R-squared:  0.0585, Adjusted R-squared:  0.05432
## F-statistic:    14 on 3 and 676 DF,  p-value: 7.294e-09
```

Output A.3: Gestational Age as an Effect Modifier for Birth Weight and Maternal Smoking

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + gestwks + gestwks * SMK1 +
##      gestwks * SMK2 + gestwks * SMK3, data = CHDS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -2.9507 -0.6687  0.0313  0.5922  3.2100
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)  -1.10650     1.06362  -1.040   0.299
```

```
## SMK1      -2.39214    2.25385   -1.061    0.289
## SMK2      -0.34265    3.16583   -0.108    0.914
## SMK3      -1.76955    2.01751   -0.877    0.381
## gestwks    0.22135    0.02661    8.320 4.91e-16 ***
## SMK1:gestwks 0.05384    0.05682    0.948    0.344
## SMK2:gestwks -0.00756    0.08017   -0.094    0.925
## SMK3:gestwks 0.03432    0.05070    0.677    0.499
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.9678 on 672 degrees of freedom
## Multiple R-squared:  0.2231, Adjusted R-squared:  0.215
## F-statistic: 27.56 on 7 and 672 DF,  p-value: < 2.2e-16
```

Output A.4: Gestational Age as a Confounder for Birth Weight and Maternal Smoking

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + gestwks, data = CHDS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -2.9444 -0.6799  0.0219  0.5883  3.1785
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept) -1.71575    0.79583  -2.156  0.0314 *
## SMK1        -0.25749    0.10764  -2.392  0.0170 *
## SMK2        -0.63221    0.12932  -4.889 1.27e-06 ***
## SMK3        -0.40392    0.09832  -4.108 4.47e-05 ***
## gestwks      0.23660    0.01989  11.896 < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.9666 on 675 degrees of freedom
## Multiple R-squared:  0.2217, Adjusted R-squared:  0.2171
## F-statistic: 48.06 on 4 and 675 DF,  p-value: < 2.2e-16
##
## % change
##      SMK1      SMK2      SMK3
## 26.89641 16.82322 13.44370
```

Output A.5: Maternal Age as an Effect Modifier for Birth Weight and Maternal Smoking

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + age + age * SMK1 + age *
##      SMK2 + age * SMK3, data = CHDS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -4.3704 -0.7152 -0.0242  0.7164  3.7605
##
```

```
## Coefficients:
##           Estimate Std. Error t value Pr(>|t|)
## (Intercept)  7.999695   0.264100  30.290 < 2e-16 ***
## SMK1        -0.636015   0.531049  -1.198  0.23147
## SMK2        -1.084608   0.695967  -1.558  0.11960
## SMK3        -1.520342   0.553027  -2.749  0.00614 **
## age         -0.010291   0.009965  -1.033  0.30211
## SMK1:age      0.010955   0.020247   0.541  0.58865
## SMK2:age      0.012542   0.026563   0.472  0.63696
## SMK3:age      0.040463   0.020826   1.943  0.05244 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.062 on 672 degrees of freedom
## Multiple R-squared:  0.06379, Adjusted R-squared:  0.05403
## F-statistic: 6.541 on 7 and 672 DF, p-value: 1.743e-07
```

Output A.6: Maternal Age as a Confounder for Birth Weight and Maternal Smoking

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + age, data = CHDS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -4.4302 -0.7311 -0.0319  0.7220  3.6710
##
## Coefficients:
##           Estimate Std. Error t value Pr(>|t|)
## (Intercept)  7.7437494  0.2013039  38.468 < 2e-16 ***
## SMK1        -0.3524276  0.1181119  -2.984  0.00295 **
## SMK2        -0.7602196  0.1417548  -5.363 1.13e-07 ***
## SMK3        -0.4665944  0.1079818  -4.321 1.79e-05 ***
## age         -0.0004219  0.0074726  -0.056  0.95500
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.063 on 675 degrees of freedom
## Multiple R-squared:  0.0585, Adjusted R-squared:  0.05292
## F-statistic: 10.49 on 4 and 675 DF, p-value: 3.029e-08
## % change
##           SMK1           SMK2           SMK3
## -0.05725988 -0.01822295  0.01288602
```

Output A.7: Maternal Age as an Effect Modifier for Birth Weight and Maternal Smoking

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + mheight + mheight * SMK1 +
##      mheight * SMK2 + mheight * SMK3, data = CHDS)
##
## Residuals:
```

```
##      Min      1Q  Median      3Q      Max
## -4.3861 -0.6604  0.0013  0.6276  3.8070
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)   1.72466    1.36754   1.261   0.208
## SMK1          0.16650    3.10800   0.054   0.957
## SMK2         -2.57609    3.52455  -0.731   0.465
## SMK3          3.13840    2.85958   1.098   0.273
## mheight       0.09315    0.02119   4.397 1.28e-05 ***
## SMK1:mheight -0.00757    0.04837  -0.157   0.876
## SMK2:mheight  0.02940    0.05507   0.534   0.594
## SMK3:mheight -0.05604    0.04417  -1.269   0.205
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.042 on 672 degrees of freedom
## Multiple R-squared:  0.09864,    Adjusted R-squared:  0.08925
## F-statistic: 10.51 on 7 and 672 DF,  p-value: 1.445e-12
```

Output A.8: Maternal Age as a Confounder for Birth Weight and Maternal Smoking

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + mheight, data = CHDS)
##
## Residuals:
##      Min      1Q  Median      3Q      Max
## -4.3901 -0.6779 -0.0048  0.6394  3.7952
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)   2.23166    1.04577   2.134  0.03320 *
## SMK1          -0.32189    0.11585  -2.779  0.00561 **
## SMK2          -0.70440    0.13931  -5.056 5.51e-07 ***
## SMK3          -0.48885    0.10591  -4.616 4.69e-06 ***
## mheight       0.08529    0.01619   5.267 1.86e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.042 on 675 degrees of freedom
## Multiple R-squared:  0.09567,    Adjusted R-squared:  0.09031
## F-statistic: 17.85 on 4 and 675 DF,  p-value: 6.072e-14
## % change
##      SMK1      SMK2      SMK3
##  8.612399  7.325258 -4.755978
```

Output A.9: Maternal Age as an Effect Modifier for Birth Weight and Maternal Smoking

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + BMI + BMI * SMK1 + BMI *
```

```
##      SMK2 + BMI * SMK3, data = CHDS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -4.5371 -0.6979  0.0077  0.6899  3.6178
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)  6.84268    0.44593  15.345  <2e-16 ***
## SMK1        -0.83185    1.09138  -0.762  0.4462
## SMK2        -0.34462    1.60278  -0.215  0.8298
## SMK3        -0.31620    0.81426  -0.388  0.6979
## BMI          0.04080    0.02029   2.011  0.0447 *
## SMK1:BMI     0.02574    0.05223   0.493  0.6223
## SMK2:BMI    -0.01826    0.07563  -0.241  0.8093
## SMK3:BMI    -0.00617    0.03755  -0.164  0.8695
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.06 on 672 degrees of freedom
## Multiple R-squared:  0.06855,    Adjusted R-squared:  0.05885
## F-statistic: 7.065 on 7 and 672 DF,  p-value: 3.732e-08
```

Output A.10: Maternal Age as a Confounder for Birth Weight and Maternal Smoking

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + BMI, data = CHDS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -4.5381 -0.6864  0.0140  0.6775  3.6173
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)  6.83464    0.34636  19.733  < 2e-16 ***
## SMK1        -0.30162    0.11903  -2.534  0.01150 *
## SMK2        -0.72880    0.14152  -5.150 3.42e-07 ***
## SMK3        -0.44781    0.10767  -4.159 3.61e-05 ***
## BMI          0.04117    0.01568   2.626  0.00885 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.058 on 675 degrees of freedom
## Multiple R-squared:  0.06801,    Adjusted R-squared:  0.06249
## F-statistic: 12.31 on 4 and 675 DF,  p-value: 1.136e-09
## % change
##      SMK1      SMK2      SMK3
## 14.367561  4.115376  4.038391
```

Output A.11: Full Association Model

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + gestwks + BMI, data = CHDS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -3.1911 -0.6411  0.0124  0.5925  3.1337
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept) -2.51900    0.84650  -2.976  0.00303 **
## SMK1         -0.21063    0.10855  -1.940  0.05274 .
## SMK2         -0.60350    0.12916  -4.672 3.60e-06 ***
## SMK3         -0.38657    0.09808  -3.941 8.94e-05 ***
## gestwks       0.23573    0.01980  11.905 < 2e-16 ***
## BMI           0.03841    0.01427   2.692  0.00728 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.9621 on 674 degrees of freedom
## Multiple R-squared:  0.2299, Adjusted R-squared:  0.2242
## F-statistic: 40.25 on 5 and 674 DF,  p-value: < 2.2e-16
```

Output A.12: Creation of New Full Model with Outlier Removed (See C.6)

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + gestwks + BMI, data = CHDS_60)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -3.1929 -0.6312 -0.0012  0.5793  3.1058
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept) -2.90394    0.85123  -3.411 0.000685 ***
## SMK1         -0.21458    0.10792  -1.988 0.047169 *
## SMK2         -0.60595    0.12840  -4.719 2.88e-06 ***
## SMK3         -0.39169    0.09751  -4.017 6.57e-05 ***
## gestwks       0.24570    0.01996  12.308 < 2e-16 ***
## BMI           0.03817    0.01418   2.691  0.007294 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.9564 on 673 degrees of freedom
## Multiple R-squared:  0.2396, Adjusted R-squared:  0.234
## F-statistic: 42.42 on 5 and 673 DF,  p-value: < 2.2e-16
```

Output A.13: Confidence Intervals for Full vs Reduced Models — Association

```
## For the crude model:
```



```
##              2.5 %      97.5 %
## (Intercept)  7.6259530  7.8396639
## SMK1         -0.5838591 -0.1205927
## SMK2         -1.0381668 -0.4819955
## SMK3         -0.6785080 -0.2548011

## For the adjusted model:

##              2.5 %      97.5 %
## (Intercept) -4.57533007 -1.232559664
## SMK1         -0.42647420 -0.002690799
## SMK2         -0.85806889 -0.353825765
## SMK3         -0.58315619 -0.200217851
## gestwks      0.20650008  0.284891594
## BMI          0.01032253  0.066019190
```

Output A.14: Prediction Model Backwards Elimination Procedure Step 1 — All variables

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + gestwks + age + BMI +
##       mheight, data = CHDS_60)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -3.2771 -0.6106  0.0142  0.5561  3.2634
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept) -8.100887   1.256253  -6.448 2.16e-10 ***
## SMK1         -0.180649   0.105766  -1.708  0.0881 .
## SMK2         -0.550760   0.126018  -4.370 1.44e-05 ***
## SMK3         -0.410902   0.095487  -4.303 1.93e-05 ***
## gestwks      0.241351   0.019546  12.348 < 2e-16 ***
## age          -0.003674   0.006626  -0.554  0.5795
## BMI          0.044959   0.014016   3.208  0.0014 **
## mheight      0.082446   0.014603   5.646 2.43e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.9358 on 671 degrees of freedom
## Multiple R-squared:  0.2743, Adjusted R-squared:  0.2667
## F-statistic: 36.23 on 7 and 671 DF, p-value: < 2.2e-16
```

Output A.15: Prediction Model Backwards Elimination Procedure Step 2 — Maternal Age Removed

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + gestwks + BMI + mheight,
##     data = CHDS_60)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
```

```
## -3.2487 -0.6078 0.0073 0.5562 3.2309
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) -8.16421    1.25041  -6.529 1.30e-10 ***
## SMK1        -0.18009    0.10571  -1.704 0.08890 .
## SMK2        -0.55037    0.12595  -4.370 1.44e-05 ***
## SMK3        -0.41179    0.09542  -4.315 1.83e-05 ***
## gestwks      0.24136    0.01954  12.355 < 2e-16 ***
## BMI          0.04403    0.01391   3.166 0.00162 **
## mheight      0.08226    0.01459   5.638 2.54e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.9353 on 672 degrees of freedom
## Multiple R-squared:  0.274, Adjusted R-squared:  0.2675
## F-statistic: 42.26 on 6 and 672 DF, p-value: < 2.2e-16
```

Output A.16: Confidence Intervals — Prediction

```
##             2.5 %      97.5 %
## (Intercept) -10.61938216 -5.70903683
## SMK1        -0.38764413  0.02746481
## SMK2        -0.79767379 -0.30306260
## SMK3        -0.59915690 -0.22442405
## gestwks      0.20300269  0.27972030
## BMI          0.01671973  0.07133750
## mheight      0.05360913  0.11090837
```

Appendix B: Plots and Figures

Figure B.1 Scatterplot Matrix

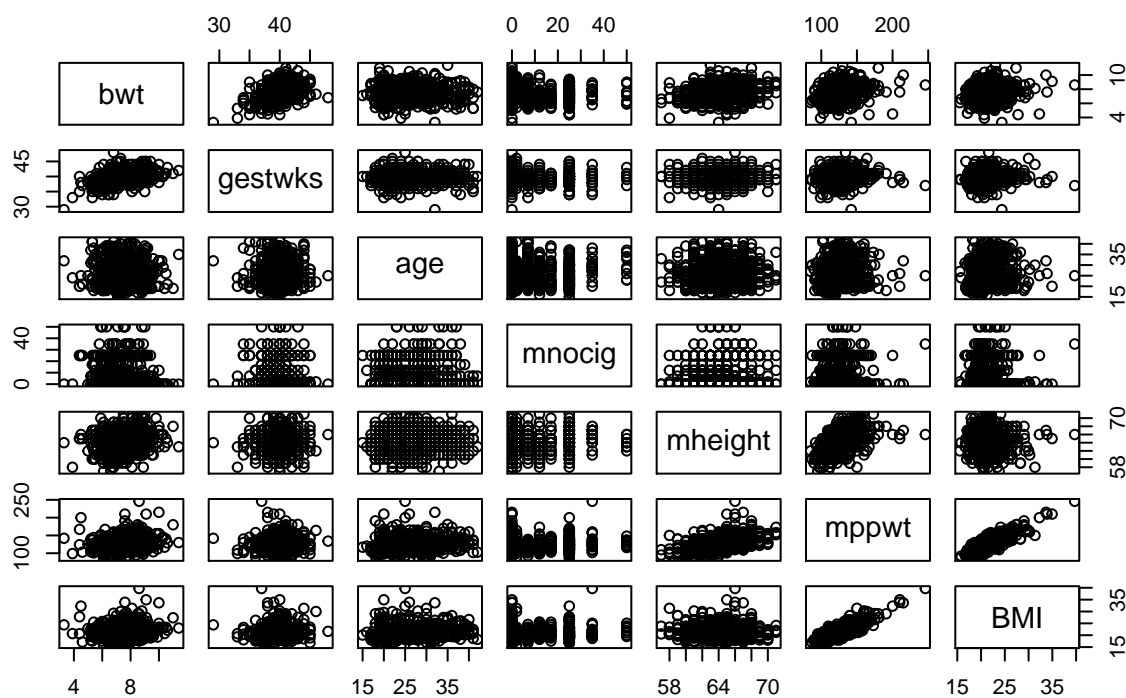
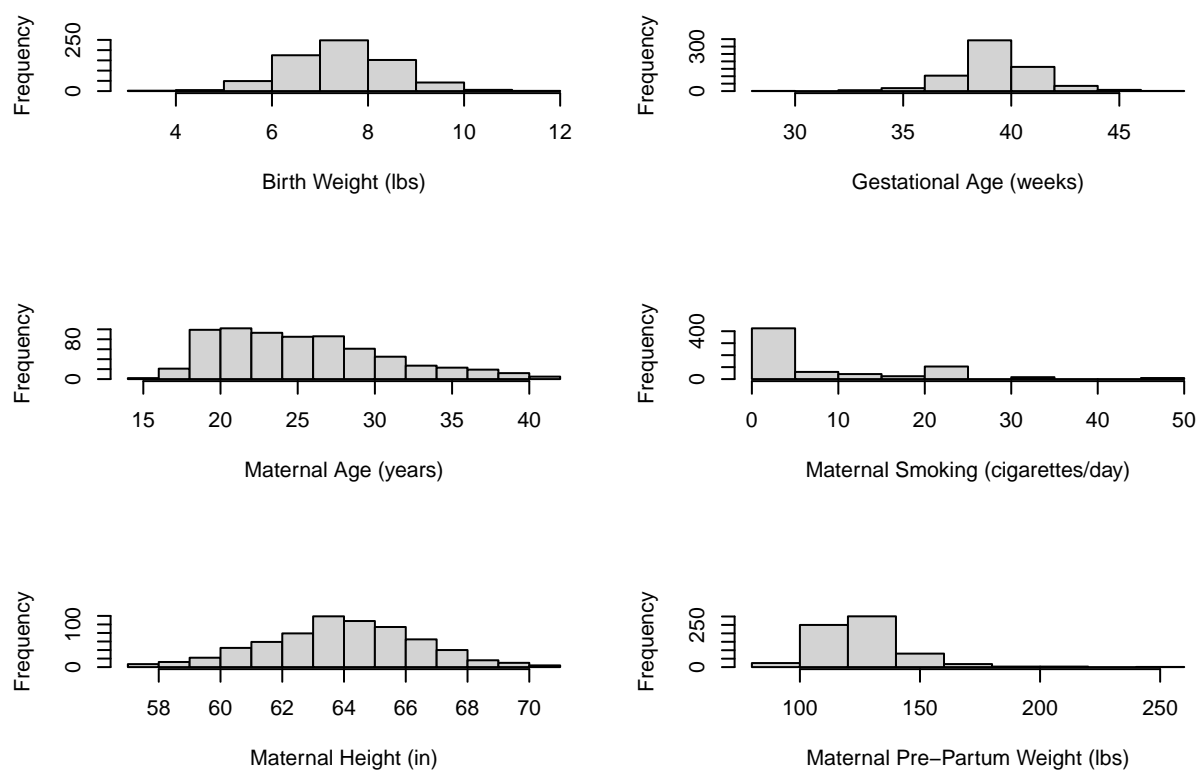


Figure B.2 Distributions of Sample Variables



Appendix C: Model Diagnostics

Figure C.1: Plot of Standardized Model Residuals as a Function of Fitted Values for Birth Weight — Association

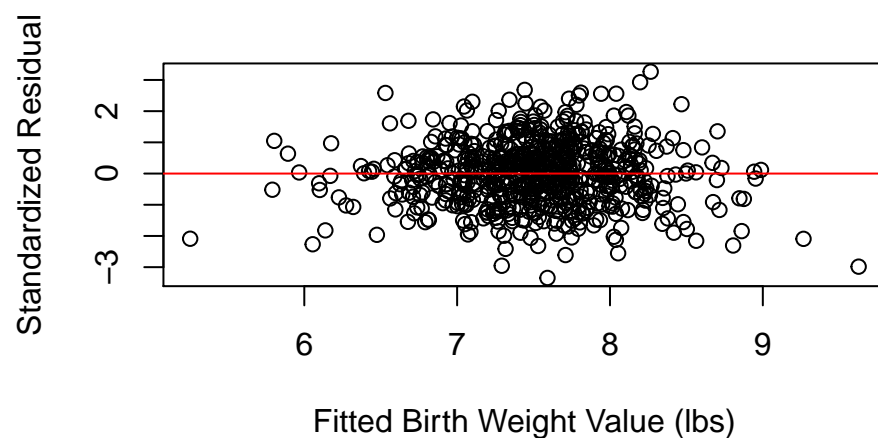


Figure C.2: Plot of Studentized Model Residuals as a Function of Fitted Values for Birth Weight — Association

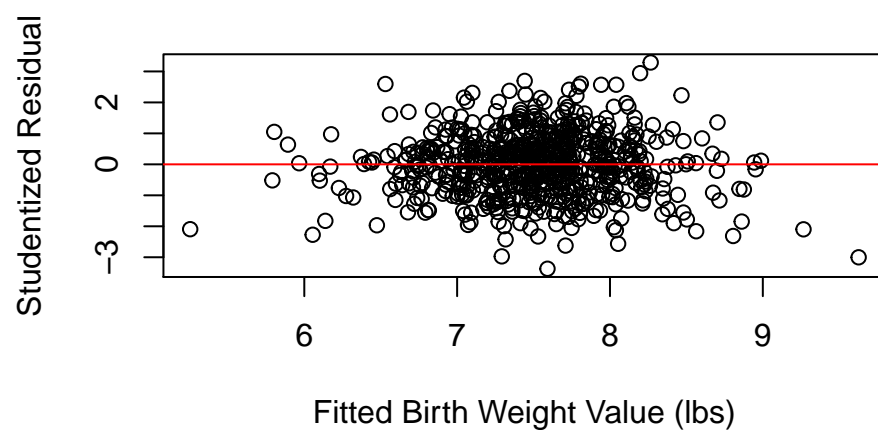


Figure C.3: Q-Q Plot of Residuals

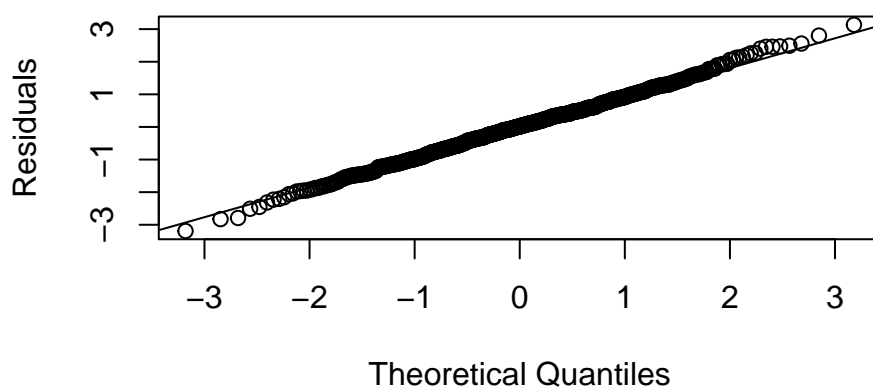


Figure C.4: Q-Q Plot of Standardized Residuals

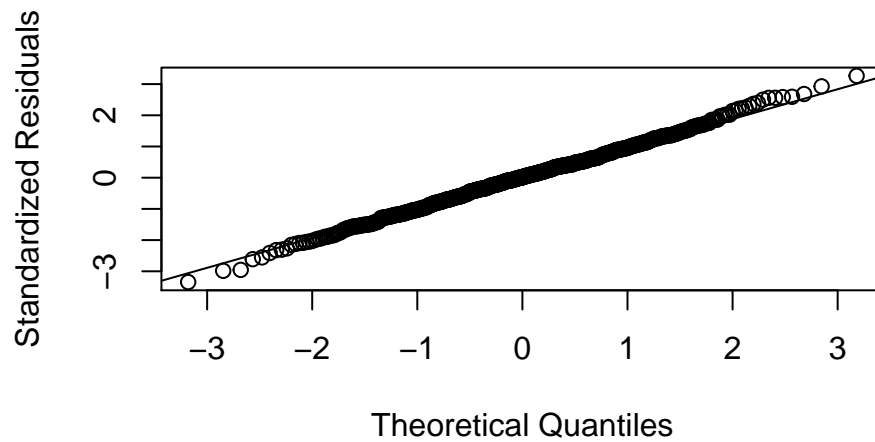
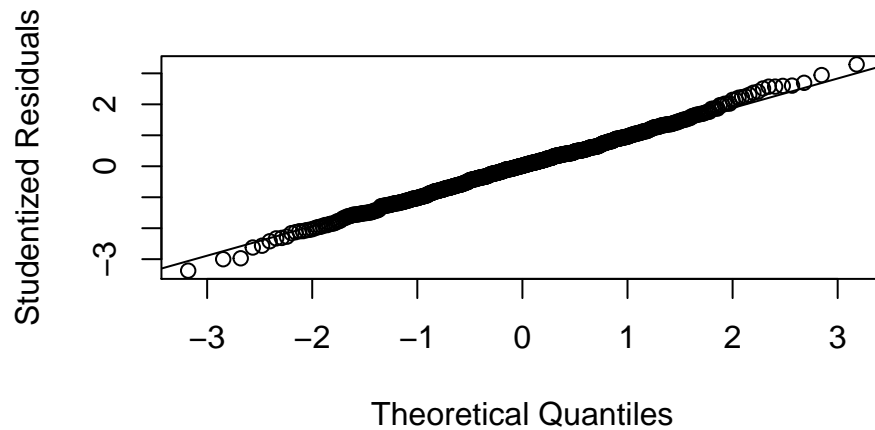


Figure C.5: Q-Q Plot of Studentized Residuals



Output C.6: Influential Outlier Detection with Cook's Distance

```
## The output below shows all potential outliers from this data
## [1] bwt      gestwks age      mnocig  mheight mppwt   BMI      h        c
## <0 rows> (or 0-length row.names)

##      bwt gestwks age mnocig mheight mppwt   BMI      h        c
## 9    3.3      29  32      0      64    142 24.3716 0.0550 0.0423
## 60    6.8      48  25      0      66    134 21.6258 0.0302 0.0462
## 166   5.3      33  20      7      63    109 19.3064 0.0281 0.0013
## 167   8.6      37  25     35      66    246 39.7011 0.0852 0.0290
## 356   8.1      44  30      2      58    150 31.3466 0.0431 0.0047
## 400  10.0      38  32      0      67    215 33.6701 0.0353 0.0352
## 404   7.6      39  26      0      66    210 33.8912 0.0352 0.0010
## 445   7.3      46  22      2      62    164 29.9927 0.0463 0.0354
## 506   4.5      38  25     25      66    200 32.2773 0.0353 0.0532
## 610   9.1      40  20      0      65    210 34.9420 0.0405 0.0057
```

Output C.7: Collinearity Assessment — Association

```
##      SMK1      SMK2      SMK3  gestwks      BMI
## 1.112337 1.073923 1.092602 1.010782 1.030826
## [1] 1.064094
```

Figure C.8: Plot of Standardized Model Residuals as a Function of Fitted Values for Birth Weight — Prediction

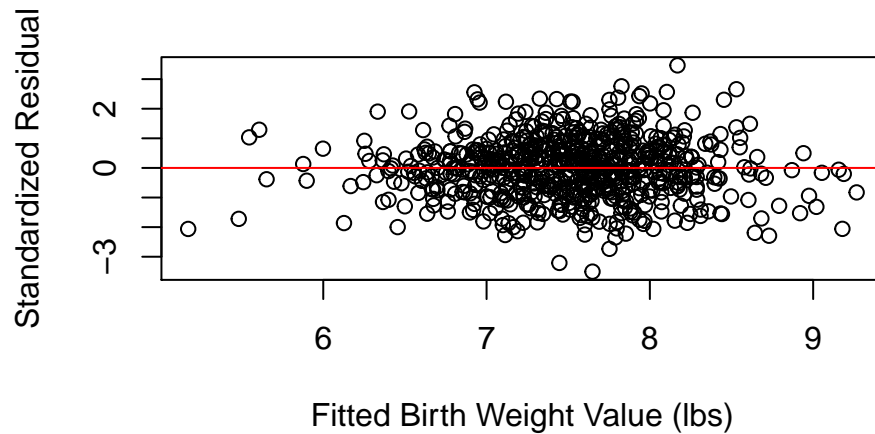
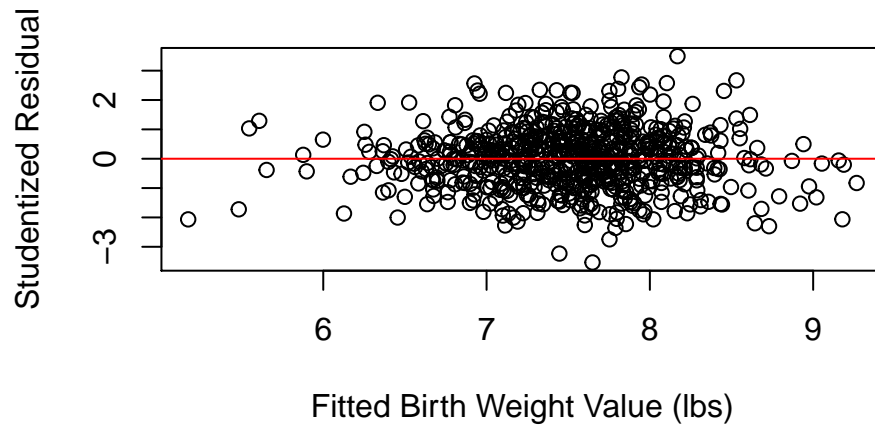


Figure C.9: Plot of Studentized Model Residuals as a Function of Fitted Values for Birth Weight — Prediction



Output C.7: Collinearity Assessment — Prediction

```
##      SMK1      SMK2      SMK3  gestwks      BMI  mheight
## 1.116076 1.080543 1.094130 1.012350 1.036611 1.018422
## [1] 1.059689
```

Appendix D: Mediation Analysis

Output D.1: Gestational Age and BMI

```
##
## Call:
## lm(formula = gestwks ~ BMI + SMK1 + SMK2 + SMK3, data = CHDS_60)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -10.9440  -0.9178   0.0979   1.0855   6.3526
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)  39.65007    0.60440   65.602  <2e-16 ***
## BMI           0.01206    0.02736    0.441   0.6595
## SMK1        -0.36435    0.20776   -1.754   0.0799 .
## SMK2        -0.51005    0.24699   -2.065   0.0393 *
## SMK3        -0.23840    0.18794   -1.269   0.2051
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.846 on 674 degrees of freedom
## Multiple R-squared:  0.01067,    Adjusted R-squared:  0.004795
## F-statistic: 1.817 on 4 and 674 DF,  p-value: 0.1238
```

Output D.2: Pre-Pregnancy BMI and Smoking

```
##
## Call:
## lm(formula = BMI ~ SMK1 + SMK2 + SMK3 + age, data = CHDS_60)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
##  -5.917  -1.617  -0.351   1.069  18.404
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)  20.36065    0.48860   41.672  < 2e-16 ***
## SMK1        -1.20267    0.28670   -4.195   3.1e-05 ***
## SMK2        -0.74168    0.34406   -2.156   0.03146 *
## SMK3        -0.46607    0.26212   -1.778   0.07584 .
## age           0.05609    0.01813    3.093   0.00206 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 2.58 on 674 degrees of freedom
## Multiple R-squared:  0.0432, Adjusted R-squared:  0.03753
## F-statistic: 7.609 on 4 and 674 DF,  p-value: 5.347e-06
```

Output D.3: Pre-Pregnancy BMI and Birth Weight

```
##
```

```
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + gestwks + BMI, data = CHDS_60)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -3.1929 -0.6312 -0.0012  0.5793  3.1058
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept) -2.90394    0.85123  -3.411 0.000685 ***
## SMK1         -0.21458    0.10792  -1.988 0.047169 *
## SMK2         -0.60595    0.12840  -4.719 2.88e-06 ***
## SMK3         -0.39169    0.09751  -4.017 6.57e-05 ***
## gestwks       0.24570    0.01996  12.308 < 2e-16 ***
## BMI          0.03817    0.01418   2.691 0.007294 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.9564 on 673 degrees of freedom
## Multiple R-squared:  0.2396, Adjusted R-squared:  0.234
## F-statistic: 42.42 on 5 and 673 DF,  p-value: < 2.2e-16
```

Output D.4: Light Smoking-BMI Mediation Analysis

```
## Running nonparametric bootstrap
##
## Causal Mediation Analysis
##
## Nonparametric Bootstrap Confidence Intervals with the Percentile Method
##
##              Estimate 95% CI Lower 95% CI Upper p-value
## ACME             -0.0459    -0.0974         0.00  0.024 *
## ADE              -0.2146    -0.4306         0.00  0.060 .
## Total Effect     -0.2605    -0.4802        -0.05  0.020 *
## Prop. Mediated    0.1762     0.0061         0.84  0.044 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 679
##
##
## Simulations: 500
```

Output D.5: Moderate Smoking-BMI Mediation Analysis

```
## Running nonparametric bootstrap
##
## Causal Mediation Analysis
##
## Nonparametric Bootstrap Confidence Intervals with the Percentile Method
##
##              Estimate 95% CI Lower 95% CI Upper p-value
```



```
## ACME          -0.02831      -0.06177          0.00    0.024 *
## ADE           -0.60595      -0.83816          -0.37 <2e-16 ***
## Total Effect  -0.63426      -0.87068          -0.39 <2e-16 ***
## Prop. Mediated 0.04464        0.00478          0.10    0.024 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 679
##
##
## Simulations: 500
```

Output D.6: Heavy Smoking-BMI Mediation Analysis

```
## Running nonparametric bootstrap
##
## Causal Mediation Analysis
##
## Nonparametric Bootstrap Confidence Intervals with the Percentile Method
##
##           Estimate 95% CI Lower 95% CI Upper p-value
## ACME          -0.01779    -0.04871          0.00    0.15
## ADE           -0.39169    -0.57579          -0.23 <2e-16 ***
## Total Effect  -0.40948    -0.60134          -0.25 <2e-16 ***
## Prop. Mediated 0.04345     -0.00976          0.14    0.15
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 679
##
##
## Simulations: 500
```

Output D.7: Gestational Age and Maternal Smoking

```
##
## Call:
## lm(formula = gestwks ~ SMK1 + SMK2 + SMK3 + age, data = CHDS_60)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -10.9172  -0.9125   0.0881   1.0861   6.4683
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept) 39.8960237  0.3495997 114.119  <2e-16 ***
## SMK1        -0.3788599  0.2051386  -1.847   0.0652 .
## SMK2        -0.5190000  0.2461802  -2.108   0.0354 *
## SMK3        -0.2440197  0.1875536  -1.301   0.1937
## age          0.0006606  0.0129751   0.051   0.9594
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
## Residual standard error: 1.846 on 674 degrees of freedom
## Multiple R-squared:  0.01039,    Adjusted R-squared:  0.004512
## F-statistic: 1.768 on 4 and 674 DF,  p-value: 0.1334
```

Output D.8: Gestational Age and Birth Weight

```
##
## Call:
## lm(formula = bwt ~ SMK1 + SMK2 + SMK3 + gestwks + BMI, data = CHDS_60)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -3.1929 -0.6312 -0.0012  0.5793  3.1058
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept) -2.90394     0.85123  -3.411 0.000685 ***
## SMK1         -0.21458     0.10792  -1.988 0.047169 *
## SMK2         -0.60595     0.12840  -4.719 2.88e-06 ***
## SMK3         -0.39169     0.09751  -4.017 6.57e-05 ***
## gestwks       0.24570     0.01996  12.308 < 2e-16 ***
## BMI          0.03817     0.01418   2.691 0.007294 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.9564 on 673 degrees of freedom
## Multiple R-squared:  0.2396, Adjusted R-squared:  0.234
## F-statistic: 42.42 on 5 and 673 DF,  p-value: < 2.2e-16
```

Output D.9: Light Smoking-Gestational Age Mediation Analysis

```
## Running nonparametric bootstrap
##
## Causal Mediation Analysis
##
## Nonparametric Bootstrap Confidence Intervals with the Percentile Method
##
##              Estimate 95% CI Lower 95% CI Upper p-value
## ACME             -0.0931    -0.1978      0.02  0.080 .
## ADE              -0.2146    -0.4293     -0.01  0.048 *
## Total Effect     -0.3077    -0.5618     -0.09  0.004 **
## Prop. Mediated    0.3025    -0.0686      0.89  0.076 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 679
##
##
## Simulations: 500
```

Output D.10: Moderate Smoking-Gestational Age Mediation Analysis

```
## Running nonparametric bootstrap
##
## Causal Mediation Analysis
##
## Nonparametric Bootstrap Confidence Intervals with the Percentile Method
##
##           Estimate 95% CI Lower 95% CI Upper p-value
## ACME           -0.1275    -0.2286    -0.02  0.004 **
## ADE            -0.6059    -0.8222    -0.38 <2e-16 ***
## Total Effect   -0.7335    -0.9679    -0.50 <2e-16 ***
## Prop. Mediated  0.1739     0.0357     0.33  0.004 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 679
##
##
## Simulations: 500
```

Output D.11: Heavy Smoking-Gestational Age Mediation Analysis

```
## Running nonparametric bootstrap
##
## Causal Mediation Analysis
##
## Nonparametric Bootstrap Confidence Intervals with the Percentile Method
##
##           Estimate 95% CI Lower 95% CI Upper p-value
## ACME           -0.060     -0.162     0.04  0.21
## ADE            -0.392     -0.571    -0.21 <2e-16 ***
## Total Effect   -0.452     -0.670    -0.24 <2e-16 ***
## Prop. Mediated  0.133     -0.140     0.33  0.21
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 679
##
##
## Simulations: 500
```

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