Case Study 1: Maternal Smoking and Infant Death

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Introduction

Smoking is detrimental to a person's health, which can cause respiratory disease, diabetes, and even lung cancers. However, recent studies have shown that smoking does not only cause harms on mothers' health problems, but also on their babies. Preterm birth is indeed a common and complex condition that results from multiple interactions between the maternal and the fetal genomes and conditions in the intrauterine environment, the mother's body, and her external environment (Behrman). Maternal smoking during pregnancy, therefore, can be a factor of causing the baby to be born prematurely with a low birth weight. Thus, in this study, an investigation on the relationship between the preterm birth and whether mothers' smoking habits during pregnancy is made.

Whether maternal smoking during pregnancy causes fetal harm or not is a pivotal and significant medical debate. Therefore, a variety of statistical methods are used in this research paper to draw conclusions about the relationship between maternal smoking and birth weight. The result from the research topic have the potentials to make a difference towards mothers' decisions on smoking or not during pregnancy.

The statistical methods of this research paper includes numerical, graphical and testing methods to investigate the association between low birth weight and maternal smoking during pregnancy. Numerical methods generate numerical summaries that include the mean, median, and quantiles of the birth weights for babies born to women who smoked and did not smoke during their pregnancy. Graphical methods, including histograms, box-plots, and Q-Q plots, compare the distributions of the two groups. Testing methods, including the chi-square test and two sample t-test, test whether there are significant differences of means from the two distributions. Finally, the differences of numerical values and distributions are analyzed to determine whether or not babies born to women who smoked during pregnancy have lower birth weights in comparison to women who did not smoke during pregnancy.

Data

The data from babies23.txt is part of the Child Health and Development Studies database which details pregnancies occurring between 1960 and 1967 of women enrolled in the Kaiser Foundation Health plan in the San Francisco Bay area. These women tend to seek medical care at earlier in their pregnancy compared to women not enrolled in the Kaiser Foundation Health plan. Those women seek medical care at Kaiser earlier in pregnancy compared to those who do not seek medical care at Kaiser. The data consists of women in different race. Furthermore, the education level and income bracket of the women are higher than the average California women. The dataset consists of 1236 male babies who have lived at least 28 days and were all single births (no twins). The two variables in are baby's birth weight which is a numerical, discrete variable measured in ounces, and smoking status which is a categorical variable and is represented by an integer indicator, of which will only consider 1 if the mother smoked during her pregnancy, and 0, 2, or 3 if the mother did not smoke during her pregnancy. In addition, this research paper will explore gestation time, which is a numerical, discrete variable measured in days.

Background

Fetal growth follows an exponential pattern. Factors including genetic information, nutrition in-take and uteroplacental cause and environmental changes may influence fetal development. There are three major determinants of metal growth: transplacental glucose, fetal insulin and uteroplacental and umbilical blood flow.

Infant maturity is measured by baby's gestational age and birth weight. Born too soon with lower birth weight, preterm infants are more vulnerable to organ injury, death, chronic illness, and neurodevelopmental disability than full-term newborns (Butler). In other words, with low gestational age and birth weights, preterm babies are exposed to higher mortality, which threatens babies' health. Therefore, in order to find out whether maternal smoking is bad for infants' health is equivalent to investigate whether their gestational days and birth weights are reduced as a result of maternal smoking. For clarification, a premature birth is defined as "having a gestational age of less than 38 weeks and body weight of less than 2,500 gm" (Khang-cheng 243). These thresholds can define whether an infant has low gestational days or low birth weights or not, as well as to decide whether to reject the null hypothesis in the testing method.

Low birth weight contributes to infant and childhood mortality. Study shows that infants with low birth-weight are at higher risk of dying than normal-birth-weight infants. Furthermore, low birth weight causes development of many health problems including lower-respiratory-tract disease, hyaline-membrane disease and abnormal cardiopulmonary function (Mccormick). One of studies suggests that the risk of diabetes is associated with low birth weight and it is also related to the development of paternal diabetes. If the parents have diabetes, then it tend to have babies that have lower birth weight, and those babies have a higher chance of getting diabetes (RS).

Previous studies have investigated on this topic and have drawn the conclusion that maternal smoking does reduce baby birth weights. For instance, a retrospective study using interview data from “parents of 18,297 children born in 2000/2001 and living in the UK 9 months afterwards” collected by the UK Millennium Cohort Study (MCS) concluded that maternal smoking during pregnancy reduced infants' adjusted mean birth weights by 168 g. This data reflects that UK prevalence of maternal smoking in pregnancy significantly lowers infants' birth weights. The conclusion was drawn through a randomized controlled experiment and the utilization of multiple linear regressions. This research paper will build upon these initial findings and further investigate this topic with broader statistical methods, including the chi-square test, 2-sample t-test, F-test, and simulation test, as well as graphical methods including histograms, boxplots, QQ plots and table with numerical values (mean, median, variance, etc).

Based on the background and previous study, the null hypothesis is that birth weights are independent of maternal smoking.

Investigations

The dataset babies23.txt contains physical and family information for the babies born to mothers who smoked in different frequency throughout their pregnancy. Data entries with a “9” under the smoke status column “smoke” were cleaned out because the missing of relevant information. Babies’ birth weight of rest of the data entries was standardized based on the mean and standard deviation of the surveyed population.

Numerical Summary

Table 1 below contains the numerical summary of the two distributions of birth weight for babies born to women who smoked during their pregnancy and for babies born to women who did not smoke during their pregnancy. The data sampled more non-smoking mothers than smoking mothers. The summary also indicates that in this surveyed population, the sample mean, median, 1st quartile and 3rd quartile of birth weights of those babies whose mothers smoked during pregnancy are generally lower compared to babies born to non-smoking mothers.

Table 1: Numerical Statistics for babies’ birth weights in two distributions

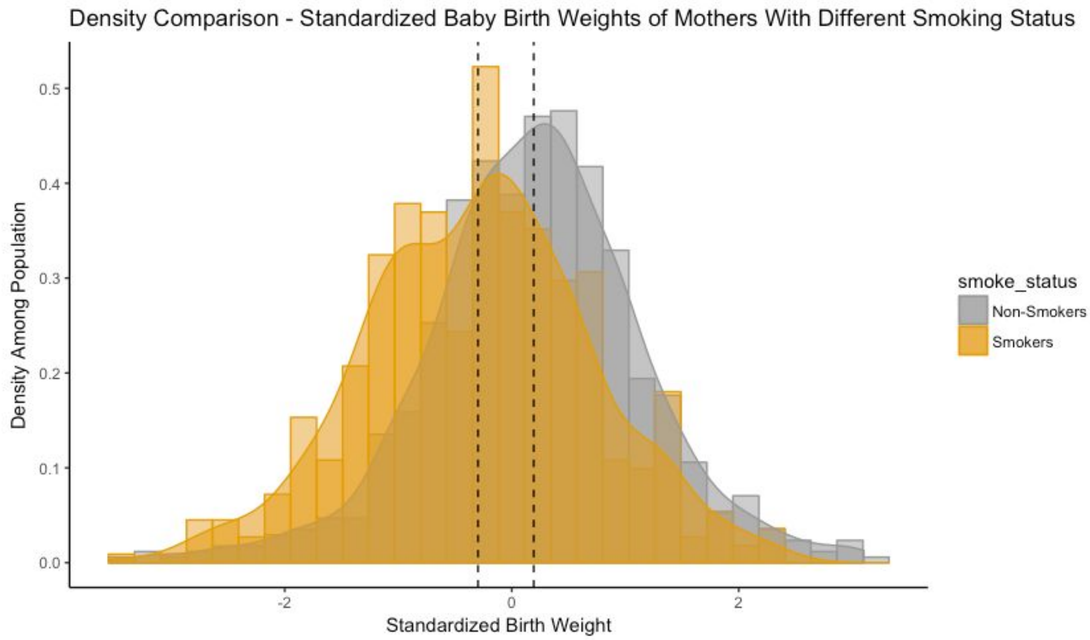
	Babies' Birth Weights born to Non-smoking mothers	Babies' Birth Weights born to Smoking Mothers
Count	742	484
Minimum	55.0	58.0
1st Quartile	113.0	102.0
Median	123.0	115.0
Mean	123.0	114.1
3rd Quartile	134.0	126.0
Maximum	176.0	163.0
Standard Deviation	17.3987	18.0990
Skewness	-0.1870	-0.0336
Kurtosis	4.0371	2.9880

Graphical Comparison

In order to investigate the difference in birth weight between babies born to mothers who smoked during pregnancy and those who did not, the data was subset to two categories: Smoker and non-smokers. Data entries with a "0", "2", and "3" under the smoke status column "smoke" are categorized to "non-smokers" during pregnancy; data entries with "1" under the smoke status column "smoke" are categorized to "smokers" during pregnancy. Figure 1 below shows the distribution of babies' weights under each category.

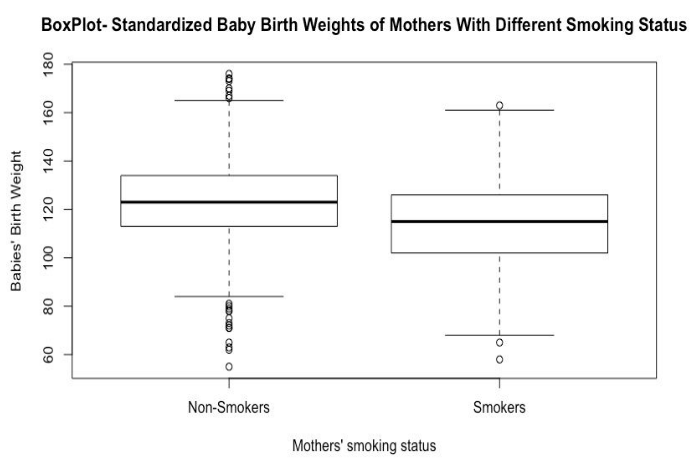
The orange histogram, which represents the distribution of baby birth weights of the smoking mothers, is bimodal and symmetric. The grey histogram, which represents the distribution of baby birth weights of the non-smoking mothers, is unimodal and symmetric. The compared density curve shows that there exists a difference between the birth weight for babies born to women who smoked during their pregnancy and for babies born to women who did not smoke during their pregnancy.

Figure 1: Histograms and Density Curve Comparison comparing standardized birth weights for two distributions



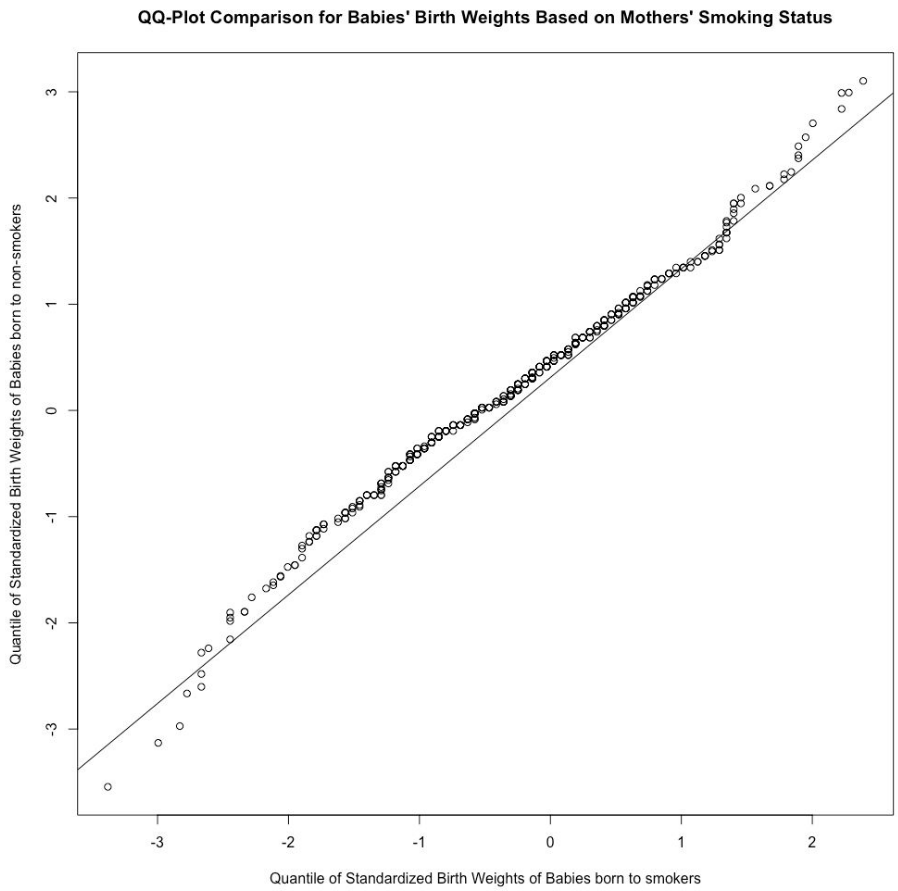
The boxplot (Figure 2) below displays the standardized baby birth weights of mothers with two different smoking status during their pregnancy. From the box plot, the median, 1st quantile and 3rd quantile for the standardized baby birth weights of smoking mothers are lower than the non-smoking ones. The box to the left also indicates that there exist many outlier cases for the the birth weights of babies born to non-smoking parents.

Figure 2: Boxplot for two distributions



In order to investigate if the data information of the smoking mothers and the non-smoking mothers comes from a common distribution, a Quantile-Quantile Plot Comparison for Babies' Birth Weights Based on Mothers' Smoking Status (Figure 3) was drawn. The QQ-plot (Figure 3) indicates that the two distributions are in the same shape but have different means or standard deviation, because the plot is roughly linear and the slope and intercept are not 1 and 0. This QQ-plot (Figure 3) has non-zero intercept, which indicates a shift between the distributions.

Figure 3: Quantile-Quantile plot comparing the two shape of distributions against each other



<u>Frequency and Incidence</u>

Figure 4 visualizes the frequency of low baby birth weights across the two populations of non-smoking and smoking mothers. It is apparent that babies of mothers who smoked during pregnancies had a higher frequency of low birth rates (0.0808) compared to babies of mothers who had not smoked (0.0306), according to *Table 2.*

Figure 4: Frequency of babies' having low birth weight in each population

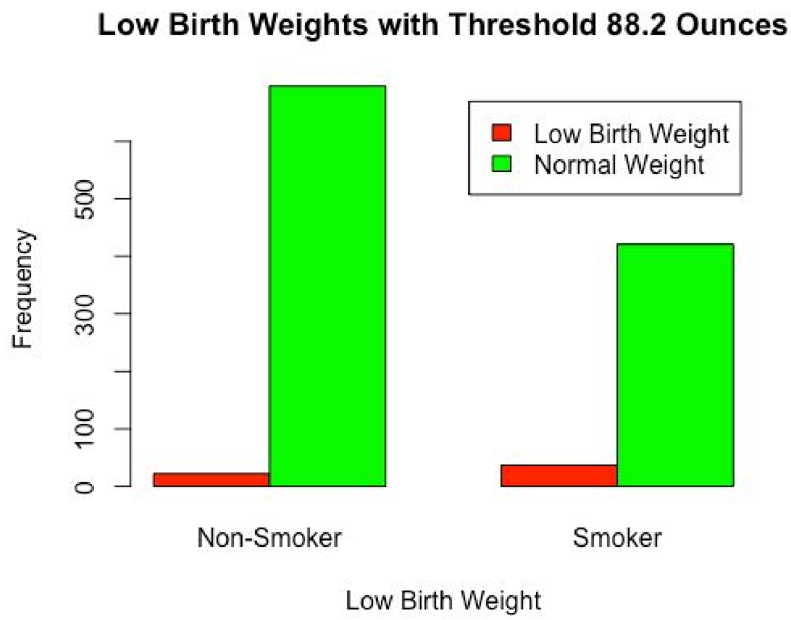


Table 2: Calculated Proportion of babies with low birth weight in each population

	Non-Smokers	Smokers
Proportion	0.0306	0.0808

In order to test the reliability and significance of this difference, the same bar graphs were constructed in *Figure 5*, but with differing "threshold" definitions of low birth rate from the original of 88.2 ounces: 86, 87, 88, 89, and 90. As can be seen in *Figure 5,* the frequencies changed minimally despite changes in the number of babies classified as low birth weight, demonstrating the reliability of our estimates. The respective frequencies are listed in *Table 3.*

Figure 5: Change in frequency of low birth weights appearing in both smoking and non-smoking Populations

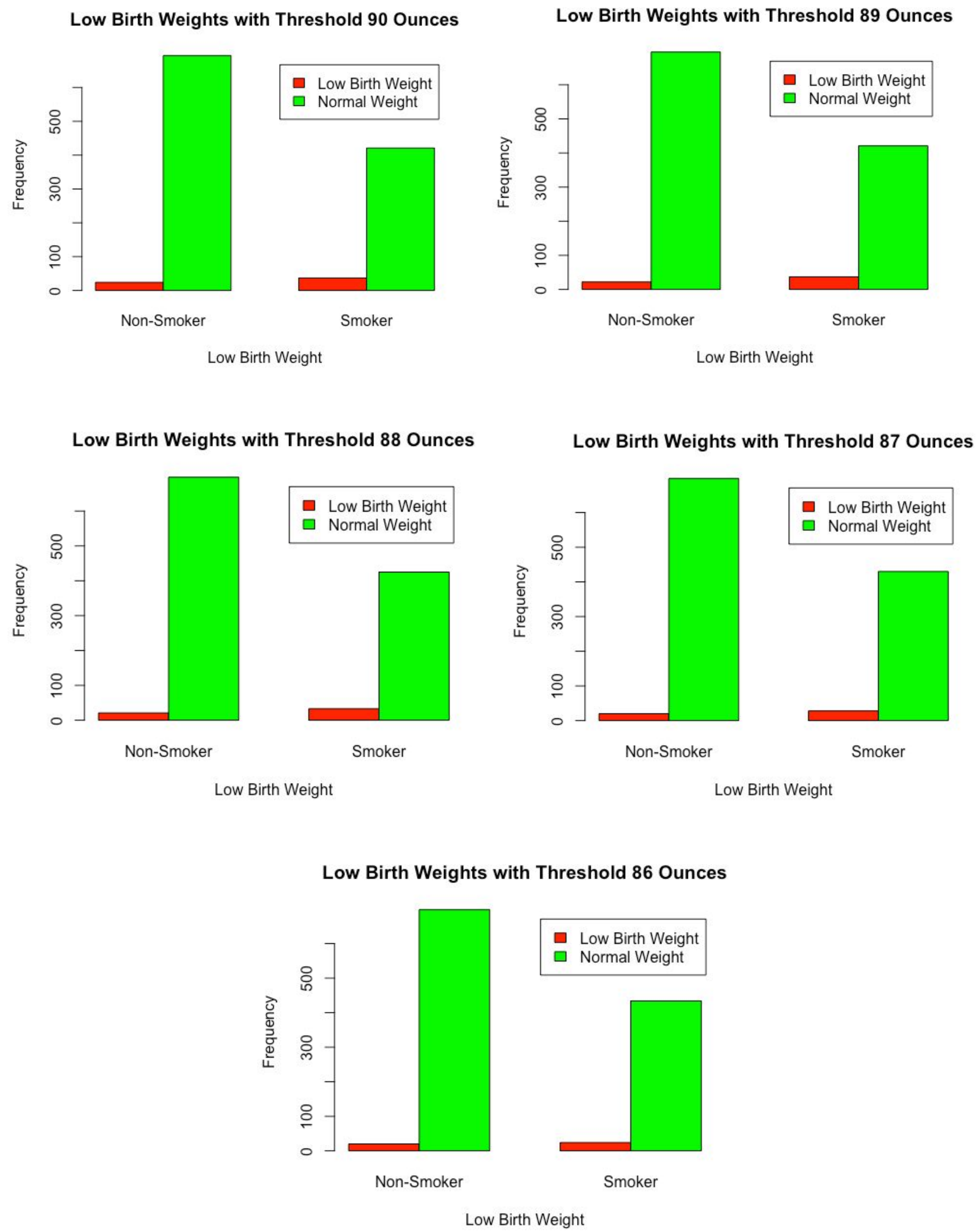


Table 3: Calculated Proportion of babies with low birth weight in each population

	Non-Smokers	Smokers
Proportion (Threshold 86 oz.)	0.0279	0.0524
Proportion (Threshold 87 oz.)	0.0279	0.0611
Proportion (Threshold 88 oz.)	0.0292	0.0721
Proportion (Threshold 89 oz.)	0.0306	0.0808
Proportion (Threshold 90 oz.)	0.0334	0.0808

In order to understand how the incidence of low birth weight changes when a few more or fewer babies were classified as low birth weight, a list of thresholds of low birth weight standard is created to test for the association between smoking and birth weight. After performing the chi-squared Test of Independence, Table 3 indicates that the p-values are smaller than 0.05 for cases where the threshold values are between 85 and 155. In the study, the weight standard measuring if the babies are underweight is 2500g, which is 88.2 in ounces that is within the range where the p-values are smaller than 0.05. It can be concluded that the weight limit set by the previous study (2500g) is a standard able to detect the dependence relationship there exists a dependent relationship between the mothers' smoking habits and the babies' birth weights given the threshold for low birth weight is between 85 to 155.

Table 4: Chi-squared testing results of association between babies' birth weight and mothers' smoking habits during pregnancy under each threshold for low birth weight

Low Birth Weight Threshold	p-value	Number of babies classified as low birth weight
88.2	**0.0001683**	59
65	0.9633	4
75	0.4946	16
85	**0.03309**	37
95	**1.645e-06**	95
105	**< 2.2e-16**	229
115	**7.015e-12**	428
125	**5.677e-11**	714

135	**6.487e-07**	957
145	**0.002237**	1095
155	0.01007	1150
165	0.02833	1176
175	1	1185

Particularly, the cases where thresholds between 86 and 90 were taken out to see if small changes of the standard for low birth weight will alternate the conclusion. Figure 7 shows that the incidence of babies with low birth weight did not change a lot when a few more or fewer babies were classified as low birth weight. Therefore, we can conclude that whether or not a pregnant mother smokes has a large association with low birth weights for thresholds between approximately 85 and 145 ounces, of which 88.2 is contained.

In order to further examine the type of distribution each data category follows, a normal distribution was used as the theoretical data to be compared to. Figure 6 is a QQ-plot comparing the observed quantiles of birth weights for babies born to smoking mothers with a theoretical normal quantiles. The roughly linear plot indicates that this is roughly a normal distribution. Figure 7 is a QQ-plot comparing the observed quantiles of birth weights for babies born to non-smoking mothers with a theoretical normal quantiles. The linear plot indicates that this is roughly a normal distribution, and the downward curve to the left and upward curve to the right indicates that this distribution has a fat tail on the two ends.

Figure 6: Quantile-Quantile plot comparing the smoking mothers distribution against normal

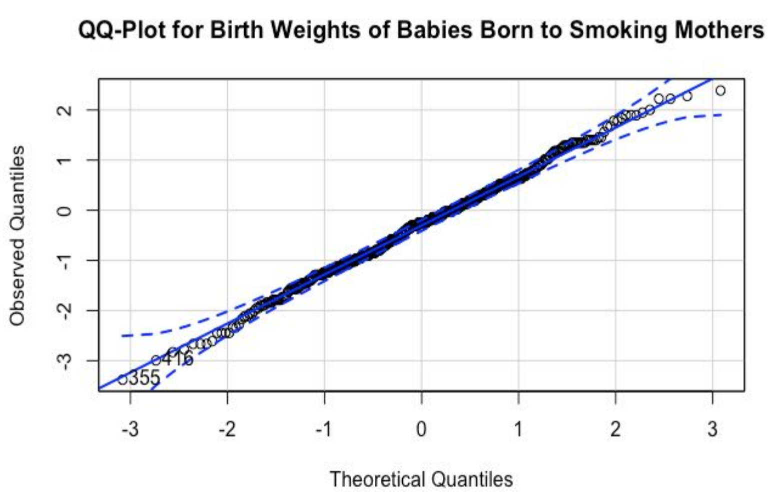
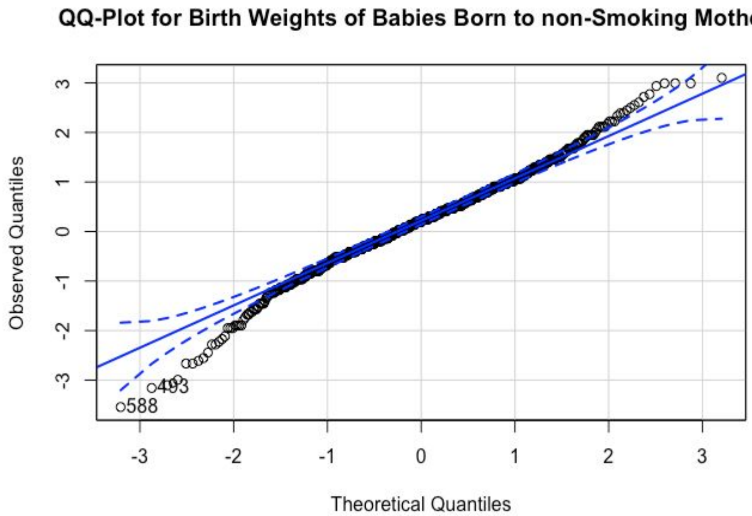
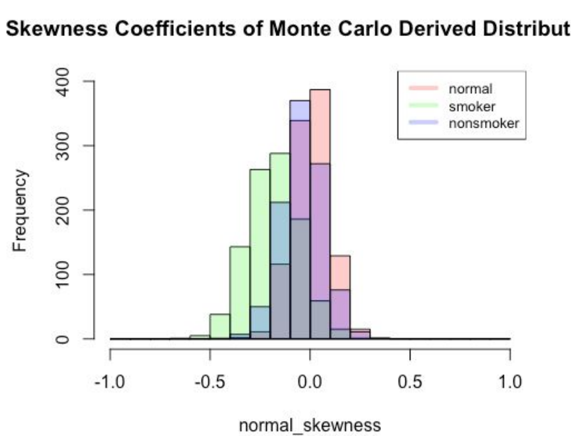


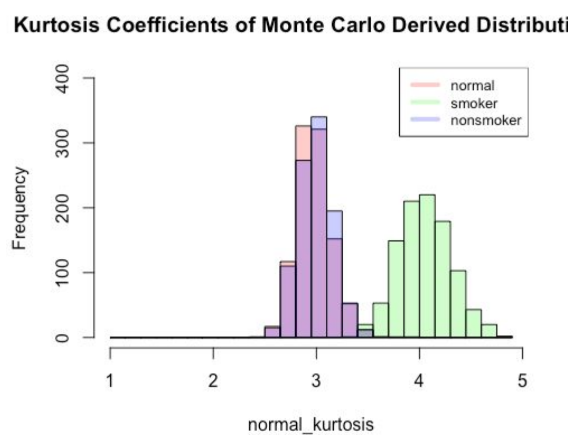
Figure 7: Quantile-Quantile plot comparing the non-smoking mothers distribution against normal



In order to further test whether or not the distributions of both populations are approximately Normal, the skewness and kurtosis of both populations were compared to those of a Monte Carlo generated Normal distribution. To do this, the smoker and nonsmoker populations were bootstrap resampled, and these distributions were overlaid over the distribution of the Monte Carlo generated Normal distribution. It can be seen that there is a high probability of both populations having a skewness coefficient of around 0 and a kurtosis coefficient of around 3, showing that both populations are approximately Normally distributed.

Figure 8: Skewness and Kurtosis Coefficients of Monte Carlo Derived Distributions





In addition to the QQ-plots and skewness and kurtosis histograms, according to the Central Limit Theorem, as sample size gets sufficiently large, the sampling distribution of the means of the sample becomes approximately Normally distributed. In this case, because we are interested in the sample mean of the birth weight across both populations, we can assume that the populations are approximately Normally distributed.

Therefore, since we know that the distributions of the birth weights across both populations are approximately normally distributed, it is safe to conduct a 2-sample t-test to determine whether there is a statistically significant difference in birth weight across non-smoker and smoker mothers. According to the 2-sample t-test comparing the distributions of the birth weights of babies of non-smokers and babies of smokers, the p-value is extremely small (< 2.2e-16), which means that there is an extremely low probability that this average difference in birth weights had happened by randomness. The 95 percent confidence interval constructed by the 2-sample t-test is [6.8747, 11.063], meaning that there is a 95 percent probability that the average difference in birth weights is contained in this interval. Therefore, we reject the null hypothesis that the average difference is zero, and we can conclude that the birth weights of smoker mothers is significantly smaller than the birth weights of non-smoker mothers.

Table 5: t-test Result

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Welch Two Sample t-test

data:  nonsmoker$wt and smoker$wt
t = 8.4049, df = 947.76, p-value < 2.2e-16
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
  6.874684 11.062952
sample estimates:
mean of x mean of y
 123.1588  114.1900
```

Importance of the Difference

Except for the minimum values of babies' birth weights, the numerical statistics suggest that babies born to smoking mothers during pregnancy have a relatively lower birth weights in the population mean, median, 1st quartile, and 3rd quartile. The general low birth weights of babies born to smokers indicate that there is some significant shift between two distributions.

The graphical methods such as boxplot and the histograms also supported this argument by visualizing the differences in median and mean. It can also be inferred from the QQ-plot that the distributions for both populations of babies born to non-smoking mothers and smoking mothers are in the same shape.

Furthermore, by comparing each distribution from the two populations with normal distribution, the QQ-plot suggests that both populations follow normal distribution. With the standard of low weight being set as 88.2 ounces (2500g), the frequency table suggests that the proportion of underweight babies is higher in the population where babies are born to smokers than non-smokers. The incidence graphs also reveal that the observation of the differences is significant and robust with differed thresholds being set.

Therefore, the results of the above methods suggest a strong association between mothers smoking during their pregnancy and the low values of their babies' birth weights. If the smoking mothers keep their smoking habits throughout pregnancy, the likelihood of getting a low-weighted baby is higher than getting a normal-weighted baby.

Limiting the influence of the confounding variables, such as mother's age, Wilcox and authors, advocate grouping babies by their gestational age, or by their relative birth weight. As what Wilcox and the other authors' study suggests, "because babies born to smokers tend to be smaller, the mortality curve is shifted to the right relative to the nonsmokers' curve", which means that the infants that are born to the smoking mothers will have a lower birth-weight and a higher possibility of dying early (Wilcox). Even with the ones who survived, there is a high chance of the babies with low birth-weight getting paternal diabetes and other respiratory diseases (Mccormick). As a result, the difference found is significant and important because the mothers' smoking habits do associate with the health and the survival rate of the babies.

Additional Analysis: Relationship between Smoking and Preterm Births

Preterm birth which comes with low birth weight would damage baby's health, because the fetal growth follows an exponential growth pattern with the fetus gains 95% of its weight in the last 20 weeks. From the journal related to our topic, the risk of preterm birth is proportional to the amount of maternal smoking. Women enrolled in the research are classified into three groups: non-smoking (non-daily smoking), moderate smoking (1-9 cigarettes per day) and heavy smoking (≥10 cigarettes per day). Other variables that may influence the result including maternal age, parity and complication during pregnancy are defined. The birth with a gestational age less than 37 weeks is defined as preterm birth. Four kinds of analysis are used in the research: descriptive analysis, logistic regression analysis, odds ratio and statistical analysis. Researchers use odds ratio and 95% confidence intervals of preterm birth to show that preterm birth is more common among smoker than nonsmoker, and the rate of preterm birth is highest in heavy smoking group (Kyrklund-Blomberg 1051).

The study shows that there is a difference between risks of preterm-birth among nonsmokers and smokers. In order to test whether the conclusion is true, we use two sample t-test. We let null hypothesis to be $\mu_1=\mu_2$. Where μ_1 is the mean of the gestation days for mothers who smoke during pregnancy, μ_2 is the the mean of the gestation days for mothers who don't smoke during pregnancy. After running the t-test, the result for p value is a 0.3951 which is greater than the significance level, so we fail to reject the null hypothesis that the true difference in means is equal to 0, and conclude that there is no significant difference between means of the gestation days for mothers who smoke and don't smoke during pregnancy.

Table 6: t-Test result

```
Welch Two Sample t-test

data:  nonsmoker$gestation and smoker$gestation
t = 0.85081, df = 1053.9, p-value = 0.3951
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -4.799252 12.147162
sample estimates:
mean of x mean of y
 288.0320  284.3581
```

Theory

Numerical Statistics Summary

Mean: Mean is the center of the data distribution.

Median: Median is the 50th percentile of the data, which is also the middle of the data distribution.

Variance and Standard Deviation: Variance is the squared deviation of a random variable from its mean. Standard Deviation is how far individual data value is away from the center of the data distribution.

The reason that we calculate mean, median, variance and standard deviation is that we want to know the distribution, and since mean represents the center of the data distribution, and median represent the 50th percentile of the data, by calculating these two values we can know the location of the data distribution. Moreover, by calculating the standard deviation we will have an idea of the spread of the data, and be able to compare the two distributions between body weight among smokers and nonsmokers.

Graphical Summary

Histogram: Histogram is a diagram consisting of rectangles whose area is proportional to the frequency of a variable and whose width is equal to the class interval.

Histogram presents a good visualization of the distribution of the data, we can identify the outliers clearly from the graph and the shape of the graph tells us the distribution of the data.

Boxplot: The box plot displays the distribution of the data based on minimum, first quartile, median, third quartile, and maximum. The bottom and the top of the box describes the first quartile and third quartile respectively, and the line in the middle of the box shows the median. The whiskers above and below the box are maximum and minimum respectively. Dots outside the maximum and minimum are uncommonly far away from the mean.

In this investigation, boxplot gives the basic information of distribution of birth weight in two groups. So helps to compare the difference between the two groups.

Quantile-Quantile plot: A Q-Q plot is a plot of the quantiles of the first data set against the quantiles of the second data set. If the two data sets come from the same distribution, the points should be located approximately along a 45-degree reference line.

We use Q-Q plot to show how close the distribution of birth weight in two groups is to the normal distribution. Because if the distribution is nearly normal, then t-test can be used to further compare the two groups.

Normal Curve

Skewness: Skewness is the average of the third power of the standardized data. Skewness is a way to check for normality, because for a symmetric distribution such as standard normal distribution, skewness coefficient is very close to zero. Skewness coefficient is calculated by the following formula: $skewness = \frac{1}{n}\sum_{i=1}^{n}(\frac{X_i - \overline{x}}{S})^3$, where n is the sample size, Xi is individual data point, X bar is the sample mean, and s is the sample standard deviation.

Kurtosis: Kurtosis is the average of the fourth power of the standardized data. It is calculated by the formula, $\text{kurtosis} = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{X_i - \bar{X}}{s}\right)^4$. Kurtosis is also a way to check normality, and it measure the thickness of the tile. For normal distribution, the kurtosis is 3.

Testing Methods Summary

Test of Independence: Test of independence is a kind of Goodness of Fit hypothesis testing, which measures the deviation of observed values and expected values. The null hypothesis is two variables are independent, while the alternative hypothesis is two variables are not independent. By comparing P-value with significance level, decision rule of the hypothesis testing can be made. In the investigation, this method can decide whether weights and smoke/no smoke statues are independent or not and check to see whether the null hypothesis is correct.

Student's t-test: A t-test is operated when the test statistic follows a normal distribution if the value of a scaling term in the test statistic were known. The t-test can be used to determine if two sets of data are statistically significantly different from each other. The null hypothesis is the mean of data set 1 equals the mean of data set 2, while the alternative hypothesis is the mean of data set 1 does not equal the mean of data set 2. If the P-value is smaller than the significance level, then the null hypothesis can be rejected and can be concluded that the two groups are statistically significant from each other.

Central Limit Theorem: Let X1 , . . . , Xn be i.i.d. random samples from a distribution with mean μ and standard deviation σ. If n is sufficiently large, then the mean of the sum of all the independent variables has an Normal distribution, even if the original variables themselves are not normal distribution.

Conclusion and Discussion

Several confounders should be considered in the investigation process. This study must account for confounders since the data used in this research was a result of a retrospective observational study. Since the data was not produced by a controlled experiment, we can only infer association and cannot establish a causal relationship. Also, because the experiment was performed to the selected groups of people whose commonalities are having relatively high income and specified babies' gender. They might be confounders influencing the conclusion.

FAccording to the article "Racial Differences in Low Birth Weight," the black to white race ratio in moderately low birth weight and extremely low birth weight was 2.3 and 3.0. In the study, researchers use odds ratios, fitted rates and standard error in BMDP logistic regression models to estimate the average risk of low birth weight for two groups, and strength of the relation between race and low birth weight is calculated using rate ratio instead of difference. The result shows that a black woman is about twice to three times as likely to have a low birth weight child as a white woman is. Another confounder that also influences birth weight is alcohol consumption during pregnancy. Independent of smoking and other social factors, a woman who drinks more than 100g per week is at twice the risk of having a baby whose weight is below 10th percentile in the distribution than a woman who drink less than 50g per week. What is also worth to mention is the impact of delayed childbearing on low birth weight. Here maternal age greater than 35 and birth weight less than 2500g is defined as delayed childbearing and low birth weight. Bivariate analysis including relative risk and chi-square test is conducted in the research, and the result shows that low birth weight delivery is 11% higher among women over 35 of age than women below the age.

Although we cannot establish a causal relationship between smoking during pregnancy and low birth weights, this report found a strong association between these two variables. In particular, smoking during pregnancy is strongly linked to low birth weights. Furthermore, according to literature and studies, this difference is important to the health of the baby. Therefore, although a causal relationship cannot be found, smoking during pregnancy is something that should not be overlooked.

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