ABSTRACT

FACTORS THAT AFFECT THE RATE OF PRETERM BIRTH: AN EXAMINATION OF THE INTER-RELATED IMPACTS OF SOCIAL DETERMINANTS, BEHAVIOR AND PHYSICAL HEALTH STATUS

by
Krystal Michelle Hunter

The work seeks to examine the factors that have significant relationships to the rate of preterm birth (PTB) along with its cost to society.

There are four papers within this work. This purpose of the first paper is to measure the impact that healthy behaviors have on the rate of PTB when modeled with other factors like household demographics, community deprivation, chronic disease and mental health. This work finds that positive health behaviors has a negative relationship with PTB. The interaction between body mass index (BMI) and social class and its relationship to PTB is examined in the second paper. This paper finds that there is a curvilinear between BMI and PTB for women who are of a lower socioeconomic status (LSES). This result is not present with women who are of a higher socioeconomic status. This work also finds an “obesity paradox” for LSES women where the rate of PTB decreases as BMI increases except for those who were morbidly obese. The third paper re-examines Black women’s risk of PTB. This study results indicate that although Black women have a higher rate of PTB than other races of women, race itself is not a risk factor. Race’s interaction with other health and social factors are more significant than race as an independent factor. The final paper is a cost effective analysis that examines the cost of free standing birth centers compared to standard hospital care with respect to the estimated reduction in PTB. The analysis shows that free standing birthing centers are the most cost effective alternative for low to no risk pregnant women. This option also

has lower rates of PTB. The final conclusion of this paper is that promotion of birthing centers can not only potentially reduce the national rate of PTB, but also can save the healthcare system money in the cost of birth and preterm birth.

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by
Krystal Michelle Hunter

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Krystal Michelle Hunter

Dr. Michael Ehrlich, Dissertation Advisor Date
Associate Professor of Finance, NJIT

Dr. Yi Chen, Committee Member Date
Professor of Business Data Science, NJIT

Dr. Jim Shi, Committee Member Date
Associate Professor of Supply Chain Management and Finance, NJIT

Dr. Alberto Martin-Utrera, Committee Member Date
Assistant Professor of Finance, Iowa State University

Dr. Jocelyn Mitchell-Williams, Committee Member Date
Interim Associate Dean for Medical Education /Associate Professor of Obstetrics and Gynecology, Cooper Medical School of Rowan University, Camden, NJ

BIOGRAPHICAL SKETCH

Author: Krystal Michelle Hunter

Degree: Doctor of Philosophy

Date: December 2021

Undergraduate and Graduate Education:

- Doctor of Philosophy in Business Data Science,
  New Jersey Institute of Technology, Newark, NJ, 2021

- Master Business Administration,
  Rutgers School of Business, Newark, NJ, 2003

- Bachelor of Arts in Economics,
  Spelman College, Atlanta, GA, 1995

Major: Economics

Presentations and Publications:

Malyack CT, Hunter KM, Hiltz SR. Twitter and the Prediction of Oscar Winners. America's Conference on Information Systems (AMCIS) Proceedings. August 10-14, 2020 (Virtual Meeting)

Hunter K, Ehrlich M. Social and Economic Factors in Birth Outcomes. Oral Poster Presentation, Northeast Business and Economics Association (NBEA) 46th Annual Conference, Newport, RI, November 7 -9, 2019.

Hunter K, Ehrlich M. Social and Economic Factors in Heart Disease and Diabetes. Poster Presentation, Northeast Business and Economics Association (NBEA) 46th Annual Conference, Newport, RI, November 7 -9, 2019.

Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, Parrillo JE, Trzeciak S. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Journal of the American Medical Association (JAMA) 2010 Jun 2; 303(21):2165-71.

I dedicate this work to God, the author and finisher of my faith. He is my provider, protector and healer who saved my life through his son Jesus Christ.

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LIST OF ABBREVIATIONS

95% CI	95% Confidence Interval
aHR	Adjusted Hazard Ratio
aOR	Adjusted Odds Ratio
aPR	Adjusted Prevalence Rate
aRR	Adjusted Risk Ratio
PR	Prevalence Ratio
HR	Hazard Ratio
OR	Odds Ratio
RR	Risk Ratio

CHAPTER 1

INTRODUCTION

1.1 Research Focus

In this work, factors that have significant relationships to the rate of preterm birth (PTB) will be examined. The study will observe the domains of physical health, mental health status, healthy behaviors and social determinants.

The rate of PTB is increasing in the United States (U.S.) and the world. The causes of preterm birth are multifactorial and not completely understood.(Romano, 2020) The WHO posits that possible reasons are better measurement, increases in maternal age, underlying maternal health problems such as diabetes and high blood pressure and changes in obstetric practices such as more caesarean births before term. They also reported that greater use of infertility treatments lead to increased rates of multiple pregnancies creating increased risk of PTB.(WHO, 2018) It is estimated that multi-gestational pregnancies account for 15 – 20% of all PTB’s with 60% of twin babies being born preterm.(Goldenberg, Culhane, Iams, & Romero, 2008) A report from the Institute of Medicaid Innovation cited infectious and inflammatory processes as triggers of spontaneous preterm birth (SPTB).(Romano, 2020) The mechanism by which this happens is the activation of the innate immune system creating activity that stimulates uterine contractility leading to a premature rupture of membrane. This is estimated to account for 25 – 40% of all PTB’s, which may be an underestimation due to the difficulty in detecting infections using conventional testing. (Goldenberg et al., 2008)

Health-related and social risk factors for preterm birth include smoking during the pregnancy, underweight status or obesity based on body mass index, short inter-pregnancy interval, food insecurity, and unstable housing. Preterm birth is also associated with community risk factors like pollution, employment, housing, occupation, poverty, racial composition, and residential stability. (Romano, 2020)

1.2 Summary of Chapters

In literature, there are common themes that describe the causal factors of preterm birth: health status and social dynamics of the mother. Many papers tend to be focused on singular topics and do not explore from a multifactorial perspective. The papers within this work will seek to contribute to the knowledge by widening the focus and examine how social determinants and health status are inter-related in their impact on PTB. In Chapter 3, the paper "The Interaction of Social Determinants and Health Behaviors: Effect on Preterm Birth" used macroeconomic data from over 3,000 counties within the U.S. Initial data collection began with several demographic, medical and social variables. I used principal components analysis (PCA) to create the following constructs:

- Chronic Disease
- Sexually Transmitted Disease
- Mental Illness
- Household Characteristics
- Healthcare Access
- Healthcare Access Barriers

- Community Deprivation
- Healthy Behaviors

In order to examine the relationships of these constructs to PTB, we used ordinary least squares (OLS) regression and LASSO regression. The results of this data will be important because it could potentially inform public health priorities regarding the reduction of PTB.

The second and third paper (Chapters 4 and 5) serve as branches out of the first paper and delve into more specific factors. In Chapter 4, the second paper "Preterm Birth: Is there an Obesity Paradox based on Socio-economic Status?" takes a closer look at obesity and how its impact on PTB differs based on maternal socio-economic status.

The literature on the effect of BMI on PTB is inconclusive. The paper was conceived with the hope that there could a more definitive relationship established. This is particularly important given that close to a third (27.3%) of women who are of childbearing years are considered obese.(Vallely et al., 2018) By using the natality files sourced by the National Vital Statistics System within the National Center for Health Statistics, we believed that we would find more conclusive evidence of the relationship of BMI and PTB because these files provide demographic and health data for all births in the U.S. occurring during the years of 2015-2018.

We used three regression models. The first one examined the impact of the full data of mothers between the ages of 25 and 45 who had singleton births. The second model examined those women who were of higher socioeconomic status and the final model examined those of lower socioeconomic status. The results could provide guidance to obstetrician and gynecologists as to how to council their pregnant patients concerning nutrition and weight control.

In Chapter 5, the third paper, "A Re-Examination of the Relationship between Race and Preterm Birth" is a response to the editorial "Beyond nature versus nurture: race matters, but how?" by Mishka Terplan. In her think piece, she is calling for researchers to "thoroughly consider the implications of race in their research or assess other factors that might confound apparent associations of outcomes with race." This chapter will examine race as an independent and complimentary factor in spontaneous preterm birth (SPTB). It will seek to provide evidence that the relationship between race and SPTB is not independent, but effected by interactions with other social and health determinants.

In Chapter 6, the fourth paper "Cost Effectiveness Analysis: Preterm Birth and Birthing Facilities" answered the question of whether alternative birth locations outside of hospitals is cost effective due to their reduced incidence of PTB. The use of midwifery care in free standing birthing centers and home births have been cited as not only reduced rates of PTB, but also lower rates of cesarean sections, birth instrumentation and higher patient satisfaction. We analyzed the data using cost effectiveness decision trees and probabilistic sensitivity analysis (PSA) with the use of Monte Carlo simulations.

1.3 Preterm Birth Etiology

PTB has occurred when a baby is born too early, before 37 weeks gestation. The earlier a baby is born, the higher the risk of death or serious disability. Babies born prematurely fall into severity categories based on their gestational age at birth. Those who are born before 28 weeks gestation account for 6% of PTB babies. Ten percent are born between 28 – 32 weeks, 12% are born between 32 – 33 weeks while the remainder are born between 34 and

37 weeks.(Dolezel, 2019)

PTB can be classified into two groups: spontaneous PTB (SPTB) that accounts for two thirds of all PTB's and medically indicated (iatrogenic) PTB (MPTB) that account for the remaining third. The causes of SPTB include preterm labor, premature rupture of membranes (PPROM) and 2nd trimester pregnancy loss.(Purisch & Gyamfi-Bannerman, 2017) Preterm labor happens in 50% of all PTB's and is diagnosed based on clinical criteria of uterine contractions that are accompanied by change in cervical dilation, effacement or both. It can also be characterized by regular contractions and a cervical dilation of at least 2 centimeters.("Practice Bulletin No. 171: Management of Preterm Labor," 2016) PPROM happens when membranes rupture before 37 weeks gestation as a result from the normal weakening of the membrane along with forces created from the uterine contractions. Some of the things that trigger PPROM are history of PPROM, infection, short cervix, second or third trimester bleeding, low BMI, low socioeconomic status (SES), cigarette smoking and drug abuse. ("Practice Bulletin No. 172: Premature Rupture of Membranes," 2016) PPROM precedes 25 – 30% of PTB's.(Goldenberg, Culhane, Iams, & Romero, 2008)

MPTB's are those where the clinician makes a decision to induce labor early due to maternal or fetal conditions. According to the American College of Obstetricians and Gynecologists, "the timing of delivery in such cases must balance the maternal and newborn risks of late-preterm and early-term delivery with the risks associated with further continuation of pregnancy. Deferring delivery to the 39th week is not recommended if there is a medical or obstetric indication for earlier delivery."("ACOG committee opinion no. 560: Medically indicated late-preterm and early-term deliveries," 2019) Some of the conditions that may necessitate MPTB's are preeclampsia, uncontrolled diabetes, intrauterine growth restriction (IUGR) and abnormal placentation (abnormal formation of the placenta).(Purisch & Gyamfi-Bannerman, 2017)

1.3.1 Preterm Birth International and National Statistics

The rates of preterm birth are increasing in the U.S. and the world. According to the WHO, "of 65 countries with reliable trend data, all but three show an increase in preterm birth rates over the past 20 years." In the world, an estimated 15 million babies are born too early every year. Approximately 1 million children die each year due to complications of preterm birth.(L. Liu et al., 2016)

There is a great variation of PTB incidences worldwide. In 184 countries, the rates of PTB ranged from 5% in northern Europe to 18% in Malawi as of 2010. The rates varied based on the level of national income. High-income nations had an average rate of 9.3%; upper middle-income nations had a rate of 9.4%. Those nations that were middle and low income had averages rates of 11.3 and 11.8%, respectively. More than 60% of PTB occurred in low resource, high fertility countries in sub-Saharan Africa and southern Asia. PTB survival statistics also varied based on the level of resources a country possesses. In the countries with higher resources, 50% of babies born at 24 weeks survive while 90% of babies born 28 weeks or less gestation in low resource nations with will die before within the first week of life.(Purisch & Gyamfi-Bannerman, 2017)

In the U.S., the birth rate increased from 10.6% in 1990 to 12.7% in 2005. In 2018, the incidence of PTB increased to 10.02% from 9.93% in 2017.(B. E. Hamilton, Martin Joyce A., Osterman Michelle J.K. , M.H.S., Rossen, Lauren M. , 2019) PTB survival rates differed for different gestational age groups: 23 weeks gestation have a 17% chance of survival, 25 weeks have 50% percent chance of survival, 27 weeks and greater have 90%

and greater chance of survival**.** (Dolezel, 2019)

The U.S. has the highest rate of PTB among high resource nations. In 2010, it had a higher rate of PTB than all European nations except Cyprus**.**(Bronstein, Wingate, & Brisendine, 2018) and accounted for 42% of all PTBs in this group of nations. The U.S. is also the only high resource nation that ranks in the top ten of PTB in all countries including low resource nations.(Purisch & Gyamfi-Bannerman, 2017) Bronstein et al. found that U.S. women have higher rates of obesity, heart disease, and poor health status than women in other developed countries. This is in part because more U.S. women are exposed to the stresses of racism and income disparity than women in other nations. This may disrupt physiological functions conducive to term birth. They also found that women in the U.S. have a higher rate of multiple gestations with twice the rate of twins and three times the rate of higher order gestations than the highest of European nations. U.S. teens also have higher birthrates than those in Europe and Canada. While the rate of teen pregnancy is 41 per 1,000 births, Great Britain leads European nations reported with 25 per 1,000 and Canada has a rate of 14 per 1,000. The authors also cited the fact that more women in the U.S. have reproduction assistance than those in other nations. It's their recommendations that some of the stresses that pregnant women experience in the U.S. can be reduced by reproduction policy that focuses on social welfare policies that can reduce the stress of income insecurity.(Bronstein et al., 2018)

1.3.2 Preterm Birth Complications

PTB accounts for 75% of all perinatal mortality and more than 50% of all long-term morbidity.(Goldenberg et al., 2008) A study by Manuck et al. included over 8,000 deliveries of neonates who were born as singleton, preterm (23.0-36.9 weeks of gestation) and non-anomalous. This study found that 1.4% died while 7.9% had a major morbidity that included intraventricular hemorrhage grade III or IV, seizures, hypoxic ischemic encephalopathy, necrotizing enterocolitis stage II or III, bronchopulmonary dysplasia, or persistent pulmonary hypertension. Thirty-eight percent of the sample had minor morbidities like hypotension-requiring treatment, intraventricular hemorrhage grade I or II, necrotizing enterocolitis stage I, respiratory distress syndrome and/or hyper - bilirubinemia requiring treatment. This study also found that while there was a great survival benefit of longer gestation, this increase did not linearly translate to morbidities. As the rate of death fell, major morbidities peaked at 54.8% for babies born at 25 weeks gestation. As death and major morbidities started to fall, minor morbidity hit its peak of 81.7% for babies born at 31 weeks gestation. Mortality and morbidity rates decreased at 32 weeks gestation.(Manuck et al., 2016)

There are studies that show being born preterm may lead to morbidities throughout one's lifecycle. It is estimated that 22% of PTB survivors may develop a severe disability that is secondary to early birth while 24% may develop a moderate disability or have special needs while 34% may develop a mild disability. It is estimated that 20% of all those who are born with less than 37 weeks may not have any long term effects.(Dolezel, 2019)

Bonamy et al. did a study of toddlers who were 2.5 years old. The authors compared those who were born extremely PTB (23.6 – 26.9 weeks gestational age at birth) to matched controls who were born at term. This study found that the proportion of those with a systolic blood pressure that was greater than the 90th percentile of all children was 44% (30 of 68) in PTB born children and 23% (15 of 65) in controls (P =

.01).(Bonamy, Källén, & Norman, 2012) In a study by Kelly et al., they included over 15,000 children who ranged from age 6 to 11 years who participated in the 2016 National Survey of Children's Health. They examined the neurodevelopment and education progress of these children based on several factors, one being PTB. This study found that those who were born preterm had 2.7 times greater odds (95% CI 2.06 – 3.60) of developmental delay, 2.54 times greater odds (95% CI 1.29 – 5.00) of intellectual disability, 2.06 times greater odds (95% CI 1.55 – 2.74) of having a speech or language disorder, 1.89 times greater odds (95% CI 1.39 – 2.58) of a learning disability and 1.55 times greater odds (95% CI 1.19 – 2.03) of having attention deficit disorder.(Kelly & Li, 2019)

In studies with adults, it was found that those born before term dealt with several health issues. In a population based cohort study that included Swedish enlisted military men born between 1973 -1981, it was shown that the odds of having a high systolic blood pressure in comparison to term born men were as follows: moderately preterm (33 to 36 weeks), 1.25 (95% CI 1.19 - 1.30); very preterm (29 to 32 weeks), 1.48 (95% CI 1.30 - 1.68); and extremely preterm (24 to 28 weeks), 1.93 (95% CI 1.34 - 2.76). It was further noted that those who were born small for gestational age (SGA) did not have increased risk of high systolic blood pressure for those under 33 weeks gestation.(Johansson et al., 2005) The explanation for the increase in blood pressure was provided by Raju et al., in a systematic review of 126 works. This review found that high blood pressure could be explained by the abnormal growth of the vascular tree and persistent endothelial malfunction following PTB that could be the pathogenesis leading to increase blood pressure. (Raju, Buist, Blaisdell, Moxey-Mims, & Saigal, 2017) In another study, it was found that those who were born before 32 weeks gestation had a 2-fold risk of cerebrovascular disease with a hazard ratio of 1.89 (95% CI 1.01 – 3.54) when compared to those term born. There were no significant risks from 34 to 36 weeks gestation.(Ueda et al., 2014)

This review also reported that being born preterm could lead to issues with the kidneys and increase the odds of type 2 diabetes. This paper explained that the reason why being a PTB survivor may increase the odds of kidney issues later in life if because 60% of adult nephrons are formed during the second and third trimesters of fetal life. PTB can either disrupt or prevent nephrogenesis. Also, nephrotoxic medications that are provided in the neonatal ICU can also cause nephrogenesis that can lead to chronic kidney disease. It was also found that survivors of PTB may have a higher risk of type 2 diabetes because being born too early created a higher prevalence of its precursors like higher insulin resistance or lower insulin reserve, higher frequencies of dysglycaemia, abnormal lipid profiles and abnormal distribution of body fat with a tendency for higher abdominal fat. (Raju et al., 2017)

In Crump et al., the study examined over 648,000 individuals from the Swedish birth registry who were born between 1973 and 1979 and followed from 2005 to 2009. They looked at this cohort to examine the odds of using diabetes medications. They found that those who were born PTB had 1.13 greater odds (95% CI 1.02 – 1.26). (Crump, Winkleby, Sundquist, & Sundquist, 2011)

Several studies found that those who were born preterm also had an increased risk of certain cancers. According to a systematic review by Paquette et al., the treatments of premature babies potentially cause damage to tissues or organs and the immature immune system is exposed to pro-oxidants like oxygen, UV light and parenteral nutrition. This oxidative stress may cause there to be premature arrest of cellular proliferation, rapid tissue differentiation, oxidative DNA and impaired DNA repair, which can make the neonate more susceptible to cancer later in life. The meta-analysis showed those born preterm had 1.45 greater odds of acute myeloid leukemia (95% CI 1.08 – 1.95). There was also 1.35 increased odds of nephroblastoma, a common kidney cancer in children (95% CI 1.19 – 1.64). There were several studies that found increased odds of hepato - blastoma, a malignant tumor in the liver in children. One study found that there were 3.12 times greater odds of cancer in those born preterm (95% CI 2.32 – 4.20) while another found that there was 2.65 times greater odds (95% CI 1.98 – 3.55).(Paquette et al., 2019) In another study by Davitz et al., the investigators found that those who were born PTB had 6.1 (95% CI 1.6 – 23.4) times greater odds of soft tissue sarcoma (a cancer that begins in the supportive tissue of the body like muscles, fat and fibrous tissues). (D. A. Savitz & Ananth, 1994) Crump et al. found that there were 3.95 (95% CI 1.67 – 9.34) increased odds of testicular cancer in those who were born preterm.(Crump, Sundquist, Winkleby, Sieh, & Sundquist, 2012)

Because those born preterm have increased risk of medical morbidities, this also leads to an increased odds of hospitalization as adults. Using Swedish data from the Swedish Medical Birth Register, the Total Population Register and the Multigenerational Register, Selling et al. observed subjects who were born in the years from 1973 – 1975. Those who were born preterm had greater odds of being hospitalized for diabetes (aOR 1.5, 95% CI 1.2 – 1.89), pancreatic disorders (aOR 2.07, 95% CI 1.22 – 3.5), congenital anomalies of the genital organs (aOR 1.69, 95% CI 1.15 – 2.5).(Selling, Carstensen, Finnström, Josefsson, & Sydsjö, 2008)

1.3.3 Preterm Birth Costs

The estimated cost of preterm birth in the U.S. is 26.2 billion dollars (or $51, 500 per infant born preterm). Medical care services contributed $16.9 billion to the total cost and maternal delivery costs contributed another $1.9 billion. In terms of longer-term expenditures, early intervention services cost an estimated $611 million, whereas special education services associated with a higher prevalence of four disabling conditions among premature infants added $1.1 billion. Estimates of lost household and labor market productivity associated with those disabilities contributed $5.7 billion.

There are several reasons why these figures are thought to be underestimated. The first is that they do not include the cost of medical care beyond early childhood outside of the disabling conditions of cerebral palsy (CP), mental retardation (MR), vision impairment (VI), and hearing loss (HL).(Behrman & Butler, 2007) Another limitation is that the figures only include maternal medical care costs associated with delivery. It is estimated that inpatient and outpatient care for PTB cost an estimated $32,325, which is ten times the cost of term infants ($3,325). (*Institute of Medicine (U.S.) Committee on Understanding Premature Birth and Assuring Healthy Outcomes*, 2007) This cost difference can be attributed to the length of stay of PTB babies compared to term babies. According to Purisch et al., PTB babies have a hospital length of stay that averaged 13 days in comparison to 1.5 days for term babies.(Purisch & Gyamfi-Bannerman, 2017) Further assessments show PTB babies with gestational ages of 26 to 32 weeks have the potential to reduce hospital length of stay by 8 days for each week increase in gestation.(Manuck et al., 2016)

Hall et al. did a study of Hamilton County, Ohio for all births in 2012 that sought to estimate the cost of PTB from a macroeconomic perspective. This study not only examined the hospital costs but also estimated the cost of loss of education and earnings of those who are born PTB. The justification of this study was to demonstrate that PTB does not only cost the individual but the community at large particularly employers, insurers and taxpayers.(Hall & Greenberg, 2016)

The Hall study had 1,444 PTB babies and 9,532 term babies. They found that hospitalization cost for PTB babies cost was 97.6 million dollars while the cost of care for term babies was 34.1 million dollars. Despite accounting for approximately 13% of all births, PTB births accounted for 74.1% of all hospital costs. If those 1,444 babies were born at term, the cost would have been reduced to 4.8 million dollars, which means that the excess hospital cost of PTB is 92.8 million dollars. It was also found that if all PTB births would have been delayed a week, the cost savings would have been 25.2 million dollars, which is a 19.2% reduction.(Hall & Greenberg, 2016)

It has been reported that adults who survived PTB have less income and education than those adults who are born at term. According to a meta-analysis by Bilgin et al., it was found that those who were born either PTB and/ or low birth weight (LBW) had a decreased likelihood of attaining higher education (OR 0.74, 95% CI 0.69-0.80), lower employment rate (OR 0.83, 95% CI 0.74-0.92), and increased likelihood of receiving social benefits (OR = 1.25; 95% CI = 1.09-1.42).(Bilgin, Mendonca, & Wolke, 2018) Similar results were found in the study of Hamilton County, Ohio. Loss of income and educational attainment was measured by looking at educational attainment and annual income information from the American Communities Survey (ACS) and using the formula

$$\textbf{\textit{Non\_degree\_rate}}_{preterm} = \textbf{\textit{odds\_ratio}} * \textbf{\textit{Non\_degree\_rate}}_{full\_term} = \textbf{\textit{Non\_degree\_rate}}_{population/1\ +\ (}\textbf{\textit{odds\_ratio-1) (rate}}_{preterm)} \quad (1.1)$$

Approximately 44% of adults over the age of 24 who were born term earned a degree in contrast to the 26.4% of those born preterm. Assuming the same rate of degrees of the term born sample, the authors estimated that if there was a 10% decrease in PTB, that would equal an additional 910 degrees conferred. It was also estimated that 42.9 % of those PTB survivors were estimated to be in the bottom third of earners while only 26.3% of them were in the upper third of earners. PTB born adults also earned 16.2% less than term born adults ($42,769 vs $51,061). It was estimated that the cost of being PTB in terms of income was $301 million.(Hall & Greenberg, 2016)

CHAPTER 2

PREVIOUS LITERATURE

The causes of PTB are multifactorial and not completely understood(Romano, 2020). Some of the causes that will be examined in this work will be chronic and mental disease, social determinants (including demographics, socio-economic status and community characteristics and access to care) and healthcare behaviors. There has been extensive scholarly work done examining these factors.

2.1 Preterm Birth and Physical Health Status

2.1.1 Hypertension

Hypertension (HTN) in pregnant women have several classifications. The American College of Obstetrics and Gynecology (ACOG) define chronic HTN in pregnancy as having a blood pressure that is ≥140 mm Hg systolic and/or 90 mm Hg diastolic either before pregnancy or within the first 20 weeks gestation. It is also marked by the use of antihypertensive medications before pregnancy (Seely & Ecker, 2014) The prevalence of chronic HTN in pregnant women is increasing with an estimated rate that ranges from 1 to 10% of all those in the U.S. Its rise in pregnant women is theorized to be a result of maternal obesity and the older age of mothers that is a result of many women delaying childbearing.(Premkumar, Henry, Moghadassi, Nakagawa, & Norton, 2016)

Those who have chronic HTN have greater risks of other forms of hypertension at the onset of pregnancy. Gestational HTN is indicated by an elevated blood pressure (SBP ≥140 mm Hg or DBP ≥90 mm Hg) after 20 weeks gestation for women who had normal blood pressures before pregnancy. Preeclampsia shares this same characteristic as gestational HTN, but is more severe as those who suffer from it have proteinuria and other systematic manifestations.(Seely & Ecker, 2014)

There is exhaustive literature examining the relationship of hypertensive conditions in relation to PTB. Tucker et al. conducted a retrospective cohort study where the sample consisted of Medicaid patients. The study subjects were screened by the Community Care of North Carolina Pregnancy Medical Home Program before 24 weeks gestation. 15,428 subjects in the sample who were screened from the study period of September 2011 to September 2012. This study found that there were 2.92 times greater odds of PTB for those who had chronic HTN (95% CI 2.35 – 3.64). (Tucker et al., 2015)

Premkumar et al. examined HTN in a retrospective cohort study conducted at the University of California in San Francisco from 2002 – 2015.They collected data on 23,425 singleton births. This study found that those who had chronic HTN had 2.74 greater odds of total PTB (MPTB and SPTB) (95% CI 2.28 – 3.29). Chronic HTN was found to have 5.25 times greater odds of MPTB (95% CI 4.17 – 6.62) after accounting for confounders. There was not a significant finding when observing chronic HTN with SPTB. (Premkumar et al., 2016) The non-significant relationship between HTN and SPTB was further confirmed by Sae-Lin et al. This study was done at Siriraj Hospital in Bangkok, Thailand and had a sample of 199 PPROM subjects and 199 control subjects. PPROM is a condition that precedes SPTB in one third of cases. This study showed that HTN was not a factor in PPROM (aOR 1.39, 95% CI 0.62 – 2.63, $p = 0.503$) (Sae-Lin &

Wanitpongpan, 2019)

Another study that examined HTN was Lee et al. Its data was sourced by administrative claims data available from the IBM MarketScan Multistate Medicaid Databases from January 1, 2014 to September 20, 2015. This dataset contained unique enrollees from thirteen states. The study cohort had 457,200 women between the ages of 15 – 44 who had singleton deliveries. In their HTN variable, they included those who had preeclampsia and eclampsia. They found that when they modeled the full cohort, those with HTN had greater odds of PTB (aOR 1.82, 95% CI 1.77 – 1.87). This pattern was also observed when they stratified by race. It was found that White women with HTN had greater odds of PTB than the White non-HTN controls (aOR 1.77, 95%CI 1.7 – 1.85). This was also true of the Black cohort (aOR 1.83, 95%CI 1.76 – 1.91) and Hispanic cohort (aOR 1.98, 95%CI 1.74 – 2.26) (Lee, Okunev, Tranby, & Monopoli, 2020)

Carter et al. did a cross-sectional study that examined late PTB (34 – 36 6/7 weeks gestation). They used data from the San Antonio Metropolitan Health District from the years 2000 – 2008. In their analysis, they found 23,312 (9%) in their sample that had late PTBs which exceeded that national average of 8.7%. They analyzed chronic, gestational HTN and eclampsia; all of which had increased odds of late PTB (aOR 2.15, 95%CI 2.77 – 3.56), (aOR 3.03, 95%CI 2.84 – 3.19) and (aOR 4.37, 95%CI 3.57– 5.36), respectively.(Carter, Fowler, Holden, Xenakis, & Dudley, 2011)

2.1.2 Diabetes

Diabetes (DM) is another chronic disease that has been shown to be a significant factor in preterm birth. There are three types of diabetes. Type 1 diabetes (T1D) happens when the body does not produce insulin that has the responsibility of helping blood sugar to get to the cells so it can be used for energy. Type II diabetes (T2D) happens when the body produces insulin, but it is not used efficiently. The final type is gestational diabetes (GDM) that develops during pregnancy. In the U.S. 1 to 2% of pregnant women have Type 1 and 2 diabetes while 6 – 9 % of pregnant women get gestational diabetes. These rates of all types of diabetes increased from 2000 – 2010. The rate of gestational diabetes increased by 56% and type 1 and 2 diabetes increased by 37%.(CDC, 2018)

There is a wealth of literature indicating that those who have diabetes (DM) have increased odds and risks of PTB. Tucker et al. found that mothers with DM had a bias corrected 3.04 times greater odds (95% CI 2.2 – 4.1).(Tucker et al., 2015) In Carter et al., it was found that those with T2D had 1.58 times greater odds of late PTB at 34 – 36 6/7 weeks gestation (95% CI 1.47 – 1.7). (Carter et al., 2011) In Premakumar et al., DM had greater adjusted odds ratio (aOR) of all PTB (aOR 2.75, 95% CI 2.18 – 3.47), SPTB and MPTB.(Premkumar et al., 2016) The study completed by Lee et al. did not only show that DM increased odds of PTB in the overall sample (aOR 1.27, 95%CI 1.23 – 1.32). This trend persisted across races. White, Black and Hispanic women with diabetes had greater odds of PTB than the healthy controls in their respective racial group. In the White DM cohort, there were 1.27 times greater odds of PTB (95% 1.2 – 1.34), Black DM mother had 1.25 times greater odds (95% 1.2 – 1.33) and Hispanic DM mothers had the greatest odds of PTB when compared to controls (aOR 1.44, 95%CI 1.27 – 1.64) (Lee et al., 2020)

An estimated 1 in 200 to 250 pregnancies are complicated by T1D.(Ludvigsson et al., 2019) The mechanisms that may increase the odds of SPTB are poor glycemic control and urogenital infections. A contributing factor of MPTB is an increased the rate of preeclampsia. .(Lepercq, Coste, Theau, Dubois-Laforgue, & Timsit, 2004) Advances in the treatment over recent decades and focus on the necessity of good care before and during pregnancy has minimally reduced the high risk of adverse pregnancy outcomes. A study by Eidem et al. of all births in Norway from 1985 – 2004 after 22 weeks gestation collected data from the Medical Birth Registry and the Norwegian Childhood Diabetes Registry. Of the over 1.1 million births, 1,199 had a mother with T1D. The rate of PTB for all PTB was 26.4% for those with T1D and 6.8% for the controls (aOR 5, 95% CI 4.4-5.7). T1D mothers also had greater odds of giving birth at 34 weeks or less (aOR 2.6, 95% CI 1.9 – 3.5).(Eidem et al., 2011) In another study by Ludvigsson et al., there were similar results that persisted when the data was stratified by the level of glycemic control. This study had a population -based cohort of births from the years 2013 and 2014. The data was collected from the following Swedish national registries: The National Diabetes Register (NDR), the National Patient Register and other data sources. There were 2,474 women with T1D. Those who had T1D had 4.52 greater risk of overall PTB (95% CI 4.18 – 4.89). (Ludvigsson et al., 2019)

Gestational diabetes (GDM) is a result of biological processes. To accommodate the growth of the fetus during pregnancy, circulating placental hormones and cytokines promote insulin resistance necessitating increased pancreatic β-cell insulin secretion. When pregnant women fail to adapt to this physiological change, they develop insulin resistance that has been shown to be responsible for GDM. The heterogeneity of insulin resistance (IR) in GDM patients can have different effects on adverse pregnancy outcomes. (Sun et al., 2020)

Hedderson et al. did a study from a cohort of 46,230 subjects from the Northern California Kaiser Permanent Medical Care Program. They screened the glucose levels between 24 – 28 weeks gestation. They found that those with GDM and abnormal (elevated) blood sugar screening had a greater risk of SPTB (aRR 1.61, 95% CI 1.3 – 1.99) and (aRR 1.28, 95% CI 1.12 – 1.46), respectively.(Hedderson, Ferrara, & Sacks, 2003)

Similar results concerning excess blood sugar was found in Sun et al. Their retrospective study included 2,647 GDM mothers who had singleton births. The sample also participated in a one-day care clinic at the Department of Obstetrics and Gynecology of Peking University First Hospital. In order to measure the level of insulin resistance, the investigators used the homeostasis model assessment (HOMA) method for IR (HOMA-IR). They examined the rate of PTB by comparing those who fell within four quartiles of insulin resistance measures. When compared to quartile 1 (the lowest level of insulin resistance as measured by HOMA-IR), there was no difference for quartile 2, but there were greater odds of PTB for those who were at quartile 3 and 4 with odds of aOR 2.1, 95% CI 1.11 – 3.97 and aOR 3.2, 95% CI 1.68 – 6.12, respectively.(Sun et al., 2020)

2.1.3 Obesity

Maternal obese and overweight status replaced smoking as the most important preventable risk factor for adverse pregnancy outcomes in many countries.(Cnattingius et al., 2013) Although obesity has been cited as complicit in the incidence of HTN and DM, thus increasing the rate of PTB, literature has yielded inconsistent results on its independent relationship to PTB. In Cnattingius et al., the authors used a population-based cohort study where births from the Swedish Birth Register were observed. The livebirths observed completed 22 weeks gestation while those stillbirths from 28 weeks gestation were included. This study found different results based on the gestational age of the PTB neonate. Being obese at any level had the greatest odds of extremely preterm birth cohort (22-27 weeks gestation):

- Obese I (BMI 30 – 34.99) the odds were 1.21 (95% CI 1.03 – 1.43)
- Obese II (BMI 35 – 39.99) the odds were 1.57 PTB (95% CI – 1.24 – 1.99)
- Obese III (BMI 40 and greater), the odds were 2.07 ((95% CI – 1.58 – 2.70)

When examining very PTB (28 – 31weeks gestation) and moderate PTB (32 – 36 weeks gestation), the effect of being obese was lost while there were stronger odds of PTB for those who were underweight.(Cnattingius et al., 2013) Several studies also showed that the effect of obesity in PTB was diminished. Tucker et al. found that those who were underweight has 1.55 times greater odds in a bias corrected analysis while the effect of being obese was eliminated by the same correction.(Tucker et al., 2015) In a systematic review and meta-analysis completed by McDonald et al., 84 studies with 1,095,834 women were included in analysis. The investigators found that even though the risk of MPTB increased with overweight and obese women when compared with women at a normal weight (aRR 1.3, 95% CI 1.23 – 1.37); this was not observed in the full PTB sample that included SPTB and MPTB.(McDonald, Han, Mulla, & Beyene, 2010)

Su et al. did a retrospective cohort study where 36,596 Chinese women who had singleton live births from January 2015 to December 2018 in the Shanghai First Maternity and Infant Hospital system. For all PTB, being obese increased the risk by

1.30 times (95% CI 1.02 – 1.69). The adjusted risk ratio (aRR) of giving birth to extremely PTB babies increased for obese women (aRR 8.26, 95% CI 1.63 – 41.88). (Su, Huang, Li, & Du, 2020)

There was one study completed by Berger et al. examined the interaction between HTN, DM and obesity in a cohort in Ontario, Canada. This study was conducted from April 2012 to March 2016 with 506,483 women who had a singleton pregnancy at 20 weeks or greater gestation. The data was collected by the Better Outcomes Registry and Network (BORN) information system (BIS). This is a registry of mothers and newborns born in a hospital, home or birthing center. The cohort was categorized as follows: (1) those who have HTN. DM and obesity only; those who suffered from all three diseases (HTN+DM+OB); those who had HTN+DM, HTN+OB, DM+OB. The rate of PTB for the women who were in the control group (no HTN, DM or obesity) was 5.6%. Of combinations, those with HTN+DM had the highest rate of PTB at 37.3%. This combination had the greatest risk of all PTB at less than 37 weeks (aRR 6.34, 95% CI 5.15 – 7.81), SPTB at less than 37 weeks (aRR 3.05, 95% CI 1.92 – 4.85), all PTB at less than 34 weeks (aRR 10.33, 95% CI 6.98 – 15.33), MPTB at less than 34 weeks (aRR 17.91, 95% CI 10.86 – 29.56) and SPTB at less than 34 weeks (aRR 5.54, 95% CI 2.69 – 11.41). Having HTN+DM+OB had the greatest risk of MPTB at less than 37 weeks (aRR 11.26, 95% CI 9.4 – 13.49).(Berger et al., 2020)

2.1.4 Sexually Transmitted Disease

At least 40% of preterm births are associated with intrauterine infection. Infection may affect prenatal activity though the infectious microorganisms that are recognized by toll like receptors (TLRs) and other pattern recognition receptors that activate the innate immune system. This system induces a pro-inflammatory cascade orchestrated by the transcription factor NF-kB and other elements. This cascade results in the elaboration of effector molecules such as cytokines [e.g., interleukin (IL)-1 and tumor necrosis factor (TNF-a)], chemokines (e.g., IL-8), prostaglandins, proteases and other enzymes, to produce a coordinated response featuring uterine contractions, placental detachment, infiltration of inflammatory cells into gestational tissues. This series of biochemical and structural changes in the cervix is known as 'ripening' and weakening of the fetal membranes thus inducing preterm labor if this reaction happens before the full term of the pregnancy. (Agrawal & Hirsch, 2012)

Literature has provided abundant evidence that infection and its associated inflammation within and outside of gestational tissues are a primary cause of a substantial proportion of preterm births.(Agrawal & Hirsch, 2012) Romero et al.. collected amniocentesis samples from 264 patients with preterm labor and intact membranes admitted to Yale-New Haven Hospital from Jan. 1, 1985, to July 31, 1988. It was found that women with amniotic fluid cultures positive for infections had lower gestational ages and more advanced cervical dilatation on admission than women with negative cultures.(Romero et al., 1989)

Burton et al. performed a retrospective case control study of indigenous women who gave birth at the Royal Darwin Hospital in Australia between January 2011 and December 2014. The reason why they used the sample of the indigenous women was because of their high rate of STD's and of PTB in comparison to non-indigenous women. This study did not provide evidence that STDs affected the PTB rate (aOR 0.90, 99% CI 0.58 – 1.39) (Burton & Thomas, 2019) Baer et al. examined the relationship between

PTB and STD's by using a sample of those from California who gave birth from 2007 – 2012. They collected data on 16, 312 who were diagnosed with an STD and matched them to healthy controls. This study found a relationship to PTB at less than 32 weeks (aOR 1.3, 95% CI 1.1 – 1.7), PPROM at less than 32 weeks (aOR 1.7, 95% CI 1.1 – 2.4) and MPTB (aOR 3.8, 95% CI 1.2 – 11.3). There was a marginal relationship between STDs and PTB at 37 weeks or less (aOR 1.2, 95% CI 1 – 1.2) and PPROM (aOR 1.2, 95% CI 1 – 1.4).(Baer et al., 2019a)

Chlamydia is a bacterial infection that is caused by chlamydia trachomatis (CT). It affected 1.17 million Americans in 2018.(CDC, 2019b) Almost two-thirds of new chlamydia infections occur among youth aged 15-24 years. (Satterwhite et al., 2013) It is estimated that 1 in 20 sexually active young women aged 14-24 years has chlamydia.(Torrone, Papp, & Weinstock, 2014)

The literature about the relationship between CT and PTB are not consistent. Olson-Chen et al. did a meta-analysis that included 56 studies with a sample of 614,892. This analysis found that those with CT had 1.27 times greater odds of PTB (95% CI 1.05–1.54) while it had marginal odds of PPROM (OR = 1.81, 95% CI 1.0 - 3.29).(Olson-Chen, Balaram, & Hackney, 2018)

Hill et al. conducted a retrospective cohort study where their source of data was Peribank. Women who are within the database delivered at four hospitals in the Houston TX area. The investigators were looking to examine the effect of (CT) on the rates of PTB. For overall PTB, MPTB and SPTB, there was no evidence of an effect. When the data was stratified, there was a demonstration of elevated risks. For women who were nulliparous, there was a greater risk of MPTB (aRR 2.46, 95% CI 1.3 – 4.8) that was not evident in SPTB (aRR 0.5, 95% CI 0.15 – 1.45). When the sample was stratified by age, women under the age of 25 had greater risk of MPTB (aRR 2.04, 95% CI 1.35 – 3.08).(Hill et al., 2020)

In Reekie et al., the study sample included western Australian women of reproductive age. Their source of data was from the Western Australia Data Linkage Branch. There were 101,558 women included in the study from age 15 – 38 who had singleton births from the years 2001 – 2012. This study did not find that CT was a factor in PTB (aOR 1.08, 95% CI 0.91 – 1.28).(Reekie et al., 2018)

Gonorrhea and syphilis have also been cited as being complicit in PTB. Gonorrhea is a sexually transmitted disease (STD) caused by infection with the Neisseria gonorrhea bacterium. This bacterium infects the mucous membranes of the cervix, uterus, urethra and fallopian tubes in women. In 2018, 583,405 cases of gonorrhea were reported to CDC. Half of the cases happen to those aged 15-24. Syphilis is a sexually transmitted disease (STD) caused by the bacterium Treponema pallidum. During 2018, there were 115,045 reported new diagnoses of syphilis (all stages). (CDC, 2019b)

Baer et al. also examined the relationship between PTB, gonorrhea and syphilis. Those who had gonorrhea had a PTB rate of 8.3% while those with syphilis had a rate of 10.9%. Those who had gonorrhea and syphilis had greater odds of PTB at less than 34 weeks with aOR 1.8, 95% CI 1.2 – 2.6 and aOR 2.6, 95% CI 1.7 – 3.9, respectively. Those with syphilis also had greater odds of PTB at 32 – 36 gestation (aOR 1.5, 95% CI 1.2 – 1.8) and less than 37 weeks (aOR 1.6, 95% CI 1.3 – 1.9).(Baer et al., 2019a) In Burton et al., those with gonorrhea had increased odds of PTB. For overall PTB, those with gonorrhea had 2.92 greater odds (95% CI 1.07 – 7.97). It was also associated with greater odds of SPTB (aOR 4.11, 95% CI 1.14–14.8) and PTB at less than 34 weeks (aOR 3.67, 95% CI 1.11–12.19). (Burton & Thomas, 2019).

Trichomoniasis (or "trich") is a very common sexually transmitted disease (STD). It is caused by infection with a protozoan parasite called trichomonas vaginalis. In the U.S., an estimated 3.7 million people have the infection. However, only about 30% develop any symptoms of trichomoniasis. Infection is more common in women than in men and older women are more likely than younger women to have been infected with trichomoniasis.(CDC, 2019b) In a systematic review by Meites, the authors reviewed articles that were published from September 2008 – January 2013. In one large retrospective study by Mann et al., 108,346 subjects who were South Carolina Medicaid recipients were reviewed. In this cohort, they found that the hazard of having PTB at less than 33 weeks was 1.22 times greater when diagnosed with trichomoniasis at 7 months (95% CI 1.02 – 1.46). Those who were diagnosed at 8 months had 1.59 greater hazard of delivering at 33 – 36 weeks (95% CI 1.18 – 2.14).(Mann, McDermott, & Gill, 2010; Meites et al., 2015) Similar results were found in an earlier study by Cotch et al. In this study, 13,816 pregnant women who were enrolled in the multicenter prospective study of genital infections and pregnancy outcome called the "Vaginal Infections and Prematurity (VIP) Study". The investigators recruited their sample from Columbia University and Harlem Hospital Center, New York; University of Washington, Seattle; University of Oklahoma Health Science Center, Oklahoma City; University of Texas Health Science Center, San Antonio; and Charity Hospital, New Orleans. This study found that those with trichomonas vaginalis had 1.3 times greater odds of PTB (95% CI 1.1 – 1.4).(Cotch et al., 1997; Meites et al., 2015) There was also a departure from these results in studies that observed women who had treatment for this disease. Various cross-sectional and cohort studies have investigated the effects of metronidazole for pregnant women with trichomoniasis. One large retrospective study of Medicaid billing data and birth certificate records from 144, 737 pregnant women delivering in South Carolina found that metronidazole treatment to be protective against preterm delivery (HR 0.69, 95% CI, .52–.92). This trend persisted in women who had at least one other genitourinary infection during pregnancy. (Meites et al., 2015)

Human immunodeficiency virus (HIV) attacks cells that support the immune system making its victim more vulnerable to infections and disease. If left untreated, it could lead to acquired immunodeficiency syndrome (AIDS) which is the end stage of HIV. The rate of HIV is estimated to have decreased by 7% between the years of 2014 – 2018.(CDC, 2020b) The birthrate of those with HIV is 7%. The number of women between in childrearing years (age 13 – 44) declined from 111,273 in 2008 to 96, 363 in 2014.(Nesheim, FitzHarris, Lampe, & Gray, 2018). Many studies did not show strong relationships between those with HIV and PTB. A study by Gagnon et al. was a single center retrospective match control study conducted in a tertiary referral center in Toronto, Canada. From the data of 14,813 deliveries, 97 women were HIV+. They were matched to those who were HIV-. The HIV+ group had a PTB rate of 19.8% while the healthy controls has a 9% rate. The unadjusted odds were 2.6 (95% CI 1.3 – 5.1). This significant result was eliminated when the data was adjusted for ethnicity, history of PTB and medical history of severe illness.(Gagnon et al., 2016) In another study that compared PTB rates of those with HIV vs AIDS, it was found that there were no significant differences. (Dos Reis et al., 2015)

2.1.5 Other Health Issues

Although there has been many studies that examined the cause of PTB, there are still a lot of gaps from a physical health perspective. An examination of less recognized potential health causes may allow research to progress in filling in the gaps in knowledge. Some diseases that may be complicit in PTB include autoimmune diseases, cancer, thyroid issues and other diseases that attack the bodies of childbearing women.

Autoimmune diseases are caused by the immune system attacking its own body tissues. Common immune diseases are rheumatoid arthritis (when the immune system attacks the joints), lupus (when the immune system attacks various body systems), and irritable bowel syndrome/ Crohn's Disease (when the immune system attacks the gastro-intestinal tract). Autoimmune diseases are the third most common category of disease in the U.S. after cancer and heart disease. They affect approximately 5%–8% of the population or 14–22 million persons. It is estimated that 6.7 million or 78.8% of the persons with autoimmune diseases are women.(Fairweather & Rose, 2004)

The pathology that underscores autoimmune diseases is the dysfunction of cytokines and chemokines that regulate the immune system activity. TNF-alpha is a key cytokine in this abnormal response of the immune system. While a woman is pregnant, TNF-alpha controls cyclo-oxygenases that affect blastocyst implantation, endometrial permeability and decasualization, and contributes to the process of labor. Abnormally high levels of TNF-alpha and other cytokines have been implicated in pregnancy complications including preterm delivery, fetal growth retardation, early and unexplained spontaneous abortions, and miscarriages.(Tsao et al., 2018)

Kolstad et al. examined the effect of several autoimmune diseases on the rate of

PTB. In this study, the data was taken from linked hospital and birth certificate records for all live singleton births in California from 2007 to 2011. The data came from the California Office of Statewide Health Planning and Development (OSHPD). Over 2.4 million deliveries were examined for the following autoimmune disorders: Systemic lupus erythematosus (SLE), Rheumatoid Arthritis (RA), Systematic Sclerosis (SSc), Polymytosis/Dermatomyosis (PD) and Juvenile Idiopathic Arthritis (JIA). They found that all those with these diseases had greater risks of PTB. The risks for those with the respective diseases were as follows:

- SLE had 3.27 times greater risk (95% CI 3.01 – 3.56)
- RA had 2.04 times greater risk (95% CI 1.79 – 2.33)
- SSc had 3.74 times greater risk (95% CI 2.51 – 5.58)
- JIA has 2.23 times greater risk (95% CI 1.54 – 3.23)
- PD had 5.26 times greater risk (95% CI 3.12 – 8.89).

The risk persisted when data was stratified by the timing of birth. Births between 20 – 31 6/7 weeks gestation was considered early PTB and those born from 32 to 36 6/7 weeks gestation was considered late PTB. Those with SLE had greater risk of early PTB (aRR 6.5, 95% CI 5.5 - 7.6) and late PTB (aRR 3, 95% CI 2.8 - 3.3). Mothers with RA had greater risk of late PTB (aRR 2.2, 95% CI 1.9 - 2.5). There were also increased risk of SLE and RA for MPTB and SPTB. SLE mothers had 4.4 times greater risk of MPTB (95% CI 3.7 – 5.2) and 3.8 greater risk of SPTB (95% CI 3.4 – 4.3). Those with RA had 2.2 greater risk of MPTB (95% CI 1.6 – 2.9) and two times greater risk of SPTB (95% CI 1.7 – 2.4).(Kolstad et al., 2020)

Other studies have found similar results when looking at SLE and PTB. Fischer et al. found that the rate of PTB is 33% of those with SLE. That is close to 3 times greater than the national average at the time (12%). Another study that used data from a Norwegian birth register found that those with SLE had 22% PTB while the control group only had 6.5%.(Fischer-Betz & Specker, 2017) In a meta-analysis that was completed by Wei et al., they found those with active SLE had 2.98 times greater risk of PTB (95% CI 2.32 – 3.83) when compared to those who were inactive. They further examined those who have SLE nephritis, disease when the immune system attacks the kidneys disrupting their function. They found that those with nephritis had greater risk of PTB (aRR 1.62, 95% CI 1.35 – 1.95). (Fischer-Betz & Specker, 2017; Wei, Lai, Yang, & Zeng, 2017)

The overall cancer survival rate has improved in recent decades. In the U.S., it is estimated that there were 15.5 million survivors in 2016. In the world, 33 million people lived for 5 years after a diagnosis back in 2012.(W. Huang, Sundquist, Sundquist, & Ji, 2020)

While increased survival rates are promising, the low specificity of curative treatments for childhood cancer often results in long-term and late effects due to their impact on normal healthy tissues. (Phillips et al., 2015) This concern has extended to reproductive health effects. Signorello et al., used data from the Childhood Cancer Survivor Study, a large multicenter cohort of childhood cancer survivors. This study included 2,201 children of cancer survivors and a non-cancer control group of 1,175 children. Children of childhood cancer survivors had 1.9 times greater odds of being born PTB (95% CI 1.4 – 2.4, $p < 0.001$). These odds were greater when the parent received high dose radiotherapy to the uterus (OR 3.5, 95% CI 1.5 – 8). (Signorello et al., 2006) There were similar results in Mueller et al. This study used four cancer registries participating in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute:

- The Cancer Surveillance System of Western Washington in Seattle
- The Karmanos Cancer Institute of Wayne State University in Detroit, Michigan
- The Utah Cancer Registry at the University of Utah in Salt Lake City
- The SEER registry in Atlanta, Georgia.

They found that children of cancer survivors had 1.5 times greater risk than the controls with non-cancer mothers (95% CI 1.3 – 1.83). This was also true of neonates born to women who survived genital cancers (aRR 1.33, 95% 1.13 – 1.56).(Mueller et al., 2009)

There were also studies that examined whether specific cancers in adolescents and young adults affected their risk of PTB. In Anderson et al., they used the North Carolina Central Cancer Registry (CCR) to examine births from 2000 – 2014. The age range of the women were from 15 – 39. The prevalence of the survivor's children being born PTB at less than 37 weeks gestation was increased with several cancers:

- Breast (PR1.98, 95% CI 1.56 – 2.51)
- Hodgkin Lymphoma (PR1.59, 95% CI 1.06 – 2.37)
- Non-Hodgkin Lymphoma (PR 2.11, 95% CI 1.42 – 3.13)
- Gynecological Cancers (PR 2.58, 95% CI 1.83 – 3.63).

For those born at less than 34 weeks, surviving non-Hodgkin lymphoma and gynecological cancers increased the prevalence of PTB (PR 3.42, 95% CI 1.88 – 6.21) and (PR 4.29, 95% CI 2.43 – 7.58), respectively.(C. Anderson et al., 2017) Huang et al. examined all singleton live births from 1973 to 2014 in Sweden as per the Swedish birth registers. This study was unique in that it examined those who had mothers and fathers who were cancer survivors. What they found was that the babies who had a mother who survived the following cancers had increased odds of being born PTB: Central Nervous System (aOR 1.6, 95% CI 1.32 – 1.94), Hematological cancers (aOR 1.5, 95% CI 1.27 – 1.78), Skin Cancer (aOR 1.24, 95% CI 1.06 – 1.46), Genital Cancers (aOR 2.42, 95% CI 2.12 – 2.77). They only cancer with significantly increased odds when examining paternal survival was central nervous system cancers (aOR 1.26, 95% CI 1.04 – 1.53).(W. Huang et al., 2020)

Studies on adult cancer survivors are emerging. The pregnancy rates of cancer survivors are 40% less than the general population when adjusted for women's age, education and parity. The pregnancy rate varies based on the type of cancer. Those with thyroid cancer or melanoma have pregnancy rates comparable to the general public while those who have breast cancer have a rate that is 70% less.(Buonomo, Azim Jr, Alviggi, & Peccatori, 2019) For those who do give birth, the rate of preterm birth can be determined by receipt and timing of treatment. In a study by Black et al., they examined records that were linked to the North Carolina birth records and Central Cancer Registry files from 1990 to 2009. They found that those with breast cancer had 1.67 times greater prevalence of PTB (95% CI 1.49 – 1.97). Breast cancer patients who underwent chemotherapy also had greater odds (aOR 1.78, 95% CI 1.25 – 2.53).(Black, Nichols, Eng, & Rowley, 2017) In another study by Harnett et al., cancer registries were used from Georgia, North Carolina and Tennessee. They found that the risk of PTB was increased by being treated for all cancers with chemotherapy only and chemotherapy + radiotherapy less than one year before conception (aRR 1.9, 95% CI 1.3 – 2.7) and (aRR 2.4, 95% CI 1.6 – 3.6), respectively. For those who conceived greater than a year after treatment, there was no significant increase in risk. For breast cancer, those who had chemotherapy only and chemotherapy+radiotherapy within one year of conception had increased odds of PTB (aRR 2.4 95% CI 1.4 – 4) and (aRR 2.9 95% CI 1.7 – 5), respectively. Having chemotherapy+radiotherapy from 1 to 2 years before pregnancy also increased the risk of PTB (aRR 2.1 95% CI 1.2 – 3.6) (Hartnett et al., 2018)

The Institutes of Medicine has cited several studies of other ailments that may contribute to PTB. There was one study where the authors found that the odds of MPTB increased in those with mullerian duct abnormality (congenital disease of the female reproductive system) (OR 7.02, 95% CI 1.69 – 29.15), proteinuria at less than 24 weeks of gestation (OR 5.85, 95% CI 2.66–12.89), history of lung disease (OR 2.52; 95% CI 1.32–4.80).(*Institute of Medicine (U.S.) Committee on Understanding Premature Birth and Assuring Healthy Outcomes*, 2007) Tucker et al. found that those with asthma had 1.36 times bias controlled odds of PTB (95% CI 1.07 – 1.68).(Tucker et al., 2015)

It is hypothesized that chronic diseases or pre-existing health issues will increase the odds of PTB. This will be addressed in Chapter 3 of this paper. Given the literature on obesity, there are two opposite hypotheses that emerge: the first is that obesity increases the odds of PTB and the second is that obesity is not a factor in PTB. We will examine obesity in Chapter 4 and test the hypotheses.

2.2 Preterm Birth and Mental Health

The prevalence rate of antenatal depression and/or anxiety ranges from 8 to 30% varying across geographical locations. A systematic review showed that 18% of women in developing countries reported depressed mood during pregnancy. Twelve percent of this group met the DSM-IV diagnostic criteria for major depression. In the U.S., 9% of the women had depressive symptoms. The percentage was higher for minority women.(Satyanarayana, Lukose, & Srinivasan, 2011)

Several studies examined the effects of the mental health issues of depression, anxiety and stress on the rate of PTB as well as other birth outcomes. Studies found that the presence of mental issues were a contributing factor in adverse birth outcomes including PTB. Mirabzabeh et al. studied 550 pregnant women who were being treated at one of four hospitals in Tehran City from June 2012 to February 2013. In order to examine the mental health of the sample, they used the following tools: Multidimensional Scale of Perceived Support, Depression, Anxiety and Stress Scale (DASS-21) and a Stressful Life Event Questionnaire. They used gestational age as a continuous measure of PTB. This study found that as the score for the tools were negatively correlated with gestational age (Depression: $r = -0.210$, Anxiety: $r = -0.210$, Stress: $r = -0.132$; $p <0.01$). In their path analysis, they found that the DASS-21 score had a direct and inverse relationship with gestational age. Stressful life events were shown to have an indirect relationship with gestational age through its interaction with the DASS-21 score.(Mirabzadeh et al., 2013)

2.2.1 Depression

Depression is one of the most common complications during pregnancy and the childbearing years. The prevalence of major depressive disorder as defined by diagnostic criteria during pregnancy is 12.7%, while as many as 37% of women report experiencing depressive symptoms at some point during their pregnancy.(Staneva, Bogossian, Pritchard, & Wittkowski, 2015) Factors that may contribute to antenatal depression were domestic violence, drug use and medical morbidities were associated with 3 to 4 fold greater odds of reporting stress during pregnancy.(Satyanarayana et al., 2011)

In a meta-analysis that was completed by Grote et al., there were 29 articles that were reviewed in all while 20 examined the effect of depression on the rate of PTB. Using random effects modeling, it was found that the pooled risk of PTB was 1.13 (95% CI 1.06 – 1.1).(Grote et al., 2010)

Another study that examined the effect of maternal and paternal depression on birth outcomes was Liu et al. The motivation for this study was the fact that previous studies have shown that social and emotional support for the mother's partner was associated with birth outcomes. Paternal depression may limit the support that a mother receives thus affect the outcome of her pregnancy. In this register-based study where data was sourced from the social and medical registers in Sweden, all singleton births from June 2007 to December 2012 were identified. Paternal data was retrieved from the Multigenerational Register and the Register of the Total Population in Sweden. Among mothers, it was found that new onset depression (depression that is indicated after 12 months of no depression) increased the odds of very PTB (22 – 31 weeks) (aOR 1.51, 95% CI 1.23 – 1.84) in model 1 that corrected for calendar year of birth, maternal age, parity, paternal education and paternal age greater than or equal to 45. This relationship became insignificant when analyzing model 2 (model 1 with the addition of BMI, smoking and chronological order of depression between the mother and father. For moderate PTB (32 – 36 weeks), maternal new onset and recurrent depression both had increased the odds of PTB in model 2 (aOR 1.34, 95% CI 1.22 – 1.46 and aOR 1.42, 95% CI 1.32 – 1.53, respectively). Paternal new onset depression also showed to increase the odds of very PTB in model 2 (aOR 1.38, 95% CI 1.04 – 1.83) and model one for moderate PTB (aOR 1.16, 95% CI 1.04 – 1.30). Father's new onset depression increased the odds of medically indicated PTB for both very and moderate PTB (aOR 1.76, 95% CI 1.17 – 2.66 and aOR 1.26, 95% CI 1.02 – 1.55, respectively for model II). For maternal depression, in model 1, there was a significant relationship with spontaneous very PTB (aOR 1.54, 95% CI 1.19 – 1.99) and medically indicated very PTB (aOR 1.48, 95% CI 1.06 – 2.06). When looking at model II for spontaneous moderate PTB, maternal depression increases the odds (aOR 1.2, 95% CI 1.07 – 1.33) (C. Liu, Cnattingius, Bergström, Östberg, & Hjern, 2016)

Not only did the literature indicate that depression in and of itself was a factor in PTB, but also its treatment. In a meta-analysis completed by Eke et al., the authors examined eight studies representing 1,237,669 women. Close to 94,000 of these women used selective serotonin inhibitors (SSRI) and the remaining were controls. Three of the studies were from the U.S., two were from Canada and the remaining studies were from Europe. This analysis found that women who were in the SSRI group had an 11.6% rate of PTB while those in the control group has a rate of 5.2% (OR 1.45, 95% CI 1.24 – 1.68). The significant relationship between SSRI use and PTB remained when accounting for confounders (OR 1.24, 95% CI 1.09 – 1.41). This relationship persisted though a rigorous sensitivity analysis. When they stratified by different study designs, they found that for prospective cohort studies, SSRI users were 1.83 greater odds of PTB (95% CI 1.3 – 2.59). In the retrospective cohort studies there were 1.51 greater odds PTB (95% CI 1.3 – 1.75). In population-based studies, SSRI users had 1.14 greater odds of medically indicated PTB (95% CI 1.1 – 1.17). This study also found that women who initiated SSRI treatment in the third trimester had greater odds of PTB. (OR 1.86, 95% CI 1.13 – 3.61) Those who received SSRI at the third trimester had greater odds than those who received at the first trimester (OR 4.17, 95% CI 2.75 – 6.30).(Eke, Saccone, & Berghella, 2016)

In another meta-analysis by Huang et al., the authors examined 28 articles that examined the effect of antidepressants on PTB. The range in risk among these studies were to 0.4 to 11.70. Overall antenatal antidepressant use increased risk of PTB (RR 1.69, 95% CI 1.52 – 1.88). Studies that observed the effect of SSRIs found that there was 1.74 times greater risk of PTB (95% CI 1.52 – 2.00). Those who took other non-SSRI antidepressants had 1.63 times greater risk (95% CI 1.38 – 1.93) (H. Huang, Coleman, Bridge, Yonkers, & Katon, 2014)

2.2.2 Anxiety and Stress

Stress and anxiety have both been complicit in PTB. There are several mechanisms through which stress and anxiety works in maternal biology. One may be a change in the hypothalamic-pituitary-adrenal (HPA) axis activity. Experiencing high levels of stress and anxiety contribute to an increase in stress hormones like cortisol and catecholamines.(Ding et al., 2014) The release of these hormones can prematurely activate placental corticotrophin-releasing hormone that precipitates the biological cascade leading to the onset of preterm labor. Also, the release of these hormones can cause changes in immunologic function which can increase the risk of infection and inflammation.(Institute of Medicine Committee on Understanding Premature & Assuring Healthy, 2007)

Hoffman et al. studied the activation of cortisol as a marker of stress. In this prospective cohort study, 92 healthy pregnant women aged 18 – 45 in their 2nd trimester were in the sample. They had the concentration of cortisol in their hair measured in an effort to assess their stress level three times between 16 and 18 weeks (16 weeks group), between 28 and 30 weeks (28 weeks group) and 38 and 42 weeks (40 weeks group) of gestation. It was found that those who delivered PTB had a greater concentration of cortisol in the second trimester than those who had term births (2.7+/-0.4 vs 2 +/- 0.7, p=0.001).(Hoffman, Mazzoni, Wagner, Laudenslager, & Ross, 2016)

Another mechanism that connects PTB to stress or anxiety is placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). 11β-HSD2 catalyzes rapid inactivation of maternal corticosterone to inert 11-dehydrocorticosterone which may serve as a physiological 'barrier' to maternal glucocorticoids. Maternal anxiety negatively correlated with placental 11β-HSD2 mRNA expression and activity that depresses the placental barrier. Evidence indicated that overexposure to maternal glucocorticoids induced by downregulation of 11β-HSD2 mRNA expression and activity predicted subsequent PTB and low birth weight.(Ding et al., 2014)

Prenatal anxiety can be subdivided into three types:

- Trait anxiety – mother has a relatively stable propensity for anxiety

- State anxiety – temporary feeling due to an event that may or may not be related to pregnancy
- Pregnancy specific anxiety – concerns that are pregnancy dependent. (Rose, Pana, & Premji, 2016)

Several studies have examined the relationship between stress/anxiety and PTB. Rose et al. did a meta-analysis that included 24 studies. Using the random effects analysis, the pooled odds of PTB in those who suffered from anxiety was 1.46 (95% CI 1.27 – 1.67). The odds were more pronounced when they examined state and pregnancy specific anxiety (aOR 1.7, 95% CI 1.33 – 2.18).(Rose et al., 2016)

There was another meta-analysis by Ding et al. that included 15 studies, 12 that examined the relationship between anxiety and PTB. The 12 studies had a total sample of 17,304 pregnant women. Using the fixed effects modelling, it was found that women with anxiety had 1.5 times increased risk of PTB (95% CI 1.33 – 1.70). When the study was stratified by geography, it was found that U.S. women had 1.52 times greater risk of PTB (95% CI 1.31 – 1.87) while women from Europe had 1.35 times greater risk of PTB (95% CI 1.1 – 1.66). This study also found that those with symptoms of anxiety had a greater risk of PTB (RR 1.51, 95% CI 1.33 – 1.71). This finding was not found in those with persistent anxiety disorders.(Ding et al., 2014)

In another study by Catov et al., the authors looked at the continuous variable of gestational age as the outcome. This data in this study was prospectively collected from the Pregnancy Exposure and Preeclampsia Prevention (PEPP) Study. The anxiety measure was gathered from giving the sample a copy of Speilberger Trait Anxiety Inventory (STAI), a standard self-report 10-item tool to assess relatively stable individual differences in vulnerability of anxiety. After adjustments were made, it was found that those who are in the highest quartile of anxiety (STAI > 12) had gestational ages that were 3.3 days shorter than those who were not within this quartile (P = 0.03).(Catov, Abatemarco, Markovic, & Roberts, 2010)

There have been several studies that sought to answer the question about effects of the stress of local, national and international tragedies on pregnancy outcomes. One of these events was 9/11. This tragedy that happened in New York City; Arlington, Virginia; and Shanksville, Pennsylvania. This event took approximately 3,000 lives. The unanticipated nature of the attacks and the devastating imagery of the event produced high levels of psychological stress throughout the nation. In a paper by Brown et al., 35,809,694 birth certificates for children born between January 1, 1995 and December 31, 2003 were used. They were collected by the National Center for Health Statistics available in the Vital Statistics Natality Birth Data (VSNB). The study looked at rate of PTB and other birth outcomes of those babies who were conceived between January and August 2001. What they found was that those children who were conceived in Feb 2001 – May 2001 had a positive relationship with being born PTB (Beta = 0.51, 0.98, 067, 0.35, respectively, p <0.01).(Brown, 2020)

In a study by Kim et al., there was an observation of the birth outcomes after the 1994 Northridge earthquake. The Northridge earthquake shook the greater Los Angeles area with a moment-magnitude of 6.7. It was felt over approximately 21,400 km^2 in Southern California, Nevada and Arizona. According to the U.S. Geological Survey (USGS), 57 people were killed, more than 9000 were injured, 20,000 people were left temporarily homeless and at least 90,000 buildings were damaged. At this time, it is estimated that 2.7% of the population in Los Angeles was pregnant at the time. California birth records over the years 1992–1995 were taken from the National Center for Health Statistics (NCHS). The primary identification strategy proxies for earthquake exposure using mothers' city of residence and the radial distance between that city and the epicenter. An alternate model relies on a "community decimal intensity" (CDI) scale derived from survey responses. The investigators found that gestational age was significantly lower in areas that were most affected by the earthquake. There was also a higher percentage of PTB in the affected areas as well. When this variable was entered into the model, the earthquake did not have an effect on the rate of PTB.(Kim, Carruthers, & Harris, 2017)

It is hypothesized that mental health will be a significant factor in PTB because not only does it have a potentially direct effect on the maternal fetal health, but it also has an indirect effect through being present in social determinants and physical health. Mental health will be addressed in Chapter 3.

2.3 Preterm Birth and Social Determinants

The Healthy People initiative is designed to guide national health promotion and disease prevention efforts to improve the health of the nation. Released by the U.S. Department of Health and Human Services (HHS) every decade since 1980, Healthy People identifies science-based objectives with targets to monitor progress and motivate and focus action.(CDC, 2020a) One area of focus of the Healthy People Initiative are social determinants of health (SDOH).

Social determinants are conditions in the places where people live, learn, work, and play that affect a wide range of health risks and outcomes. The 2020 release of

Healthy People uses a place-based framework that outlines five key areas of SDOH:

- Health and Healthcare – The connection between financial resources (socioeconomic status, income etc.) and the health of an individual. This area of focus also includes an examination of poverty, employment, food security and housing stability.

- Education – The connection between education and health. This includes a focus on literacy, completion of high school, enrollment into college and educational attainment in general.

- Social and Community Context – The connection between where people live, work and play and their health. Topics covered under this area is civic activity, workplace environment, discrimination and incarceration.

- Economic Stability – The connection between people's understanding and access to care and their health. Areas of focus are access to primary care and insurance coverage.

- Neighborhood and Built environment – this is the connection to one's physical environment and health. The areas of focus is air quality, quality of foods and neighborhood crime and violence.(CDC)

Many of these domains have been examined in the context of PTB and have been shown to have significant relationships.

2.3.1 Race

According to the National Center for Health Statistics final natality data; the U.S. preterm birth rates were highest for black infants (13.8%), followed by American Indian/Alaska Natives (11.6%), Hispanics (9.6%), Whites (9.1%) and Asian/Pacific Islanders (8.7%).("March of Dimes Peristats," 2020) These differentials have also been observed in Canada and Europe. In a study by McKinnon et al., the authors used the data from all singleton births in Canada as provided by the Canadian Live Birth, Infant Death and Stillbirth Database and the 2006 Canadian census data. They found similar PTB rate differences between Black and White Canadians. Black mothers had an 8.9% PTB rate and White mothers had a 5.9% rate (RR 1.49, 95% CI 1.32 – 1.66).(McKinnon et al.,

2016) This difference was also found in a study of European women. Patel et al. used data on 122,415 women from The St Mary's Maternity Information system (SMMIS). SMMIS is a database that covers 18 of 20 hospitals in the former North West Thames Health Region. This study found that Black mothers had births at 28 weeks gestation at a rate of 0.90% compared to the 0.23% rate of White mothers. For those babies born at 35 weeks, Black women had a rate of 2.6% versus 1.26% for White European women. For overall PTB, Black women had greater odds than White women (aOR 1.33, 95% CI 1.15 – 1.56). This trend persisted when the White sample was compared to the Black sample stratified by area of natality. African women had increased odds (aOR 1.41, 95% CI 1.23 – 1.56) like Caribbean women (aOR 1.69, 95% CI 1.52 – 1.92). There was also a significant difference in PTB rates when between Asian and White European women who had 7% and 5% rate, respectively (aOR 1.41, 95% CI 1.23 – 1.56) (R. R. Patel, Steer, Doyle, Little, & Elliott, 2004)

When examining differences in race and PTB, there is increasing study of babies born to interracial couples. This is due to the 2010 U.S. Census Bureau reporting an increase of inter-racial or inter-ethnic couples by 28% over the decade to a rate of 10%. One study that examined the relationship of PTB based on the maternal and paternal racial makeup was Shachar et al. Using all livebirth in California from 2007 to 2010, the gathered data on 1,664, 939 births. When comparing to White-Father/White-Mother combination, they found that all other parental combinations with White fathers had greater odds of PTB:

- White-Father/Black-Mother - (aOR 1.5, 95% CI 1.3 – 1.6)
- White-Father/Asian-Mother - (aOR 1.4, 95% CI 1.3 – 1.4)

- White-Father/Hispanic-Mother - (aOR 1.1, 95% CI 1.1 – 1.2)

When other parental racial combinations were compared to Black-Father/Black Mother combinations, they found that all other parental combinations with Black fathers had lesser odds of PTB except for those with Asian women:

- Black-Father/White-Mother - (aOR 0.7, 95% CI 0.7 – 0.8)
- Black-Father/Asian-Mother - (aOR 1.1, 95% CI 1.0 – 1.3)
- Black-Father/Hispanic-Mother - (aOR 0.8, 95% CI 0.8 – 0.9)

When other parental racial combinations were compared to Hispanic-Father/Hispanic Mother combinations, they found that all other parental combinations with Hispanic fathers had greater odds of PTB except for those with White women:

- Hispanic-Father/White-Mother - (aOR 1.0, 95% CI 0.9 – 1)
- Hispanic-Father/Asian-Mother - (aOR 1.5, 95% CI 1.4 – 1.7)
- Hispanic-Father/Black-Mother - (aOR 1.4, 95% CI 1.3 – 1.5) (Shachar et al., 2018)

Inter-racial couples were also studied in a meta-analysis completed by Srinivasjois et al. This analysis included eight studies in total, five of which had data on PTB representing a sample of 22, 943, 616. The study found that when compared to the White Father/White Mother combination, all others had increase odds of PTB with the White-Father/Black Mother combination having 1.19 times greater odds (95% CI 1.34 – 1.77) and Black Father/Black Mother combination have 1.90 greater odds (95% CI 1.54 – 2.35) (Srinivasjois, Shah, & Shah, 2012)

Black women have the highest rates of PTB in the U.S. and the disparity with other races does not seem to improve. This motivated research that has sought to examine reasons for the differences in PTB rates. One study was done by Thoma et al. This study had a sample of 2,268,217 from the 2016 national birth certificate data file from the CDC. The authors ran a decomposition analysis that explained 38% of the disparity between the Black and White rates of PTB. The two biggest factors in the disparity was maternal education (which accounted for 11.3% of the disparity) and marital status (which accounted for 13.8% of the difference).(Thoma et al., 2019)

According to Desisto, one possible reason for the increase PTB rate for Black women is the cultural and intergenerational legacy of slavery, discrimination and segregation in the U.S. This has created persistent racial disparities in SES status and privilege at both the individual and neighborhood levels. (DeSisto, Hirai, Collins, & Rankin, 2018) Psychological stress and depressive symptoms may be the pathway by which racial discrimination increase the risk of PTB for Black women.(Giurgescu & Misra, 2018) One study that examined the role of racial discrimination and PTB was Fryer et al. They did a cross-sectional analysis from the data from the Community Child Health Research Network (CCRN). CCRN is a 5-year multisite prospective cohort study where the women were recruited from Baltimore, Chicago, Los Angeles, North Carolina and Washington, DC. There were 1,732 Black and Hispanic women in the study. The William's Everyday Discrimination Scale was administered to them in an effort to assess their individual experiences with racial discrimination. The authors of this study did not find a significant relationship between discrimination and PTB for Black women (aHR 1.5, 95% CI 0.7 – 3.1) or Latino women (aHR 3.6, 95% CI 0.9 – 14.4).(Fryer, Vines, & Stuebe, 2020) Another study that examined the role of institutional racism was Mendez et al. This study team used data from the Stress Pregnancy and Evaluation Community

Project (SPEAC). The study included approximately 3,400 women who gave birth between 1999 and 2004 in Philadelphia, PA. The study examined the effects of discrimination, redlining, segregation and neighborhood quality on PTB. What they found was that everyday discrimination increased the risk of PTB (aRR 1.1, 95% CI 1 – 1.2) for Black women.(Mendez, Hogan, & Culhane, 2014) Orchard et al. examined the role of racial prejudice and the effect on PTB. They used data from the restricted-use natality files in the U.S. from 2002 – 2012 combined with county-level data measures of both explicit and implicit racial prejudice. The source of data was Project Implicit, a program where they administered over a million Implicit Association Tests to individuals. The results provided evidence that the black-white gap in preterm births is 29 percent larger in the high prejudice counties. The gaps are even larger when the study examined explicit measures of racial prejudice with high prejudice counties having a black-white gap that is 36 percent larger for preterm births.(Orchard & Price, 2017)

In addition to the experience of racism, the stress that is caused by the experience has been studied with respect to PTB. Braveman et al. used the California Maternal and Infant Health Assessment (MIHA), a population-based survey of postpartum women in California conducted annually since 1999. The goal of the study was to examine role of stress and worry about discrimination. Discrimination was defined by the response to the question "Overall during your life until now, how often have you worried that you might be treated or judged unfairly because of your race or ethnic group?" The responses "very often" or "somewhat often" (in contrast to "not very often" or "never") were categorized as chronic worry (worrying often) about racial discrimination. They found that Black women reported worry 7 times more than white women (36.9%, 95% CI 32.9 – 40.9%

and 5.5%, 95% CI 4.5 – 6.5%, respectively). Of those Black women who reported worry, 12.5% had PTB babies while those who did not worry had 7.2% PTB. For White women, those who reported worry had PTB rate of 9.9% and those who did not had a rate of 5.6%. When placed in two separate models, there was a significant prevalence ratio for the Black women and PTB (PR 2, 95% CI 1.33 – 3.01). White women did not have a significant prevalence of PTB that was due to worry (PR 1.84, 95% CI 0.91 – 3.7). This study also found that for Black women, those who worried about discrimination were older, married and had higher incomes than those who did not worry. Among White women, those who reported worry were those with lower income and education.(P. Braveman et al., 2017)

This finding was consistent with another study completed by Braveman and her colleagues. They found that the disparity in PTB between Black and White women were most pronounced for high status women and almost non-existent for low status women. For women who live with less than 100% of the poverty level, Black and White women had an insignificant difference (aOR 1.14, 95% CI 0.78 – 1.85). For those who were above 100% of the poverty level, Black women had greater odds of PTB (aOR 1.82, 95% 1.42 – 2.34). For those who did not graduate from high school, there was not a difference between the races (aOR 0.91, 95% CI 0.51 – 1.61). For those who did have a high school education and above, Black women had greater odds of PTB (aOR 1.63, 95% CI 1.29 – 1.61). This pattern persisted when looking paternal occupation with there being no differences between the races (aOR 0.97, 95% CI 0.15 – 6.09); but becoming significant for fathers with high status jobs (aOR 1.90, 95% CI 1.25 – 2.88).(P. A. Braveman et al., 2015)

Given that the racial disparity in PTB is partially due to issues outside of the pregnancy itself, it has been suggested that the issue should be observed from a life-cycle perspective. This prospective allows practitioners to examine pregnant women overall, outside their current condition. One mechanism of the life cycle perspective is “early programming mechanism” that suggests that exposures and experiences during sensitive developmental periods in early life may encode functions of the organs and systems that manifest later in life. There have been studies that looked at the influences of prenatal factors of babies on their lifelong chances of developing coronary heart disease, diabetes mellitus, and hypertension. It has also been demonstrated that exposure to stress hormones during sensitive periods of immune maturation in early infancy may also alter immune function, leading to increased susceptibility to infectious or inflammatory diseases later on in life. According the early programming mechanism, it is possible that maternal stress could prime the HPA axis and immune system of her developing fetus with stress hormones, leading to higher stress reactivity and immune-inflammatory dysregulation that could increase her female offspring’s vulnerability to preterm labor.(Lu & Halfon, 2003)

Another mechanism is the “cumulative pathway mechanism” which posits how wear and tear can add up over time to affect health and function. Several studies have related health disparities to cumulative differential exposures to damaging physical and social environments at different life stages. This mechanism can explain how the allostatic load over the life course can also affect reproductive health. Women who are subjected to chronic and repeated stress may respond to stressors during pregnancy with higher output of norepinephrine and cortisol, which could increase CRH gene expression leading to preterm labor. Higher levels of glucocorticoids can also lead to relative immune suppression, which could increase the likelihood of chronic colonization of the genital tract by pathogens at conception and during early pregnancy. If they are not cleared by midgestation, spontaneous preterm labor or preterm premature rupture of membranes may follow. (Lu & Halfon, 2003)

A synthesis of these two mechanisms can explain why Black women have more adverse outcomes. According to Lu et al., this disparity happens for the following reasons: 1) lower starting point due to intergenerational effect, 2) smaller acceleration and greater deceleration in their developmental trajectory during sensitive periods, and/or 3) exposures to more risk factors and less protective factors across their life span. The ways that they propose to address this issues are: 1) closing the gap in one generation to give the next generation an equal start, 2) targeted interventions during sensitive developmental periods (e.g., in utero development, early childhood, puberty, pregnancy), and 3) risk reduction and health promotion strategies across the life span. (Lu & Halfon, 2003)

2.3.2 Immigrant Status

Census data shows that the number of immigrants residing in the U.S. grew from approximately 19 to 40 million from 1990 to 2010. Over this period, the share of immigrants has grown for 8 – 13% of the population. If this trend continues, the immigrant population will have an important role in determining the health of this country.(T. G. Hamilton, 2015)

The "Healthy Migrant Effect" describes the observation of favorable health status among selected migrants compared to the majority population in the host country. It has been observed that this health advantage dissipates as the health of the migrants start to mirror that of those in the host country the longer they stay. Lower PTB prevalence had been reported among selected immigrants from Latin America, Asia and Sub-Sahara Africa.(Araneta et al., 2020)

Possible reason for the health advantages are cultural buffering and selective migration. Cultural buffering has been found in Mexico-born Mexicans. They have cultural practices that protect their initial health status despite a range of social and economic disadvantages. This can further explain why health advantages of U.S. immigrants are more pronounced in those who are less educated.(T. G. Hamilton, 2015)

There have been several studies that examined cultural buffering. Scribner and Dwyer used the Hispanic Health and Nutritional Examination Survey to create an index of acculturation. It was found that those Mexican immigrants who are more acculturated to the American lifestyle had a higher risk of low birth weight. (T. G. Hamilton, 2015) Another study by Ruiz et al. conducted a cross-sectional study of PTB that observed 470 Mexican-American women in Texas from 2003 – 2007. This study examined stress, family cohesion and acculturation. Stress was measured by the amount of cortisol that was collected via blood sample. Family cohesion was assessed using the Family Adaptability and Cohesion Evaluation Scales (FACES – II). Acculturation was measured by using the self-report instrument, the Language Proficiency Subscale (LPS) of the Bi-dimensional Acculturation Scale (BAS) for Mexican American women. Those who judged themselves to have a high proficiency in English were deemed to be more acculturated. They found that Mexicans who were born in Mexico had a PTB rate of 5.6% and those born in the U.S. was 10.1%. In the model, acculturation had a positive relationship with PTB (Beta = 0.56, p = 0.011). There was also a significant relationship between PTB and the interaction between stress and acculturation.(R. J. Ruiz, Pickler, Marti, & Jallo, 2013)

Another reason why those who are foreign born have a health advantage is "selective migration". An example are those who immigrate for economic reasons. This group is selected based on relative youth, labor market skills and motivation.(T. G. Hamilton, 2015) This group generally come with socio-economic advantages that place them in better health.

Papers have compared foreign-born (FB) U.S. citizens to their U.S. Born racial counterparts. Almeida et al. used the New York City (NYC) Pregnancy Risk Assessment Monitoring System (PRAMS) survey for the years 2004–2007.(Almeida, Mulready-Ward, Bettegowda, & Ahluwalia, 2014) PRAMS is a surveillance project conducted by the Center of Disease Control and Prevention (CDC) and state health departments. They used state specific population-based data on maternal attitudes and experiences before, during and shortly after pregnancy.(R. L. Ruiz, Shah, Lewis, & Theall, 2014) Of the 4,433 subjects the investigators found that mothers who were U.S. born had a PTB rate of 28.2% while foreign born women had a rate 25% (p = 0.069). For Latin women, 27.2% of those who were U.S. born and 26.1% of those who were FB had premature babies (p = 0.622).(Almeida et al., 2014)

Araneta et al. conducted a retrospective study that looked at a sample of singleton births in San Diego County, California from January 2007 to December 2012. The sample was restricted to mother and infants who were linked to the birth cohort database maintained by the California Office of Statewide Health Planning and Development. This study of 230, 878 births found that the differences between U.S. born and FB counterparts varied based on the race or ethnicity. The difference in PTB between White, Philippine and non-Mexican Latin women was not significant (aRR 1, 95% CI 0.9 – 1.1) for all. There were significant differences between Mexican born and U.S. born Latin women (aRR 0.9, 95% CI 0.9 – 1, p = 0.05) and Somali's and U.S. born Black women (aRR 0.6, 9% CI 0.5 – 0.8). Similar trends were found in SPTB, but not MPTB.(Araneta et al., 2020)

Several studies found that FB Black women have PTB rates that are consistently lower than U.S. born Black women. One study that examined this was by Desisto et al. Using 2013 U.S. Natality file, they ran Oaxaca Blinker Decomposition (OAB) method for analysis. This econometric technique applies the counter-factual prevalence distribution factor in one group to that of a comparison group in order to isolate specific variables contribution to an overall disparity. This study found that U.S. born Black women had greater odds of PTB compared to FB Black women (RR 3.2, 95% CI 3 – 5) and U.S. born White women (RR 4.4, 95% CI 4.3 – 4.5). In comparison to FB Black women, the results of the Oaxaca decomposition demonstrated that 18.0% of the disparity in PTB with U.S.-born black women was explained by the variables in their model. Paternal acknowledgment (12.4%) and maternal hypertension (10.7%) were responsible for the largest portions of the disparity. The lower level of maternal education and higher rate of smoking among U.S.-born black women contributed 6.3% and 5.1%, respectively, to the disparity. Maternal age, prenatal care entry, pre-pregnancy BMI, and maternal diabetes were negative contributors to the disparity, indicating that if U.S.-born black women had the same age, prenatal care entry, pre-pregnancy BMI and maternal diabetes distribution as FB black women the PTB disparity would be wider.(DeSisto et al., 2018)

Another study that added to the evidence of the "healthy immigrant effect" in FB Black women was Agbemenu et al. The researchers used the enhanced electronic birth certificate data extracted from the hospital systems in Erie County, New York. This location was chosen because of the significant refugee population. There were 77, 891 women included in the study. Of those who were FB, 68.3% were from Somalia while 9.8% were form the Congo. This study found that the refugee cohort had the lowest rate of PTB (6.3%), followed by U.S. born Whites (8.9%) and U.S. Born Blacks (13.6%). Some of the reasons for the differences in the rates of PTB are the fact that smoking rates were higher for U.S. Born Whites (12.7%) and Blacks (15.3%) than the refugees (0.5%) ($P < 0.001$). Also, U.S. Born women had higher pre-pregnancy medical issues (Whites - 44%, Black - 41.3%) than refugees (34.5%) ($p < 0.001$). There were also significant differences in the rates of marriage among the groups: Refugees – 76%, U.S. born Whites – 67% and U.S. born Blacks – 13.1% ($p < 0.001$). (Agbemenu, Auerbach, Murshid, Shelton, & Amutah-Onukagha, 2019)

The reasons for the disparity in PTB rates can be due to differences in social conditioning and health differences. FB Black women do not have the experience and historical trauma of racism as those who are U.S. born, although this may change the longer that the FB woman stay in the U.S. In addition, Black women who were born in the Caribbean or Africa tend to have better health statuses. (DeSisto et al., 2018)

The immigrant advantage seems to affect the Asian population as well. Girsen et al. conducted a retrospective cohort study using linked birth certificate and maternal discharge data from the California Office of Statewide Health Planning and Development. This study included 112,473 who were U.S. born Asian women and 31,082 who were FB. Being FB was protective against PTB across the different Asian ethnicities. FB Chinese had lower odds of PTB and SPTB (aOR 0.84, 95% CI 0.74 – 0.95) and (aOR 0.81, 95% CI 0.71 – 0.93), respectively than those who were U.S. born. FB Japanese women had lower odds of PTB (aOR 0.80, 95% CI 0.64 – 0.99). FB Vietnamese women had lower odds of PTB and SPTB (aOR 0.78, 95% CI 0.64 – 0.95) and (aOR 0.76, 95% CI 0.60 – 0.95), respectively. FB Indian also had lower odds of PTB and SPTB (aOR 0.74, 95% CI 0.62 – 0.88) and (aOR 0.72, 95% CI 0.59 – 0.88), respectively.

Although mother's who are FB were found to have better birth outcomes, there has been literature that provided evidence that they are subject to psychological stressors that may reduce the healthy immigrant effect. Tsai et al. examined the effect of stressors in U.S. and FB Black women who were a part of a Boston birth cohort. The variable of lifetime and pregnancy stress were ascertained from a standard questionnaire item that asked, "How would you characterize the amount of stress in life in general?" and "How would you characterize the amount of stress during your pregnancy?" What they found was that those who experienced lifetime stress had increased odds of PTB and SPTB (aOR 1.34, 95% CI 1.08 – 1.66, $p < 0.001$) and (aOR 1.30, 95% CI 1.02 – 1.95, $p = 0.03$), respectively. When this analysis was stratified by natality, FB women had increased odds of PTB and SPTB (aOR 1.56, 95% CI 1.10 – 2.2, $p = 0.01$) and (aOR 1.57, 95% CI 1.05 – 2.36, $p = 0.03$), respectively. This result was not seen in U.S. born Black women. Similar patterns were found for those with pregnancy stress that increased the odds of

PTB and SPTB for the full sample (aOR 1.38, 95% CI 1.13 – 1.68, p <0.001) and (aOR 1.32, 95% CI 1.06 – 1.66, p = 0.01), respectively. This was also found FB women also had increased odds of PTB but not SPTB (aOR 1.51, 95% CI 1.09– 2.11, p =0.01) and (aOR 1.40, 95% CI 0.95 – 2.05, p =0.09), respectively.(Tsai et al., 2017)

Social and political changes can cause stress for immigrants in the U.S. An example was the U.S. 2016 presidential election and its aftermath. The heightened anti-immigrant, anti-Hispanic and anti-Muslim policies, discrimination and hate crimes constituted severe sociopolitical stressors with adverse impacts on health, including increased PTB rates. In a study by Krieger et al., a trend analysis was used with the data for all singleton births in New York from September 2015 to August 2017. There were 230,105 subjects in the study. When comparing the period before the U.S. presidential nomination (from September 2015 to July 2016) to the time after the inauguration of President Donald Trump (January 2017 – August 2017), it was found that there was an overall 7.3% increase in PTB (RR 1.04, 95% CI 1 – 1.07). The risk for immigrant groups increased by 1.06 times (95% CI 1.01 – 1.11). This post-inauguration pattern was found when the data was stratified by geography of natality. Those who were Hispanic had a 1.07 times greater risk of PTB (95% CI 1.01 – 1.13). Those who were U.S. born but had Mexico/Central America ancestry had 1.13 times greater risk (95% CI 1.01 – 1.28); those who were U.S. born with South American ancestry had 1.4 times greater risk (95% CI 1.02 – 1.92); those who were born in Mexico had 1.15 times greater risk (95% CI 1.01- 1.31).(Krieger, Huynh, Li, Waterman, & Van Wye, 2018) Similar results were found in Gemmill et al., where national data was used from the CDC Wonder database. This study examined births from January 2009 to July 2017. What this study found was that there were 1,342 more PTB's of male children and 995 more for female children of Latin women than would have been expected if the 2016 election did not happen. This translates to a 3.2 – 3.6% more PTB.(Gemmill et al., 2019)

There is some variation when examining the PTB rates of immigrants to countries outside of the U.S. In the United Kingdom (UK), there is an increasing proportion of births that are occurring to women born outside of its borders. In 2017, 28.4% of the births occurred among women who were born to immigrants, which is an increase from the 26.5% in 2013. This trend is observed in high-income nations. In other countries in the European Union (EU), the fertility rate for EU born women was 1.7 while it was 1.88 for those who were born outside of the EU. The data was retrieved from the statutory birth and death registration for England and Wales linked to the National Health Service numbers for babies born notifications system. The racial groups that they examined were White British, White Non-British, Indian, Pakistani, Bangladeshi, Black Caribbean and Black African. When the researchers did analysis, they categorized the racial groups into the following categories based on their native country: (1) Born in the UK (2) Born in country of origin (example: Indian women who were born in India) and (3) Born elsewhere (mothers who were not born in their country nor in the UK). When all the data was pooled, they found that there was reduced risk ratio (RR) of PTB among those who were born in their country of origin (RR 0.96, 95% CI 0.95 – 0.97) and those who were born elsewhere (RR 0.84, 95% CI 0.82 – 0.86). The stratified analysis found that White Other, Indian and Pakistani mothers who were born in their country or region of origin had a lower rate of PTB in comparison to their UK born counterparts. White (other) – aRR 0.90, 95% CI 0.87 – 0.94); Indian (aRR 0.91, 95% CI 0.87 – 0.96) and Pakistani (aRR 0.85, 95% CI 0.82 – 0.88)(Opondo et al., 2020).

2.3.3 Social Class

Socio-economic status (SES) has been conceptualized and measured in different ways internationally. In the UK, social class (usually based on occupation) and area deprivation (ranking resident populations of small geographical areas by the prevalence of a range of characteristics) have commonly been used. In other areas of Europe, the use of educational attainment has been more widespread and in the U.S. income measures are more common(McCartney et al., 2019) The relationship between health and SES generally follows a "gradient." For example, as one's family income increases, so does one's average life expectancy and self-rated health. Researchers have speculated that this gradient in health and longevity by SES arises in part from perceptual factors, such as hierarchical social comparisons between members of a society. More specifically, the perception that one is on the "bottom" of a social hierarchy (e.g., with respect to income) is thought to produce more psychological stress and depression than being at the top. This psychological stress induced by one's subjective social status is thought to damage biological systems, thereby reducing both health and longevity.(Li, Zhang, & Muennig, 2018)

The observations of the effect of SES on health in general also has been found in PTB along with other birth outcomes. MBRACE is a British organization that has a collaboration with other health quality organizations that seeks to conduct surveillance to investigate the causes of adverse maternal outcomes. (http:// npue.ox.ac.ok/mbrace-uk) According to their report there was a 1.5 times greater likelihood of infant mortality to babies born to a SES deprived mother. In an effort to study SES and very PTB, McCall et al. did a population-based cohort study using data from the Aberdeen Maternity Neonatal Databank. They collected data on deprivation using the measures of employment, car ownership, crowding and social class. The investigators also looked at job characteristics which they categorized as professional, managerial, skilled/non-manual, skilled-manual, semi-skilled and unskilled. This study found that those who were most deprived had greater odds of very PTB (less than 32 weeks gestation) (aOR 2.16, 95% CI1.27 – 3.67). Similar results were also found in unskilled workers who had greater odds of PTB (aOR 2.77, 95% CI 1.54 – 4.99). While this pattern persisted for non-smokers, the significance was eliminated for those who smoked. Smokers did not have significant differences in very PTB by deprivation and job class.(McCall, Green, Macfarlane, & Bhattacharya, 2020)

Another study showed similar results. Chiavarini et al. collected from Umbria Italy. The used all birth data in 2007 by use of the Standard Certificate of Live Birth (SCLB) that was linked to census data. The linkage was used to ascertain the neighborhood deprivation index. There were 7,068 births in the city of Umbria. Univariate analysis showed that holders of white-collar jobs, blue-collar jobs and homemakers had PTB rates of 4%, 6.31% and 5%, respectively. Being in a white-collar profession was protective against PTB (OR 0.71, 95% CI 0.56 – 0.91). The blue-collar workers had greater odds of PTB (OR = 1.44, 95% CI 1.09 – 1.99). The multiple variable regression showed that blue collar workers had significantly more PTB than the white-collar cohort (beta= 1.543, p=0.05) (Chiavarini, Bartolucci, Gili, Pieroni, & Minelli, 2012)

Studies examined the relationship between father's SES and PTB. Collins et al.

used the Illinois transgenerational birth file of infants who were born from 1989 to 1991. They linked this data with census data in order to get parental and income data. They found that 3.9% of fathers who had a lower lifetime SES had children who were PTB at gestational ages less than 34 weeks, while fathers of higher SES had a 1.4% rate (RR=3.03, 95% CI 2.48 – 3.69). The gap narrowed slightly when looking at fathers of those children born at 34 – 36 weeks gestation. Low SES fathers had PTB babies at a rate of 9.1% while their high SES counterparts had a 4.7% rate (RR = 2, 95% CI 1.79 – 2.23).(J. W. Collins, Rankin, Desisto, & David, 2019)

In studies of life-course epidemiology, there are three distinct hypotheses that attempt to explain how SES effects health over time:

- Critical/Sensitive Period Hypothesis proposed that early life SES influences health later in life through specific windows of development
- The Accumulation of Risk Hypothesis – posits that that effects of adverse SES gradually accumulates through one's life thus effecting health
- The Social Mobility Hypothesis that claims that a change in SES in one's life influences health.(Osypuk, Slaughter-Acey, Kehm, & Misra, 2016)

In a study by Osypuk et al., the data was retrieved from the Life Course Influences of Fetal Environments (LIFE) study. The LIFE study is a retrospective cohort of self –reported data provided by Black women aged 18-45 years of age who gave birth in a Detroit, Michigan suburban hospital. The purpose of this study was to test the social mobility hypothesis on maternal outcomes including PTB. This study surveyed the mothers and grandmothers to compare whether the mothers has more or less education and perceived income through their life cycles. The life cycles that were birth to 10 years of age, 10 – 18 years of age and greater than 18years of age. The overall results that included all data did not provide evidence that social mobility had an effect on PTB when corrected for confounders. For educational mobility between mother and daughter: aRR=0.934, 95% CI 0.79 – 1.1. Financial mobility between maternal childhood (Birth to age 10) to adulthood, aRR=0.924, 95% CI 0.774 – 1.1 and middle childhood (age 10 -18) to adulthood, aRR=0.907, 95% CI 0.775 – 1.1.(Osypuk et al., 2016)

2.3.4 Education

Education is an element of SES that is associated with health in general and birth outcomes specifically. The association between education and PTB has been reported in several papers. Bushnik et al. used the Canadian Birth-Census cohort of the 127,694 singleton births in 2006. The authors found that the rate of PTB increased as the level of education decreased. Those mothers who were university educated had 5.6% (95% CI 5.3 – 5.9%) PTB while those who completed post-secondary/certificate program, secondary education and less than secondary education had rates of 6.5% (95% CI 6.2 – 6.7%), 6.6% (95% CI 6.3 – 7%), and 7.7% (95% CI 7.3 – 8.1%), respectively. In the regression model where university education served as the reference, all other education levels has increased odds of PTB. For those who did not complete their secondary had 1.4 greater odds of PTB (95% CI 1.28 – 1.53); secondary education graduates had 1.24 greater odds ((95% CI 1.28=1.15– 1.34); post –secondary education graduates had 1.21 greater odds (95% CI 1.13– 1.29).(Bushnik, Yang, Kaufman, Kramer, & Wilkins, 2017)

Baron et al. used data from the DELIVER, a nationwide multicenter cohort study that ran from September 2009 to March 2011 in Netherlands. This study included 2,768 nulliparous women. Baron and colleagues found that those with “low education (vocational education or less) had 1.72 greater odds (95% CI 1.14 – 2.58) of SPTB than those who had higher education (college, university and post graduate).(Baron et al., 2017)

There were studies that used multiple datasets from European nations to observe the effect of education on PTB and other birth outcomes. The first study was Ruiz et al. This study was a prospective cohort study that included 72,296 newborns in their data. The study was implemented under the remit of the DRIVERS for health equity research program. The program's philosophy was that "equity from the start of life is instrumental to reducing health equities in Europe". The data came from 12 countries: Czech Republic, Finland, France, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom and Ukraine. The associations between maternal education and birth outcomes were estimated to infer relative and absolute SES inequality in each cohort sample by using the relative and slope index of inequality. (M. Ruiz et al., 2015) The relative index of inequality (RII) is the weighted measure of inequality that represents the ratio difference in estimated values of the health indicator between most and least advantaged while taking other subgroups into consideration. The slope index of inequality (SII) does that same thing differing only in it use of absolute differences between the most and least advantaged groups.(WHO, 2016-2017) The mean RII indicated that there was a significant increase in the relative risk in PTB for mother with low education (RII=1.48, 95% CI 1.29 – 1.69). The SSI did not indicate a significant increase in risk (SII=1.84, 95% CI 0.99 – 2.69).(M. Ruiz et al., 2015)

In another study by Augur et al., using data from vital statistics data compiled from the birth registration certificates for all residents of Quebec Canada from 1995 – 2005. They examined maternal education at the time of delivery. In Canada, education up to 11 years is equal to having a high school diploma; 13 years is equal to post-secondary non-university degree; 16 years of education was equal to a university degree while having greater than or equal to 17 years is equal to a graduate or professional degree. In Quebec, education is compulsory up until 10 years. (Auger, Abrahamowicz, Park, & Wynant, 2013)

The study showed that the rates of PTB increased as the years of education decreased. Those with less than 11 years of education had a PTB rate of 7.9% (95% C 7.7 – 8.2%) while those with greater than equal 17 years of education had 4.9% (95%b CI 4.8 – 5.1%). This pattern was present in all subgroups except for foreign-born women between the ages 25 – 29. In this group, those with less than 11 years education ha 5.9% PTB while those with 11 years of school had 6.3%. In the cox regression model, the adjusted model compared all educational levels to eight years of education. They found that 10 years of education yielded a 9% reduction in the hazard of PTB (aHR 0.91, 95% CI 0.90 – 0.91), 20 years education yielded 45% reduction (aHR 0.55, 95% CI 0.53 – 0.58) and 30 years of education reduced the risk by 66% (aHR 0.34, 95% CI 0.31 – 0.37). The relationship between PTB and education varied with nativity and age as indicated by the significant relationship of the interaction between education by age ($p=0.009$) and education by nativity ($p < 0.001$). (Auger et al., 2013)

There have been studies that examined the effect of paternal education on PTB. One such study also used the 2006 Canadian Birth Census Cohort. There were 113, 296 births included in their analysis. The findings were similar to what many other studies found with maternal education. When compared to fathers who are university educated, it was found that that with less than a high school diploma, high school education and post-secondary education had greater risk of PTB (aRR 1.22, 95% CI 1.1 – 1.35), (aRR

1.14, 95% CI 1.06 – 1.24) and (aRR 1.14, 95% CI 1.06 – 1.22), respectively. This persisted when they examined the data stratified by gestational age at birth. Those with less than a high school diploma, high school education and post-secondary education still had greater risk of PTB at less than 34 weeks gestation (aRR 1.35wh, 95% CI 1.09 – 1.66), (aRR 1.29, 95% CI 1.11 – 1.5) and (aRR 1.25, 95% CI 1.09 – 1.45), respectively. When compared to university educated fathers, those without a high school diploma were the only cohort with an increased risk of PTB at 34-36 weeks gestation (aRR = 1.18, 1.04 – 1.34). (G. D. Shapiro et al., 2017)

The education advantage that has been revealed in literature persists across races. Ma et al. did a study with data from the birth certificates of livebirths in South Carolina from January 2008 through December 2009. After exclusions, there were 123, 759 live births. This study found that when they did separate models for White and Black women, they found that those with more education have lesser odds of PTB when compared to those with lower education in their racial cohort. For White women with some college and bachelor's degree, the odds of PTB were (aOR 0.85, 95% CI 0.79 – 0.91) and (aOR 0.65, 95% CI 0.60 – 0.72), respectively. For Black women with some college and bachelor's degree, the odds of PTB were (aOR 0.87, 95% CI 0.81 – 0.94) and (aOR 0.61, 95% CI 0.54 – 0.70), respectively (Ma et al., 2015).

2.3.5 Housing

One possible contributor to adverse birth outcomes is poor housing and living conditions. Housing is socio-economically patterned and associated with health conditions like infectious diseases and respiratory conditions.(Harville & Rabito, 2018) Tucker et al. found that those who lived in unstable or unsafe housing had greater odds of PTB (aOR

1.26, 95% CI 1.04 – 1.53).(Tucker et al., 2015) Harville et al., examined the effect of housing conditions by use of the data from the National Child Development study. Exposures to adverse housing conditions was sourced from the "Your Life" survey where mothers were asked to provide a residential history along with information about their present living conditions. There were 1,927 women who reported having at least one birth at their present home. The housing factors that were examined were crowding as measured by having greater than one person per room, dampness and mold, and central heating. While there were significant relationships with other birth outcomes, there were no associations with PTB.

In another study that examined housing and PTB, Leung et al. used data from the "Children of 1997" which was a representative Chinese birth cohort that had 8, 327 births. They examined six elements of SES, one being housing. Housing was categorized into their following categories: public rental housing / squatter, subsidized home ownership and private housing. This study found that those who had private housing had marginally decreased odds of PTB (OR = 0.79, 95% 0.62 – 1, p = 0.046)(Leung, Leung, & Schooling, 2016)

2.3.6 Neighborhood Deprivation

Living in a more disadvantaged economic and social environment can lead to relative deprivation, increased exposure to crime, increased economic strain and stunted growth and social mobility opportunities. (Ncube, Enquobahrie, Albert, Herrick, & Burke, 2016) The Neighborhood Deprivation Index (NDI) synthesizes multiple dimensions of the neighborhood socioeconomic context that allows comparisons across geographic area.(Ma et al., 2015) The NDI includes indicators of education, occupational prestige, poverty, and income.(Bruckner, Kane, & Gailey, 2019) Ma et al. did an analysis of deprivation using NDI values that were categorized into quartiles. This study did a stratified analysis where they did separate analysis for White and Black women. They found that White women did not have significant PTB prevalence differences between the highest and lowest NDI quartile (1.42; 95% CI -0.46 – 2.84) while Black women did have a significant prevalence differences (2.91, 95% CI 1.48 – 4.92). When they ran the random effects model, the results were reversed. White women in the highest NDI quartile had greater odds of PTB than those in the lowest quartile (aOR 1.13, 95% CI 1.01–1.27). This pattern was not seen in Black women (aOR 1.07, 95% CI 0.96–1.21).(Ma et al., 2015)

In a meta-analysis by Ncube et al., they examined deprivation by using observational studies conducted in the U.S. An analysis of the 11 papers with an outcome of PTB found that those who live in the most disadvantaged communities had 27% increased odds of PTB when compared to the most advantaged (OR 1.27, 95% CI 1.16 – 1.39). The association was lost when placed in a model and was adjusted for confounders (aOR 1.01, 95% CI 0.94 – 1.09). For White women who live in the most disadvantaged areas, there was 48% chance of PTB (OR 1.48, 95% CI 1.25 – 1.75) in comparison to other White women who live in advantaged areas. For Black women in most disadvantaged areas, there is 15% increased odds of PTB (OR 1.15, 95% CI 1.09 – 1.21)(Ncube et al., 2016)

All these elements can contribute to maternal stress that may lead to increased risk of PTB. (Ncube et al., 2016) One study that examined the interaction between mental health and neighborhood deprivation was Adhikari et al. who used datasets from two community-based prospective pregnancy cohort studies in Alberta, Canada. The All Our Families (AOF) cohort study recruited 3341 pregnant women and the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort study recruited 2,187 pregnant women. After exclusions, 5,297 pregnant women were included in the study. Measures of neighborhood deprivation were categorized based on quintile deprivation where quintile 1 was the least deprivation and quintile 5 was the most deprivation. For those with both anxiety and depression, those who were in quintile 3 and quintile 4/5 had greater odds of PTB than those who did not have either mental health issues: (aOR 2.1, 95% CI 1.2 – 5.8) and (aOR 2.2, 95% CI 1.3 – 4), respectively. Also, for those who had both anxiety and depression but lived in areas of least deprivation, there was not increased odds of PTB (aOR 0.2, 95% CI 0.1 to 1.5).(Adhikari et al., 2020)

2.3.7 Macroeconomic Conditions

There is a lot of evidence of the effect of macro-economic factors that may also have an effect on the rates of PTB in affected areas. Studies have shown that increases in macro-level unemployment during pregnancy led to births of smaller babies. The fear of losing one's employment led to declines in birthweight and length of gestation. In a study by Margerison-Zilko, the effect of unemployment was examined. The data used was from the Michigan Birth Certificate from 1990 – 2012. There were 2,657,272 births to 1,717,561 mothers included in the study. They examined PTB rates unemployment rates for Michigan and U.S. Through the use of random effects regression models, it was found that for every one-percent increase in the state unemployment rate in the first trimester, there was a 3% increase in the odds of the PTB (aOR 1.03, 95% CI 1.02 – 1.04). These trends did not persist when looking at unemployment in the second trimester. For Michigan state unemployment increase, there was a significant decrease in gestational age (−0.02, 95% CI (−) 0.03 – (−) 0.01). For national increases in unemployment, there was a protective relationship with PTB (aOR 0.97, 95% CI 0.97 – 0.97)(Margerison, Luo, & Li, 2019)

2.3.8 Access to Healthcare

The CDC has recommendations that they propose in the effort to reduce PTB. Many of these are related to taking advantage of the access to healthcare. A couple of these recommendations are (1) women of childbearing age need access to preconception care services including screening, health promotion, and interventions that will enable them to achieve high levels of wellness, minimize risks, and enter a pregnancy in optimal health. As the prevalence of chronic diseases in women of reproductive age increases, improving health before and between pregnancies is an important strategy to reduce maternal risk factors for preterm birth and (2) women at risk for preterm delivery need to be identified and offered access to effective treatments to prevent preterm birth. For example, for women who have had a spontaneous preterm delivery, the risk for preterm delivery in subsequent pregnancies is 1.5–2.0 times higher. Among women with a singleton pregnancy and history of spontaneous preterm delivery, 17 alpha-hydroxyprogesterone caproate (17P) can reduce the risk of preterm birth by approximately 30%.(Shapiro-Mendoza et al., 2016)

There is ample evidence that the access and usage of healthcare affects the rates of PTB and that effect is dependent on the quantity and quality of exposure. Receiving adequate prenatal care (PNC) has implications for both the expected mothers and their children. The increased number of visits provides greater opportunity for health education around PTB, nutrition and smoking. PNC also provides physicians more opportunity to identify health risks like HTN and DM that are complicit in the incidence of PTB.(Williams et al., 2017)

In a retrospective cohort study, the researchers used the birth cohort that was linked to birth-infant death and the fetal death data files from the National Center of Health Statistics. This file contained 28,729,765 records. Partridge et al. examined birth outcomes based on levels of PNC based on the adequacy of PNC utilization (APNCU) index. The levels of adequacy were as follows:

- Inadequate – initiated after four months gestation or fewer than half of necessary visits.
- Intermediate Care – initiated prior to four months and between 50 – 79% of expected visits.
- Adequate Care – initiated four months with 80 – 109% of expected visits.
- Adequate Plus Care – initiated by four months gestation with 110% or more of expected visits.(Partridge, Balayla, Holcroft, & Abenhaim, 2012)

This study found a curvilinear relationship between PTB and the level of PNC adequacy. The PTB rates for each level was as follows: inadequate care – 13.3%; intermediate care – 3.5%; adequate care – 3.1% and adequate-plus 22.5%. With adequate care as the reference, those with inadequate care had 3.75 times greater odds of PTB (95% CI 3.73 – 3.77), intermediate care had 1.05 times greater odds of PTB (95% CI 1.04 – 1.06) and adequate plus levels of care had 9.10 times greater odds of PTB (95% CI 9.07 – 9.13). The reason why adequate plus level of care had the greatest odds of PTB was because many in this category were very high risk thus necessitating more care that exceeds that of one who is not high risk.(Partridge et al., 2012)

Those who live in rural areas may have issues may have accessing care. In 2010, nearly 18 million reproductive age women lived in rural counties in the U.S. The percentage of rural counties with hospital based obstetric services declined from 55% to 46% from 2004 to 2014. Kozhimanni et al. examined how this decrease in services affected the rate of PTB. The data for the study was received from the nationwide data from the natality detail files from 2004 to 2014. The American Hospital Association Annual survey was used to identify all rural counties availability of hospital based obstetric (OB) services in each year. The items that were observed were provision of OB services, level 1 or higher maternal care, at least one dedicated OB bed and at least ten births per year. This analysis included 4.9 million births to women who lived in 1,086 rural U.S. counties where hospital-based OB services existed in 2004. When compared to the time before the loss of services, the percent point change in PTB one year after the loss in rural areas not adjacent to urban centers was 0.67 (95% CI 0.02 – 1.33, p = 0.04).(Kozhimannil, Hung, Henning-Smith, Casey, & Prasad, 2018)

Perceived access to healthcare services is an important contributor to future health outcomes. Women who perceive that there are barriers in their access of PNC are less likely to get the needed care. Phillips defined barriers based on three classifications: (1) Societal, (2) Maternal and (3) Structural dimensions. Societal and maternal reasons cited for poor motivation included a fear of medical procedures, reluctance in disclosing pregnancy to others, depression and a belief that prenatal care is unnecessary. Structural barriers included long wait times, the location and hours of the clinic, language barrier, attitude of the clinic staff and provider, the cost of services, and a lack of child-friendly facilities.(R. L. Ruiz et al., 2014)

In Ruiz et al., the effect of perceived (lack of) access to care on PTB was examined. This secondary study used the Louisiana Pregnancy Risk Assessment Monitoring System (PRAMS). In order to examine perceived (lack of) access, they used responses to questions like “I couldn’t get an appointment when I wanted one” and “the health provider explained breastfeeding, testing etc.” It was found that for all women, those with a perceived lack of access to care had greater odds of PTB (aOR 1.97, 95% 1.10 – 3.64). When the data was stratified, there was a significant difference in perceived lack of access in Black women (aOR 2.94, 95% 1.05 – 8.29) but not in White women (aOR 1.60, 95% 0.75 – 3.38). (R. L. Ruiz et al., 2014)

There have been several local, state, national and international efforts seeking to increase the access to care to pregnant women with mixed results. One such program is Centering Pregnancy (CenPr). CenPr is a unique service delivery model that has been implemented as a group PNC model across the U.S. and the world. Usually, the group sessions meet in an open space (like school gym etc.) as opposed to a clinical session. There are ten 2-hour sessions that cover three components: (1) Health Assessment, (2) education and (3) support. Tandon et al. examined the impact of CenPr by looking at a sample of Hispanic mothers to be who used the service in Palm Beach County in Florida. The study compared these women to those who used traditional care (clinics) for care. There were 150 subjects in the CenPr cohort and 66 in the traditional care cohort. The study found was that the rate of PTB was 5% in the CenPr group and 13% in the traditional group ($p = 0.04$).(Tandon, Colon, Vega, Murphy, & Alonso, 2012)

“Home visiting” is an umbrella term that defines a vast array of programs and models that provide information on prenatal education, social support, referral services, motherhood classes and breast-feeding support. It also serves to remind families of the importance of routine and prenatal care as well as well-child visits. In 2010, Congress established the Maternal, Infant, and Early Childhood Home Visiting (MIECHV) program with a $1.5 billion investment over 5 years. MIECHV supports pregnant women and families in developing additional parenting skills and accessing the resources they need to raise children who are physically, socially and emotionally healthy and ready to learn. This was, in part, in response to the poor birth and child outcomes currently observed in the U.S.(Williams et al., 2017)

In order to examine and substantiate previous studies showing that home visiting programs any decrease adverse birth outcomes, Williams et al. examined the impact of the Kentucky Health Access Nurturing Development Services (HANDS) program for at-risk first-time parents. This was a quasi-experimental study designed to meet the standards for the department of Health and Human Services Home Visiting Evidence of Effectiveness (HomVEE) review. The sample were women who received at least one HANDS home visit from July 2011 to June 2012. There were 2,253 women included from the HANDS program who were matched to the same number of those who were outside of the program. To get the HANDS group, they used the HANDs administrative data and the controls were received from the birth certificate data for all Kentucky births as provided from the Kentucky office of vital statistics. This study found that those in the HANDS program had lower odds of PTB (OR 0.74, 95% CI 0.61 – 0.88). There was also a significant decrease in PTB based on the number of visits. Those who had less than seven visits had greater odds of PTB than those with seven visits or greater (OR 1.39, 95% CI 1.05 – 1.83). (Williams et al., 2017)

In the late 1980's and early 1990's, Medicaid spending grew at an average annual rate of 20%. The driving force of this increase was the rapid enrollment of low-income pregnant women, infants and children following an expansion of Medicaid eligibility. In an effort to slow down the growth in cost, states initiated managed care systems in their Medicaid programs. The percentage of those on managed care programs grew from less than 10 in 1991 to 71 in 2010.(Yan, 2020)

Disadvantaged pregnant women and their infants can benefit from managed care organizations because they provide incentives like capitations to discourage unnecessary or inappropriate care, improves access and continuity of care and promotes preventative and coordinated care.(Yan, 2020)

Some concerns about managed care are that health professionals can respond to cost containment efforts by limiting provision of high quality and medically necessary care. Many plans exclude safety net providers who had developed significant expertise in serving low income people. The steering of Medicaid childbearing women to managed care networks can lead to unmet demand for preventative care which causes gaps in care.(Yan, 2020)

In order to examine whether Medicaid managed care programs affect the rate of preterm birth, Yan et al. examined the Pennsylvania Health Choices program. This program implemented mandatory HMO enrollment among Medicaid recipients. This program was introduced to 25 counties from 1997 – 2004. Forty-two counties served as controls with 25 of these counties having fee for service program and 17 counties with voluntary capitated programs. The main source of data was from the Pennsylvania natality file from 1994 to 2004. When those Health Choices program counties were compared to the fee for service counties, the increase in PTB was 11.6% (p = 0.001). When compared to the voluntary counties, the rate increased by 1.5% (p = 0.002).(Yan, 2020)

Beginning in the 1980's, federal law required all states to provide Medicaid coverage to low-income pregnant women up to 138% of the federal poverty level. Since this time, many states provide at higher levels with the median being 200% of the federal poverty level in 2019. In 2014, the Affordable Care Act (ACA) provided federal funds for the states to expand their Medicare program to cover adults with incomes that are at or below 138% of the federal poverty level. As of 2019, 37 states and DC have adopted or passed ballot measures to adopt Medicaid expansion. Although the ACA did not change the criteria for pregnant women, Clapp et al. hypothesized that the ACA Medicaid expansion may have affected access to PNC though two mechanisms:

- The "Welcome Mat Effect" – when women who were previously eligible for pregnancy benefits did not enroll until the passage of ACA
- The "Pre-pregnancy Coverage Effect" – with the lower rate of un-insurance in childbearing aged women led to improved pre-pregnancy health, planning and earlier access to PNC. (Clapp, James, Kaimal, Sommers, & Daw, 2019)

Clapp and his colleagues used a quasi-experimental approach to their study using a difference in difference design to look at PTB before and after Medicaid expansion in expansion and non-expansion states (which served as the control group). Their data was retrieved from the county identified birth certificate data from 2009 – 2017. Descriptive analysis showed that expansion states had 9.7% PTB before expansion and 9.4% after expansion while non-expansion states had a rate of 11.1% before expansion and 10.7% after. The difference estimate was not significant (0.2, 95% CI (-) 0.2 – 0.5). This pattern persisted when the data was stratified by education (0.1, 95% CI (-)0.4 – 0.6, p =

0.66) and parity (0.1, 95% CI -0.4 – 0.6, p = 0.57).(Clapp et al., 2019)

McRae et al. conducted a study that examined the difference in outcomes between those who went to general practitioners (GP), Obstetricians (OB) and midwives (MW) in Canada. GP's and OB's are funded by the ministry of health for each antenatal visit. MW's are compensated according to a partial or full trimester of care regardless of the number of visits. MW's provide holistic continuity of care where a MW is available 24 hours a day. The MW model is a relationship based. The antenatal visits last about 30 – 60 minutes. They facilitate counseling, education and emotional support.(McRae et al., 2018)

In their retrospective cohort study, the investigators used data from the British Columbia Perinatal Registry (BCPDR). The study sample had the following characteristics:

- Residents of British Columbia
- Received care from MW, OB and GO
- Singleton Pregnancy
- Low to medium risk
- Delivery from January 2005 to December 2012

The rates of PTB was as follows for MW, GP and OB: 4.4%, 6.3% and 8.7%, respectively. After adjusting for SES and health status, those who went to MW's had lower odds of PTB than those who went to GP's (0.74, 95% CI 0.53 – 0.82) and those who went to OB's (0.53, 95% CI 0.45 – 0.62).(McRae et al., 2018)

2.3.9 Marital/Relationship Status

Literature has provided an overwhelming evidence of the protective relationship between PTB and being married. The lack of progress in consistently reducing the rate of PTB may be attributable to the fact that more than 40% of births in the U.S. and 30% of births in Canada are to unmarried women. In the providence of Quebec, the percentage of birth to legally married women decreased to less than 50% in 1995 and continued to decrease in following years.(Gabriel D. Shapiro et al., 2018)

Some of the mechanisms that may give married women a perinatal advantage is increased access to care, financial security and social support. In a study by Sullivan et al., they stated that those who co-habit tend to have less financial resources than those who are married.(Sullivan, Raley, Hummer, & Schiefelbein, 2012)

Social support that is provided by marriage may contribute to better mental health as it may provide a buffer from other social stressors.(El-Sayed, Tracy, & Galea, 2012) Pregnancy anxiety is a key factor in adverse birth outcomes. A pregnant woman's stress can be exacerbated by a lack of safety guarantees, having tension and insecurity in their relationship or having weak support from a partner.(Merklinger-Gruchala & Kapiszewska, 2019)

Another explanation for the birth outcome advantage of married women is what El-Sayed et al. called "marital selection". Marital selection are certain characteristics of married women that lend themselves to better birth outcomes. Evidence suggests that healthier women are more likely to get and stay married than their less healthier counterparts.(El-Sayed et al., 2012) This is evidenced by the Sullivan et al. who cited a study that showed that unmarried cohabiting couples tend to spend more money on alcohol and tobacco than those who are married.(Sullivan et al., 2012)

The effect that marriage has on PTB may vary based on geographic location. Zeitlin et al. included the birth outcomes in 16 European nations. They found that there is a significantly elevated risk of preterm birth associated with both cohabitation (OR = 1.29, 95% CI 1.08, 1.55) and single motherhood (OR = 1.61, 95% CI 1.26 - 2.07) for women living in countries where fewer than 20% of births occur outside marriage. There is no excess risk associated with marital status when out-of-marriage births are more common. (Zeitlin, Saurel-Cubizolles, & Ancel, 2002)

In Bushnik et al., it was found that women who were single the highest rate of PTB (8%, 95% CI 7.5 – 8.5%), followed by common law mothers (6.7%, 95% CI 6.4–7%) and married couples (6%, 95% CI 5.8 – 6.2%). (Bushnik et al., 2017) Shapiro et al. used the 2006 Canadian Birth-Census Cohort that was linked to birth registration data. The data showed that married women had a 6.4% rate of PTB (95% CI 4.4 – 6.6%), cohabitating women had 7% (95% CI 6.7 – 7.3%) and single women had 8.9% rate of PTB (95% CI 8.4 – 9.4%). This translated to greater odds of PTB for those who cohabitate (OR 1.09, 95% CI 1.03 – 1.15) and those who are single (OR 1.36, 95% CI 1.27 – 1.46).(Gabriel D. Shapiro et al., 2018) Similar results were also found in Chiavanini et al. and Tucker et al. where married couples had lower odds of PTB compared to those who were single (OR 0.71, 95% CI 0.55 – 0.92, p = 0.007) and (OR 0.83, 95% CI 0.74 – 0.93), respectively.(Chiavarini et al., 2012; Tucker et al., 2015).

There is a persistent pattern of birth advantage for married women based on age and race. El-Sayed et al. used data obtained from the Michigan Department of Community Health. This study included 1,529,159 singleton births from 1995 – 2006.

The researchers found that those who were not married had 1.38 increased odds of PTB (95% CI 1.36 0 1.40). This pattern persisted when they examined different age groups. Mothers who were unmarried had increased odds of PTB when compared to their married counterparts across the age groups: those under 20-25 had 1.20 greater odds of PTB than their married age counterparts (95% CI 1.12 – 1.24), 26 – 30 years of age had 1.38 times greater odds (95% CI 1.35 – 1.41), 31 – 35 years of age had 1.61 times greater odds (95% CI 1.57– 1.66),36 –41 years of age and greater had 1.58 times greater odds (95% CI 1.35 – 1.41).(El-Sayed et al., 2012)

A study that examined race and marriage was Hibbs et al. The investigators use the Illinois transgenerational dataset to obtain data. The data was restricted to examined singleton births to Black and White mothers in Cook County. They did a stratified analysis where the data was separated by race and income level. They also compared those who were married (MAR), single with paternal acknowledgement (SPA) and single with no paternal acknowledgement (SNPA). For black women with lifetime high income, there was not a significant difference in the odds of PTB between MAR and SPA women (OR 0.85, 95% CI 0.65 – 1.10) while MAR women had lower odds of PTB than and SNPA women (OR 0.28, 95% CI 0.22 – 0.36). For Black women with lifetime low income, MAR women had lower odds of PTB than SPA women (OR 0.61, 95% CI 0.56 – 0.66) and SNPA women (OR 0.39, 95% CI 0.37 – 0.42).(Hibbs, Rankin, DeSisto, & Collins, 2018)

For White women with lifetime high income, whose who were MAR had lower odds of PTB than SPA women (OR 0.57, 95% CI 0.44 – 0.73) and SNPA women (OR 0.32, 95% CI 0.25 – 0.42). This trend persisted in White women who were low income.

MAR women had lower odds of PTB than SPA women (OR 0.47, 95% CI 0.41 – 0.54) and SNPA women (OR 0.35, 95% CI 0.30 – 0.41).(Hibbs et al., 2018)

Other papers stratified their data by paternal acknowledgement. In a study that examined data from the 2006 birth record from Texas vital statistics, they found that while those who were married had the lowest rates of PTB. Women who had father's name listed on the birth certificate had lower rates of PTB (15.5%, 95% CI 14.7 – 15.6%) than those that did not have a father listed on the birth certificate PTB (16.6%, 95% CI 16.2 – 16.9%).(Sullivan et al., 2012)

Merklinger-Gruchala et al. also examined paternal acknowledgement and the timing of marriage with respect to conception. They collected data on all singleton births at 25 – 42 weeks gestation between October 1995 and December 2009 in Krakow, Poland. The data source was the Central Statistical Office in Poland. Looking at 87,916 subjects, they found that when compared to those who were married before conception, those who were single and did not have the father listed (UMFA) in the birth certificate had 2.1 times greater risk of PTB (95% CI 1.86 – 2.30). Those who were not married but had fathers listed (UMFP) had 1.3 times greater risk of PTB (95% CI 1.26 – 1.50). This persisted when they stratified the analysis by parity. For those who were primiparous, those who were UMFP had 1.2 times greater risk of PTB (95% CI 1.05 – 1.36) while UMPA had 1.83 times greater risk (95% CI 1.57 – 2.13). For those records of those who were multiparous, UMFA's had 2.2 times greater risk of PTB (95% CI 1.81 – 2.58) and UMFP's had 1.5 times greater risk of PTB (95% CI 1.33 – 1.72). In the examination of the timing of conception with respect to marriage, it was found that there was not a significant difference between those who conceived before and after marriage for the full sample (RR 0.96, 95% CI 0.88 – 1.04) and those who were primiparous (RR 1, 95% CI 0.90 – 1.11). Multiparous women had greater odds of PTB if child was conceived before marriage in comparison to after marriage (RR 1.29, 95% CI 1.03 – 1.60).(Merklinger-Gruchala & Kapiszewska, 2019)

There are several social determinants that are studied in this work. We are exploring race, immigrant status, social class, education, deprivation, access to healthcare and marital status. The factors that are hypothesized to increase the risk of PTB are being on the Black race, lower SES (as indicated by lower education and higher levels of deprivation), and having a marital status of single. Factors that are hypothesized to be protective against PTB is being a foreign born citizen, higher SES, having access to healthcare and having a marital status of married. This will be further examined in Chapters 3 and 5 in this work. Chapter 5 will focus on race and SES. This issue of access to care will be addressed further in Chapter 6 which is a cost analysis of different birthing locations with a motivation for government help to increase payments to alternatives to hospital births.

2.4 Preterm Birth and Healthy Behaviors

2.4.1 Physical Activity

Physical activity is defined as any skeletal muscle body movement that results in energy expenditure.(Sharif et al., 2018) Exercise is defined as physical activity that consists of planned, structured and repetitive bodily movements and is essential element of healthy lifestyle.(L. Huang et al., 2019)

Pregnant women were advised against exercise because of presumed risks of pregnancy loss and PTB due to possible reduced placental circulation. There have been two opposite theories about the relationship between PTB and physical exercise. One theory is that exercise may lead to the release of catecholamines like norepinephrine that may stimulate myometrial activity that precipitates PTB.(Di Mascio, Magro-Malosso, Saccone, Marhefka, & Berghella, 2016) The second theory is that exercise may reduce oxidative stress and improve placental vascularization. This leads to the intermittent reduction of uterine blood flow that keeps membranes intact and prevents PTB. (L. Huang et al., 2019)

It used to be standard to recommend activity restriction to women with high-risk pregnancies in an effort to reduce the risk of PTB despite there being no evidence of its efficacy. On the contrary, several studies show that bedrest can possibly increase odds of PTB. In a 14-study meta-analysis by Matenchuk et al., maternal and fetal outcomes were similar between women with and without activity restriction. When data was stratified, the authors found that bed-rest was associated with *worse* obstetric outcomes like an earlier gestational age at delivery and a doubling in the number of 'very premature' births (defined variously as before 32–35 weeks gestation). Bed rest has also been complicit in the increased odds of low birth weight for the infant and venous thromboembolism, increase anxiety, depression and sleep disturbances for the mother. (Walsh, 2020)

Physical activity is so important to a healthy birth, that several obstetrics and gynecology societies have created policy to address the need. The American College of Obstetrics and Gynecology (ACOG) had recently updated its guidelines on physical activity during pregnancy concluding, "Physical activity and exercise in pregnancy are associated with minimal risks and have shown to benefit most women. The Royal Australian and New Zealand College of Obstetrics and Gynecology (RANZCOG) has stated "Women without contraindications should participate in regular exercise during pregnancy.(Walsh, 2020)

Literature has confirmed the effectiveness of exercise in healthy pregnancies. In a case control study by Huang et al., the authors got their sample from two hospitals in in Guangdang, China. Their study subjects were asked to complete a structured questionnaire during a prenatal visit. There were 2,155 mother –child pairs where 1,306 had term births and 849 had PTB's. Frequency of exercise was categorized as follows:

- Low Frequency – 1 -3 times per week
- Medium Frequency – 4 -6 times per week
- High Frequency – 7 times per week or greater

They also looked at exercise durations that were classified as follows:

- Short – 1 – 29 minutes
- Medium – 20 – 59 minutes
- Long – 60 minutes greater

When compared to having no exercise, those with low, medium and high frequency had lower odds of PTB: aOR 0.69, 95% CI 0.52 – 0.91), aOR 0.57, 95% CI 0.43 – 0.77) and aOR 0.58, 95% CI 0.45 – 0.75), respectively. When they looked at short, medium and long durations, they also found that there were decreased odds of PTB: aOR 0.75, 95% CI 0.57 – 0.99, aOR 0.57, 95% CI 0.44 – 0.74 and aOR 0.53, 95% CI 0.40 – 0.71, respectively. When the frequency and duration were composited, it was found that those with low frequency and short duration did not have significantly different PTB rate than those who did not exercise (aOR 1, 95% CI 0.72 – 1.39). Those with medium frequency and duration and high frequency and long duration were shown to have a protective relationship against PTB: (aOR 0.58, 95% CI 0.41– 0.82) and (aOR 0.56, 95% CI 0.40 – 0.79), respectively.(L. Huang et al., 2019)

In a cohort study by Giannubilo et al., the researchers observed pregnant women at 12 weeks of gestation recruited between 2014 and 2016 and prospectively followed until delivery. This study found that those who exercised had lower risk of SPTB (aRR 0.21, 95% CI 0.07 – 0.60). 67.9% of those who had term birth reported exercising while 31.6% of those who had SPTB reported exercising (p = 0.004).(Giannubilo et al., 2020)

There have been several studies that did not find a relationship with PTB. In a meta-analysis by Di Mascio et al., nine studies including 2,059 women were used. This study found those who exercised did not have different rates than those who did not exercise 4.4% vs 4.5% (aOR 1.01, 0.68 – 150)(Di Mascio et al., 2016) Another meta-analysis that was completed by Du et al. used studies that observed several exercises like biking, walking 11,000 steps, strength training and aerobic and muscle exertion. This study also did not find any difference in the risk of PTB (RR 1.24, 95% CI 0.63 – 2.42).(Du, Ouyang, Nie, Huang, & Redding, 2019) Another study that included 10,132 African American women collected from the PRAMs data found that diet and exercise reduced the rate of PTB by 27% (aOR 0.73, 95% CI 0.55 – 0.96, p = 0.029). When exercise was analyzed on its own, there was not a significant difference.(Dow & Coleman-Cowger)

2.4.2 Use of Tobacco Products (Smoking)

Smoking is one of the most important modifiable risk factors of pregnancy complications.(Moore, Blatt, Chen, Van Hook, & DeFranco, 2016) Nicotine is a highly lipid soluble that easily diffuses across cell membranes. Its traces have been found in amniotic fluid, fetal hair and placental tissues. A previous in-vitro study using chorionic villi taken from pregnant women who smoked found that the presence of nicotine diminished the mitotic potential of cytotrophoblasts which are cells that are responsible for maintaining implantation. This disruption in cell expression may be responsible for compromised placental development associated with PTB.(Hoyt et al., 2018)

In 2011, the prevalence of smoking in the U.S. was 11.5%. There was a study completed that was set in Ohio which had 23% smoking prevalence. Moore et al. used Ohio birth records to perform a retrospective cohort trial with the purpose of examining the effect of smoking on PTB. In this sample of 913,757, they found smoking had different effects based on the timing of quitting. When compared to those who never smoked, those who only smoked preconception had reduced odds of PTB (aOR 0.91, 95% CI 0.88 – 0.94). Quitting in the first trimester did not have a significant effect on PTB (aOR 1.02, 95% CI 0.98 – 1.07). Quitting in the second trimester and smoking through full pregnancy created increased odds of PTB (aOR 1.7, 95% CI 1.6 – 1.8) and (aOR 1.21, 95% CI 1.19 – 1.24), respectively. The results indicating that those who only smoked preconception had better odds of term birth than those who never smoked is counterintuitive. Possible reasons for these results are that those in the "never smoked" cohort also had higher rates of single mothers and Medicaid recipients which are noted factors in PTB. Similar patterns were found when the investigators stratified data by gestational age and whether the birth was spontaneous or medically indicated.(Moore et al., 2016)

Smith et al. also examined the timing of smoking during pregnancy. The data was collected from a prospective population in the United Kingdom from September 2009 through December 2010. This study had 922 late PTB and 968 term births. They found that compared to those who never smoked, there was not a significant difference in PTB for those who quit before pregnancy (OR 0.82, 95% CI 0.65 – 1.03) and first trimester (OR 1.09, 95% CI 0.76 – 1.56). Those who did not stop smoking had 1.46 times greater odds of PTB (95% CI 1.16 – 1.83).(Smith et al., 2015)

Ratnasiri et al. was a retrospective study which evaluated 435,280 PTBs out of 5,137,376 live births stored in the California Birth Certificate Master Files from 2007 – 2016. This study found that those who smoked had increased odds of PTB (aOR 1.57, 95% CI 1.53 – 1.62).(Ratnasiri et al., 2018) Carter et al. found that smokers had 1.5 times greater odds of PTB (95% CI 1.3 – 1.73). This finding was driven by the cohort of White women who were the only group adversely affected by smoking (OR 1.64, 95% CI 1.38 – 1.94).(Carter et al., 2011) Tucker also found that smoking increased the rates of PTB (OR 1.37, 95% 1.21 – 1.57).(Tucker et al., 2015)McCall et al. found that there were 1.74 times greater odds of very PTB among mothers who smoked (95% 1.36 – 2.21)(McCall et al., 2020) Baron et al. found that those who smoked greater than 10 cigarettes per day had greater odds of PTB (OR 2.44, 95% CI 1.11 – 5.37). The significant effect was eliminated when placed in a model with demographic, social and psychological factors.(Baron et al., 2017)

There have been studies that also discussed the effect of second-hand exposure to smoking. One such study was Hoyt et al., which used data from the National Birth Defects Preventative Study. In this multi-site population-based case control study, the sample consisted of those who were administered surveys assessing their smoking exposures from October 1997 to December 2011. The paper reported that those who were exposed to second-hand smoke at home and school or work had 1.99 times greater odds of PTB (95% CI 1.13 – 3.50). There were no significant relationships for those who were exposed to second-hand smoke at work or school (OR 1.06, 95% CI 0.79 – 1.42) and home only (OR 1.1, 95% CI 0.8 – 1.52).(Hoyt et al., 2018)

2.4.3 Alcohol Usage

With the use data from the National Survey on Drug Use and Health (NSDUH), the CDC estimated that the prevalence of alcohol use during pregnancy of women aged 12 – 44. What they found was that 64.7% of pregnant women drank alcohol within 12 months before the survey and 19.6% of pregnant women reported drinking within the last 30 days while in their first trimester. The percentage of women who reported taking drugs was 38.2% with the most prevalent substances being marijuana and nicotine. (England et al., 2020)

Given the prevalence of alcohol consumption in women in general and pregnant women specifically, there is literature to assess whether this has an effect on birth outcomes. The deleterious effects that alcohol has on a developing baby is well documented in literature and guidelines of medical societies. Literature has mixed results concerning the effect of alcohol on birth. Umer et al. completed a study set in West Virginia. West Virginal is a primarily rural Appalachian state with high rates of chronic diseases, substance abuse and smoking during pregnancy. Based on a PRAMS 2015 survey, 2.7% of women from West Virginia reported drinking in the last 3 months of pregnancy. Due to the self-report nature of the survey, this figure might be underestimated by 30%. The authors of this study had 1,830 newborn residual dried bloodspots in the West Virginia newborn screening repository. They tested these bloodspots for prosphatidylethanol (PETH). PETH is a metabolite that is formed from alcohol or ethanol consumption that manifests as a phospholipid that is situated in the membranes of red blood cells. This study found was that those who had PETH in their system had increased odds of PTB (OR 1.88, 95% CI 1.23 – 2.89).(Umer et al., 2020) This finding is similar to the results of Tucker et al. which also found increased odds of PTB for those who consumed alcohol within the last month (aOR 1.24, 95% CI 1.06 – 1.44).(Tucker et al., 2015)

Strandberg-Larsen used several European study cohorts representing Denmark, Netherlands, Norway, Spain, France, Italy and Greece. These databases had data on 193,747 live births from 2005 to 2011. What they found was that when compared to abstainers, those who drank less than one drink a week had decreased hazard of PTB (HR 0.83, 95% CI 0.72 – 0.94). No other comparisons showed a dose dependent relationship to PTB. When compared to having 1 -2 drinks a week, the hazards were HR 0.82, 95% CI 0.57 – 1.17; when compared to 2 – 3 drinks the HR 1.07, 95% CI 0.63 – 1.82; when compared to having 3 or more drinks the HR 0.59, 95% CI 0.27 – 1.31. (Strandberg-Larsen et al., 2017) These findings were similar to Baron et al. who also did not find a significant relationship between alcohol use and PTB (OR 0.98, 95% CI 0.57 – 1.68).(Baron et al., 2017)

Smith et al. examined the effect of alcohol consumption based on timing of pregnancy. Those who gave up alcohol before pregnancy had a marginally decreased risk of PTB (RR 0.80, 95% CI 0.64 – 1.00). Those who gave up alcohol during the first trimester of pregnancy also had decreased odds of PTB (RR 0.75, 95% CI 0.59 – 0.95). There was no relationship for those who drank throughout their pregnancy (RR 0.85, 95% CI 0.66 – 1.09) (Smith et al., 2015)

Lee et al. observed the effect of alcohol abuse stratified by race. They found was that overall, those who abused alcohol had 2.09 times greater odds of PTB than those who did not (95% CI 1.71 – 2.55). This trend persisted for White women (aOR 2.11, 95% CI 1.58 – 2.80) and Black women (aOR 2.03, 95% CI 1.47 – 2.81) but not for Hispanic women (aOR 1.44, 95% CI 0.34 – 6.29).(Lee et al., 2020)

2.4.4 Cannabis Use

There has been an increase in the usage of cannabis in the U.S. and abroad. In the U.S., marijuana is the most commonly used illicit substance during pregnancy with up to 4.6% pregnant women reporting usage within the last 30 days of being surveyed by the Substance Abuse and Mental Health Services Administration in 2013. According to hospital admission data from 1998 – 2003, the number of reproductive age women who were screened positive for cannabis increased by 35% and the rates of pregnant women admitted to substance abuse treatment programs increased by 50% from 2002 – 2012.(Mark, Desai, & Terplan, 2016) In June 2018, the Canadian government passed the Cannabis Act that provides a legal framework for the possession, distribution, sale and production of cannabis. With the help of this law, rates of cannabis has increased for women as well as the Canadian population at large.(Luke, Hutcheon, & Kendall, 2019)

Cannabinoids readily cross through human placenta with the greatest concentration transfer during the first trimester. This is particularly concerning when considering many pregnancies are unplanned and unknown for much of the first trimester. This has led to research on the effect of marijuana usage on birth outcomes. A study by Luke et al. used the population of births in British Columbia. British Columbia Perinatal Data Registry provided data collected from April 2008 to March 2016. There were 243,140 women in the study with 5,801 being cannabis users. The rate of PTB for users was 7.5% and 6.5% for non-users (OR 1.64, 95% CI 1.50 – 1.79). When adjusted for confounders relationship persisted (OR 1.47, 95% CI 1.33 – 1.61). (Luke et al., 2019)

Another study by Mark et al. included 396 women recruited from a single urban university affiliated clinic found that the rate of PTB rates for cannabis users was 17.7% while non-users had a 12% rate (p=0.325).(Mark et al., 2016) Chabarria et al. used Peribank, a perinatal database curated by Baylor College of Medicine. The cohort included 12, 069 in the study and found that the use of marijuana by itself was not a factor of PTB (aOR 0.84, 95% CI 0.35 – 3.87, p = 0.68). The odds increased when marijuana use was combined with nicotine use (aOR 2.56, 95% CI 1 .33 – 4.95, p < 0.001).(Chabarria et al., 2016)

2.4.5 Opioid and Harder Drug Use

Rates of hospitalization and death due to opioid overdose have increased significantly during the last decade in the U.S. and Canada. Concurrent rates of opioid use and misuse in pregnancy have been increasing with corresponding increases in maternal and neonatal morbidity. In Ontario, Canada, there has been a 16-fold increase in the number of infants born to women with opioid dependence from 46 in 2002 to 800 in 2014. The incidence of neonatal abstinence syndrome (NAS), which occurs in infants exposed o opioids in utero, has increased from 0.28 per 1,000 in 1992 to 4.29 per 1000 livebirths in 2011.(Corsi, Hsu, Fell, Wen, & Walker, 2020)

There have been several studies that examined the role of opioid abuse and PTB. Corsi et al. used the Better Outcomes Registry and Network (BORN), a comprehensive province wide perinatal registry of Ontario. It holds data for 40% of all births in Canada. In their sample of 711, 911, they found opioid use increased the risk of PTB at all gestational age groups. The risk of overall PTB increased (RR2.33, 95% CI 2.20 – 2.46). The risk of PTB at 34 – 36, 32-33, 28 – 31 and less than 28 weeks gestations also increased: (RR 2.28, 95% CI 2.13 – 2.43), (RR 3.03, 95% CI 2.56 – 3.60), (RR 3.07, 95% CI 2.51 – 3.75) and (RR 2.39, 95% CI 1.80 – 3.18), respectively. (Corsi et al., 2020) Similar findings was found in Tucker et al. where those who abuse substances have 1.26 timed greater odds of PTB (95% CI 1 – 1.58).(Tucker et al., 2015)

Lee et al. assessed at the effect of substance abuse stratified by race. Overall, those who abused drugs had 2.21 times greater odds of PTB than those who did not (95% CI 2.02 – 2.42). This trend persisted for White women (aOR 2.12, 95% CI 1.91 – 2.34) and Black women (aOR 2.56, 95% CI 1.92 – 3.4). This did not persist for Hispanic women (aOR 1.42, 95% CI 0.42 – 4.78).(Lee et al., 2020)

In Baer et al., the data was received from all live births in California from 2007 – 2012 provided by the California Office of Statewide Health Planning and Development. There were 2,890,555 women included in the study. This study found an increased risk of SPTB at 32 weeks for the following substances:

- Opioids increased the risk by 2.6 times (95% CI 2.0 – 3.4)
- Cocaine increased the risk by 2.2 times (95% CI 1.6 – 3.0)

- Amphetamines increased the risk by 1.8 times (95% CI 1.6 – 2.2)
- Polysubstance cocaine increased the risk by 2.0 times (95% CI 1.7 – 2.4)

There were also increased risks of SPTB at 32 – 36 weeks for those who used the following substances:

- Opioids (RR 2, 95% CI 1.8 – 2.3)
- Cocaine (RR 2.3, 95% CI 1.9 – 2.6)
- Amphetamines (RR 2, 95% CI 1.9 – 2.2)
- Polysubstance cocaine (RR 1.9, 95% CI 1.7 – 2.0).(Baer et al., 2019b)

A study that did not find a significant relationship with drugs was Smith et al. (RR 1.61, 95% CI 0.83 – 3.13, p=0.156).(Smith et al., 2015)

2.4.6 Sleep

In 2004, the U.S. Surgeon General observed that sleep disorders, sleep deprivation, and sleepiness affect as many as 70 million Americans and result in $16 billion in annual health-care expenses and $50 billion in lost productivity. Chronic sleep deprivation has detrimental effects on fat and glucose metabolism, inflammatory processes, learning and cognitive functioning, social relationships, job performance, mental health, and overall quality of life. At the cellular level, even a single brief episode of acute sleep restriction (4–8 h) is associated with robust declines in immune cell activity. Prior research has demonstrated that sleep deprivation alters the immune response and significantly increases circulating levels of inflammatory markers such as interleukin-1 (IL-1), IL-2, IL-6, tumor necrosis factor (TNF) α, and C-reactive protein which is also complicit in PTB.(Chang, Pien, Duntley, & Macones, 2010)

There is a general decline in the average sleep time in the general population. American women bear most of the burden of sleep deprivation despite evidence that they have better quality of sleep than men. There was one study that reported that 24% of women in their study were sleep deprived compared to 16% of the male sample. This can be a results of women's role at work and public life that makes sleep less of a priority.(Chang et al., 2010)

In a recent poll conducted by the National Sleep Foundation, over 79% of women reported that their sleep was different in pregnancy than at any other point of their life. Empirical studies have found that 25% of pregnant women reported significant sleep disturbance in the first trimester. This figure increased to 75% of pregnant women in their third trimester.(Okun, Schetter, & Glynn, 2011)

Given the importance of sleep in pregnant women, there has been some research that provides evidence of the role of sleep in birth outcomes. One study was by Okun et al. In this study of 166 women, study subjects were administered the Pittsburgh Sleep Quality Index (PSQI). This tool is a 19 item questionnaire used to measure habitual sleep quality over the previous month before administration. The PSQI examined the following seven subscales:

- Habitual duration of sleep
- Nocturnal sleep disturbances
- Sleep latency
- Sleep quality
- Daytime dysfunction
- Sleep medication use

- Sleep efficiency.

High scores indicated poor sleep. This study found that the mothers who experienced PTB had higher PSQI scores than those who had term births in the first and third trimester. In the first trimester, the mean score was 7.79+/- 4.4 for PTB mothers and 4.97 +/- 2.68 for mothers of term babies ($p = 0.05$). In the third trimester, the mean score was 7.79+/- 4.1 for PTB mothers and 5.26 +/- 2.73 for mothers of term babies ($p = 0.03$). These results also found that the relationship between sleep and PTB could also be affected by stress and anxiety which had significant correlations to PSQI.(Okun et al., 2011)

Another study that used the PSQI was Tomfohr –Madsen et al. They included 290 pregnant women from a sub study of the Alberta Pregnancy Outcomes and Nutrition (APRON) cohort study. The investigators did not find any relationship between the PSQI and PTB (beta = 0.03, $p = 0.82$) or gestational length (beta = 0.04, $p = 0.30$).(Tomfohr-Madsen et al., 2019)

Wang et al. conducted a meta-analysis that found those with the shortest duration of sleep had increased risk of PTB (aRR 1.23, 95% CI 1.01 – 1.50). It also found a greater risk of PTB for those who had poor sleep quality (aRR 1.54, 95% CI 1.18 – 2).(Wang & Jin, 2020) Loy et al. conducted a prospective mother – offspring cohort study called Growing Up in Singapore towards Health Outcomes (GUSTO). The sample included women who attended antenatal care in their first trimester at KK Women's and Children's Hospital and National University Hospital from June 2009 to September 2010. The investigators did not find any significant relationship between sufficient sleep and PTB. Those with sufficient sleep (those with greater than 6 hours of sleep) had a PTB rate of 6.4% while those without sufficient sleep had a 9.5% rate (p = 0.253). When gestational age was examined, they found that those with insufficient sleep had reduced gestational age (b = -0.33, 95% CI -0.66 – (-) 0.01). When bedtime and gestational diabetes were added to the model, the relationship between sleep duration and gestational age became insignificant.(Loy et al., 2020)

There have been negative studies that examined sleep quality and PTB. One such study was Nakahara et al. This study used the data from the Japan Environment and Children's Study which is an ongoing large – scale cohort study. This study used the M-T1 and M-T2 sleep questionnaires where study subjects were asked about their sleep duration, bedtime and sleep quality. Sleep duration did not show a significant relationship with PTB when compared to 7-8 hours. Those with less than 6 hours of sleep had 1.11 times greater odds of PTB (95% CI 0.93 – 1.28) while those with greater than 10 hours of sleep had 1.01 times greater odds of PTB (95% CI 0.87 – 1.18). Bed times also had a random relationship with PTB. Compared to those whose bed time was between 10p and 12a, study subjects with bedtimes from midnight to 3a nor any other time had similar odds of PTB(aOR 1, 95% CI 0.94 – 1.08) and (aOR 0.91, 95% CI 0.75 – 1.11), respectively. Sleep quality was measured by the depth of sleep. When compared to normal depth of sleep, those with very light sleep had increased odds of PTB (aOR 1.19, 95% CI 1.04 – 1.35). None of the other depths was significantly related to PTB. (Nakahara et al., 2020)

There have been studies that observed the effect that sleep disorders on PTB. In a 65-study meta-analysis by Yang et al., they found that having a sleep disorder created 1.95 times greater odds of PTB (95% CI 1.55 – 2.45). Sleep disorders examined were sleep apnea, snoring, extreme sleep duration and poor sleep quality.(Z. Yang, Zhu, Wang, Zhang, & Zeng, 2020) Felder et al. conducted an observational study with a sample from all live births in California from January 2007 through December 2012. The data were from files linked to a hospital discharge database maintained by the California office of Statewide Health Planning and Development. There were 2,172 cases of sleep disorders that were propensity – matched to the control group. The found increased odds of preterm birth at less than 34 weeks gestation for the following sleep disorders:

- Any sleep disorder (OR 1.9, 95% CI 1.4 – 2.6, $p < 0.001$)
- Insomnia (OR 1.7, 95% CI 1.1 – 2.6, $p = 0.026$)
- Sleep apnea disorder (OR 1.9, 95% CI 1.4 – 2.6, $p < 0.001$).

This was also found when looking at all PTB at less than 37 weeks gestation:

- Any sleep disorder (OR 1.4, 95% CI 1.2 – 1.7, $p < 0.001$)
- Insomnia (OR 1.3, 95% CI 1.0 – 1.7, $p = 0.023$)
- Sleep apnea disorder (OR 1.5, 95% CI 1.2 – 1.8, $p < 0.001$). (Felder, Baer, Rand, Jelliffe-Pawlowski, & Prather, 2017)

2.4.7 Diet

Diet is important in health in general and particularly important in maternal and fetal health. Adverse dietary habits can increase the risk of adverse pregnancy issues like gestational diabetes, gestational hypertension and preeclampsia. It has been found that high consumption of saturated fatty acids, total carbohydrates, soft drinks along with low consumption of polyunsaturated fatty acids are complicit in the development of gestational diabetes which is a risk factor in PTB. It has been noted that calcium supplementation reduces the risk of preeclampsia and preterm birth.(Chen et al., 2016)

There is a body of literature that has examined different types of foods, food combinations and their effect on birth outcomes. Smith et al. compared those who consumed five fruit and vegetables per day at least once a week against those who did not. They also looked at those who adhered to the Mediterranean diet. They found that those who did not consume the prescribed amount of fruit and vegetables had greater odds of PTB (OR 1.43, 95% CI 1.15 – 1.78). Those who did not adhere to the Mediterranean diet al.so had greater odds of PTB (OR 1.96, 95% CI 1.15 – 3.32).(Smith et al., 2015) Saunders et al. also examined the Mediterranean diet. This study had a sample of 728 women from the Guadeloupian prospective mother-child cohort study TIMOUN who were recruited from November 2004 to December 2007. The investigators scored adherence to the diet from a scale of zero (no compliance) to nine (maximum compliance). This study found that there was not a significant difference between the adherence score between women with PTB babies 4.8+/-1.5 and mothers of term babies 5+/-1.6 ($p = 0.27$).(Saunders et al., 2014) Baron et al. did not find any relationship between the consumption of vegetables and fruits and SPTB (OR 1.51, 95% CI 0.94 – 2.41) and (OR 1.18, 95% CI 0.45 – 3.10).(Baron et al., 2017)

Rasmussen et al. used the Danish National Birth Cohort (DNBC) to provide the data on 60,000 mother – child pairs as a part of the prospective longitudinal cohort. The study found that the western diet, which was characterized by food like potatoes, french fries, white bread, meat, butter and dressing, increased the odds of PTB (OR 1.3, 95% CI 1.13 – 1.49). This effect was more pronounced in MPTB (OR 1.66, 95% CI 1.30 – 2.11) than in SPTB (OR 1.18, 95% CI 0.99 – 1.39).(Rasmussen, Maslova, Halldorsson, & Olsen, 2014) Chia et al. used a sample of 923 women aged 18 – 50 in their first trimester of pregnancy. They were recruited from the KK Women's and Children's Hospital between June 2009 to Sept 2010 as a part of the GUSTO trial. These women used 24-hour recall and three day food diaries to record their consumption. They used principal components analysis to create three food groups out of the 68 food items. The three food groups were as follows: Pasta, cheese and white rice (PCA), vegetable, fruit and white rice (VFR) and seafood and noodle (SFN). VFR was protective against overall PTB (aOR 0.67, 0.50 – 0.91) and SPTB (aOR 0.55, 95% CI 0.37 – 0.82). This results was not seen for MPTB (aOR 1.18, 95% CI 0.69 – 2.03). The other eating patterns were not associated with overall PTB: SFN (aOR 1.27, 95% CI 0.93 – 1.74) and PCP (aOR 0.79, 95% CI 0.55 – 1.12)(Chia et al., 2016)

Some studies used the Food Frequency Questionnaire (FFQ). FFQ's are a type of dietary assessment instrument that attempts to capture an individual's usual food consumption by querying the frequency at which the respondent consumed food items based on a predefined food list. Given that food lists are culturally specific, FFQs need to be adapted and validated for use in different contexts.(Thompson & Subar, 2017) Teimouri used a 168-item FFQ to assess the diets of 140 women who attended Social Security and Nohome Dey Hospitals from October 2013 to October 2014. Participants were given the FFQ in order to record their food consumption over the previous year. Based on their answers, they were placed in a favorable diet and not favorable diet group. To have a favorable diet, a participant would have to consume 3 – 4 units of fruit, 7 -10 units of bread and cereals, 4- 5 units of vegetables, 3 – 4 servings of meats or beans and 3 -4 unit of dairy daily. Failure to meet these standards are considered unfavorable. This study found 35.7% PTB mothers and 54.3% term birth mothers had a favorable diet (p=0.023). It was also found 37.1% of the women who had PTB and 57.1% of women with term births met the vegetable requirements (p=0.001). The recommended consumption of dairy was met in 57.1% percent of mothers with PTB babies and 71.7% of mothers of term babies (p=0.05)(Teimouri, Dolatian, Shishehgar, Ajami, & Majd, 2015)

Another study that used an FFS was Grieger et al. This retrospective cross-sectional study was part of a bigger prospective cohort study from the Lyell McEwin Hospital in Australia. There were 309 women who completed the Council of Victoria's Dietary Questionnaire of Epidemiological Studies FFQ were included. This questionnaire was administered to assess their dietary intake in the previous year. Each standard deviation increase in the high protein/fruit pattern was associated with decreased odds of PTB (aOR 0.31, 95% CI 0.13 – 0.72, p=0.007). Increases in the fat/sugar/takeaway food (processed snack foods) was associated with increased odds of PTB (aOR 1.54, 95% CI 1.1 – 2.15, p =0.011) and decreased gestational age (beta -2.7, 95% CI -4.3 – (-) 1.1, p=0.001).(Grieger, Grzeskowiak, & Clifton, 2014)

Given that individual behaviors do not work in isolation, it is hypothesized that engagement in healthy behaviors is protective against PTB. These healthy behaviors included abstinence from drugs, alcohol and nicotine in addition to sufficient sleep, healthy diet and exercise. This will be addressed in Chapter 3.

CHAPTER 3

INTERACTION OF SOCIAL DETERMINANTS AND HEALTH BEHAVIORS: EFFECT ON PRETERM BIRTH

3.1 Abstract

3.1.1 Introduction

Health behaviors, also called health-related behaviors, are actions taken by individuals that affect health or mortality.(Short & Mollborn, 2015) The elements of health behavior that will be explored in this work are smoking, excessive alcohol/drug consumption, sufficient sleep, consumption of fruit and vegetables, and engagement in physical activity.

This work seeks to: (1) Present previous and current evidence that healthy behaviors have a protective effect on the rate of PTB, (2) Report barriers to pursuing healthy behaviors in lower socio-economic status populations (3) Review previous policies that seek to increase the prevalence of health behaviors along with novel ideas that will seek to fill in gaps that are not addressed. Our hypothesis is that engagement in healthy behaviors is protective against PTB. Given this hypothesis, policies whose goal is to reduce PTB through the promotion of protective behaviors will be discussed.

3.1.2 Methods

This study uses U.S. county data. The data was primarily compiled from the county health rankings website (https://www.countyhealthrankings.org). Additional sources of data came from Peristats from the March of Dimes, America's health rankings and other sources. Data were analyzed using principle components analysis (PCA) and ordinary

least squares (OLS) regression. There were two models used with dependent variables of PTB and health behavior. LASSO regression was also used in analysis.

3.1.3 Results

The results of the PTB model showed that health behaviors had a significant and inverse relationship with PTB ($\beta = -0.529$, $p < 0.001$). The results of the behavior model showed that household economics was the most significant factor in determining community engagement in healthy behaviors ($\beta=0.452$, $p < 0.001$).

3.1.4 Conclusion

This study reaffirms the importance of healthy behaviors in the prevention of PTB. This work adds to the literature because it does not look at behaviors in a vacuum, but within a social context by examining the barriers of engagement due to poverty and low economic status. This study examines existing programs and seeks to present ideas that are missing in existing programs with the hopes of removing the barriers that those in poverty face in pursuing healthier lifestyle.

3.2 Background/Introduction

The WHO defines preterm birth as any birth before 37 completed weeks of gestation, or fewer than 259 days since the first day of the woman's last menstrual period. Causes of preterm birth are complex and the pathophysiology that triggers preterm birth is largely unknown. However, contributing maternal, fetal and placental predisposing factors have been identified.(Quinn et al., 2016) Risk factors complicit are chronic diseases, mental illness and social determinants like race, social status, access to healthcare and area of residence.

Discovering unexplored factors in PTB is very important because of the financial and societal costs. Complications of preterm birth were the leading cause of death in children younger than 5 years of age globally in 2016. It is estimated that in the U.S., PTB costs the healthcare system an estimated $26 billion dollars. This figure only includes hospital costs and does not take account of the side effects that may present during the survivors' life cycle like therapy for disabilities. It is estimated that 22% of PTB survivors may develop a severe disability that is secondary to early birth, 24% may develop a moderate disability or have special needs while 34% may develop a mild disability.(Dolezel, 2019)

Health behaviors, also called health-related behaviors, are actions taken by individuals that affect health or mortality.(Short & Mollborn, 2015)   The elements of heathy behavior that will be explored in this work are smoking, excessive alcohol/drug consumption, sufficient sleep, consumption of fruit and vegetables and other elements of diet, and engagement in physical activity.

This work seeks to: (1) Present previous and current evidence that healthy behaviors have a protective effect on the rate of PTB, (2) Report barriers to pursuing healthy behaviors in lower socio-economic status populations (3) Review previous policies that seek to increase the prevalence of health behaviors along with novel ideas that will seek to fill in gaps that are not addressed. Our hypothesis for this study engagement in healthy behaviors is protective against PTB. Given this hypothesis, policies whose goal is to reduce PTB through the promotion of protective behaviors will be discussed.

3.2.1 Review of Literature on Healthy Behaviors

Literature has found that smoking can increase the odds of preterm birth. According to Rajia et al., it was found that those exposed to cigarette smoke had greater odds of PTB (OR 4.03, 95% CI 1.2 – 13.5).(Rajia, Massi, Ahmad, Arifuddin, & Miskad, 2020) There have also been studies that found a dose dependent relationship between smoking and PTB.

The effect of alcohol on the rate of PTB is inconclusive. In Umer et al., it was found was that those who had PETH, a metabolite that is formed from alcohol or ethanol consumption increased odds of PTB (OR 1.88, 95% CI 1.23 – 2.89).(Umer et al., 2020) Another significant result was found in Tucker et al. which also found increased odds of PTB for those who consumed alcohol within the last month (aOR 1.24, 95% CI 1.06 – 1.44).(Tucker et al., 2015) Contrary results were found in Baron et al. who found that alcohol consumption did not increase the odds of PTB (aOR 0.92, 95% CI 0.53 – 1.60).(Baron et al., 2017)

Inconclusive relationships were found when examining using cannabis. Luke et al. found that those who used cannabis had an aOR 1.47 (95% CI 1.33 – 1.61)(Luke et al., 2019) while Khandbanda et al. found that those who tested positive for urine tetrahydrocannabinol (THC) did not have significantly higher risk of PTB (aRR 1.06, 95% CI 0.64 – 1.77).(Kharbanda et al., 2020) There were stronger results found in those who used harder drugs like opioids.(Baer et al., 2019b; Corsi et al., 2020; Lee et al., 2020; Tucker et al., 2015) Gargari et al. found that those who were substance abusers had 39.5% PTB while non-users had a 22.3% rate of PTB (RR 1.61, 95% CI 1.35 – 1.92, p <0.001). (Saleh Gargari et al., 2012)

The evidence of a relationship between physical activity and PTB is mixed. There are studies that indicate that engaging in exercise that is not related to work was protective again PTB. (Giannubilo et al., 2020; L. Huang et al., 2019). There are also studies that provide no evidence of a relationship.

There is a move in public health to recognize sleep as a critical determinant of health. Insufficient sleep has major health consequences in adults, adolescents, and young children. There is also evidence those with insufficient sleep have a significant increase in chronic disease development and incidence.(Perry, Patil, & Presley-Cantrell, 2013) The adverse effect of insufficient sleep and PTB is also seen in literature.(Okun et al., 2011) Micheli et al. found that expecting mothers with sleep deprivation (≤5 hours sleep) were at high risk for preterm births (RR 1.7 95%, 1.1 - 2.8), with the highest risk observed for medically indicated preterm births (RR 2.4, 95% CI 1.0-6.4) after adjusting for maternal age, education, parity, smoking during pregnancy and pre-pregnancy BMI.(Micheli et al., 2011)

Evidence concerning diet is very diverse as they focus on different dietary habits like the consumption of fruit and vegetables, adherence to the Mediterranean diet and a variety of food combinations. These studies have had mixed results. In a study by Haugen et al., they examined those who followed the Mediterranean diet. The elements of the diet that this study focused on were intake of fish ≥2 times a week, fruit and vegetables ≥5 times a day, use of olive/canola oil, red meat intake ≤ times 2 a week, and ≤2 cups of coffee a day. While those who adhered to all the elements did not have significantly reduced odds of PTB (OR: 0.73, 95% CI 0.32 – 1.68), those who consumed fish at least twice a week did (OR: 0.84, 95% CI 0.74 - 0.95).(Haugen et al., 2008) In a meta-analysis by Kibret et al., it was found that those who adhered to a healthy dietary pattern characterized by the consumption of vegetables, fruits, legumes and whole grains had lower odds of PTB as well as other birth outcomes (OR 0.75, 95% CI 0.57 – 0.93, $P < 0.001$). (Kibret, Chojenta, Gresham, Tegegne, & Loxton, 2018)

3.2.2 Social Context of Healthy Behaviors

The study of behavior is very complex. There are two schools of thought when it comes to the adoption of positive health behaviors. The first school of thought is that healthy behaviors should be studied with an individual focus that is reflected in theories built around educating individuals to change health beliefs and actions. A sociological approach expands the bounds of inquiry by emphasizing the need to examine individual actions in context, recognizing a role for structure as well as agency. Such an approach considers the role of constraints that limit choice, and the role of normative structures that shape the social values attached to activities, identities, and choices.(Short & Mollborn, 2015)

The second school of thought is the social approach which is a more telling focus to have when studying and attempting to motivate positive health behaviors. It acknowledges that at any given point, an individual's health and health behaviors reflect physical endowments in combination with a cumulated set of experiences and circumstances. These experiences tend to unfold over time in distinct social and physical contexts.

One sociological construct that has been shown to affect the level of healthy behavioral engagement is socio-economic status (SES). There is conclusive evidence that SES is a significant factor in PTB. (Chiavarini et al., 2012; McCall et al., 2020) One study by Nkansah-Amankra et al. found that the rate of PTB decreased incrementally by maternal income range where those making less than $10,000 had 12% PTB while those making $40,000 or greater have an 8.7% rate. They also found that babies with parents at low levels of poverty had a 8.9% rate of PTB and those with a high level of poverty have a rate of 11.1%.(Nkansah-Amankra, Dhawain, Hussey, & Luchok, 2010)

The effect that SES has on PTB can be indirectly related to its effect on differing protective health behaviors. In Danaei et al., the investigators found that among those who had less than 12 years education and were either a homemaker/unemployed, had lower odds of attempting to become more physically active (aOR 0.54, 95% CI 0.39 – 0.75) and (aOR 0.66, 95% CI 0.46 – 0.95), respectively.(Danaei, Palenik, Abdollahifard, & Askarian, 2017) Some of the reasons that those of low social class may not be involved with physical activity is due to many living in areas of lower tax funds that are available to build indoor and outdoor exercise facilities. Also, the prevalence of violent crimes in poorer neighborhoods may also make physical activity more difficult and unsafe providing a disincentive to engage.("Poorer people are less physically active," 2014)

In another study by Pisinger et al., the authors found that smokers of lower SES status were significantly more likely to report that it had been a bad experience when attempting to quit (OR 1.41, 95% CI 1.1 - 1.8) and that they had relapsed because they were more nervous/restless/depressed (OR 1.43, 95% CI 1.1 - 1.8).(Danaei et al., 2017; Pisinger, Aadahl, Toft, & Jørgensen, 2011) This is consistent with fact that 72% of all smokers are from low income communities.("Why are 72% of smokers from lower-income communities?," 2018) According to a 2008 Gallup poll of 75,000 Americans, the rate of smoking among those who make $24,000 or less is more than double the rate of those who make $90,000 or more. Some of the reasons that the smoking habit may be more difficult for those who are poor are their social circle who are more likely to continue smoking than those who are in higher classes. One other reason is the issue of access. Even though there were improvements due to the Affordable Care Act, those who are poor are still more likely to lag their middle class counterparts in availability of effective smoking cessation treatments and mental health access which can make quitting tobacco more difficult. (Humphreys, 2015)

Drugs and alcohol abuse also have disparities between the social classes. Abuse of illegal or prescription opioids may be highest among the poor and continues to affect people in Appalachia and those living in poverty at disproportionate rates. Research has also shown that Americans who are on Medicaid are more likely to be prescribed opioids, receive higher doses for opioids and take opioids for a longer period of time. Compounding this issue is the fact that Medicaid recipients are also like less likely to access appropriate addiction treatment. (Close, 2020; Volkow, 2017)This trend is also seen in communities of color with high poverty rates and lack of local economic investment.(Close, 2020; *The Opioid Crisis and the Black/African American Population: An Urgent Issue*, 2020) On the other side, alcohol use is more common among upper class, highly educated Americans. In a survey, about 80% of upper-income survey respondents reported drinking alcohol, compared with approximately 50% of lower-income respondents. Approximately 78% of individuals with an income of $75,000 or more reported that they drink, compared with 45% of individuals with an income of $30,000 or less. About 80% of college graduates reported that they drink, compared with 52% of those who had a high-school education or less. Some proposed reasons for these results could be that Americans of higher socio-economic status have greater economic resources and can likely afford to buy alcohol when they want to drink. Also, they are more likely to participate in activities that may involve drinking such as dining out at restaurants, going on vacation or socializing with coworkers. This is compounded by the higher drinking rates among working compared with non-working Americans. (Close, 2020; Jones, 2015)

Sleep is also a factor that is affected by socio-economic status. Risk factors that may affect sufficient sleep are being poor, a person of color, work multiple jobs or do shift work, victim of discrimination or live in uncomfortable housing (like being homeless or too hot, cold, or crowded in your living space) which creates stress. Stress activates one's nervous system, making him or her feel alert. This creates a dynamic that makes it much harder to relax enough to fall asleep.(Mooney, 2017) A CDC survey that was conducted on 500,000 American adults revealed direct relationships between household income and sleep. Of those who had income 4 times greater than the poverty level, 26.8% had less than the recommended 7 hours of sleep; while 30.4% of those whose income was 2 to 4 times greater than the poverty level got insufficient sleep. Those who were at 100% to 200% of the poverty level had 32.2% less than 7 hours of sleep while 33.6% of those below the poverty level had insufficient sleep.(Cushner, 2020) On the flip side, a study by Patel et al. found that higher education is protective against sleep deprivation. Those with some college, graduated from college and pursued graduate studies had incrementally decreased odds of sleep deprivation: Some college (aOR 0.67, 95% CI 0.48 – 0.93), Bachelor's degree (aOR 0.55, 95% CI 0.38 – 0.79), Graduate studies (aOR 0.47, 95% CI 0.31 – 0.71). (N. P. Patel, Grandner, Xie, Branas, &

Gooneratne, 2010)

The consumption of nutritional food like fruits and vegetables also differs based on SES. Jack et al. found that in a sample in New York City, the odds of eating ≥5 servings increased with higher income among women and with higher educational attainment among men and women. Compared with women having less than a high-school education, the OR was 1.12 (95 % CI 0.82, 1.55) for high-school graduates, 1.95 (95 % CI 1.43 - 2.66) for those with some college education and 2.13 (95 % CI 1.56 - 2.91) for college graduates. The association between education and fruit and vegetable consumption was significantly stronger for women living in more affluent neighborhoods when compared to higher-poverty zip codes. (Jack et al., 2013) An important barrier that may contribute to the disparity in fruit and vegetable consumption is the prevalence of food deserts. American Nutrition Association defines food deserts as geographical areas that lack sufficient supply of fresh vegetables, fruits, and healthful, affordable whole foods that tend to be prevalent in low-income neighborhoods. Twenty percent of individuals in food deserts have incomes that are at or below the federal poverty level and have median family incomes 80% of those in surrounding areas. There are 2.3 million Americans who live more than one mile from a supermarket and did not own a car.("Food Deserts in America (Infographic)," 2018) Additional barriers that may cause a class disparity in nutritional consumption are the cost of high quality food, transportation and the time investment needed to cook better foods.

3.3 Study Methods

This study used data from the counties within the U.S. The dependent variable was the percent PTB. The demographic data that was used were percent of population who were of African descent, households headed by a single parent and population foreign born. Socio-economic data used were median income for the county and percent of population with some college education, Health conditions or chronic diseases used for analysis were heart disease, diabetes, obesity, chlamydia and HIV which were all reported as percentages. We also examined mental health issues as measured by the percentage of those with reported mental illness outside of drug abuse and suicidal thoughts. We also examined neighborhood characteristics by observing the variables access to exercise locations/facilities, ratio of the population to primary care physicians, ratio of mental health providers, percentage of the population under age 65 without health insurance coverage, rurality, food deprivation, income inequality and the violent crime rate. Health behaviors that were included in the study were smoking, alcohol and drug use, consumption of fruits and vegetables, percentage of those who engage in physical activities and percent of those reporting sufficient sleep.

The source of PTB data was the National Center for Health Statistics, final natality data that was retrieved from www.marchofdimes.org/peristats. There was not county data available to record percentage of those foreign born, heart disease, all mental health illness, drug abuse and consideration of suicide. We used state data and applied this figure to all counties within each respective state. The data source of the foreign born percent data was found at *https://www.brookings.edu/blog/the-avenue/2019/10/01/us-foreign-born-gains-are-smallest-in-a-decade-except-in-trump-*

states/ which was sourced by the 2018 American Community Survey. Heart disease data was found in the America's health rankings website at https://www.americashealthrankings.org/ and the data was provided from the 2017 CDC's Behavioral Risk Factor Surveillance System. The mental health and drug abuse data was provided from the Substance Abuse and Mental Health Services Administration (SAMHSA), Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, https://www.samhsa.gov. The data on percentage Black race was collected from U.S. Census Bureau - American Fact Finder's Annual Estimates of the Resident Population by Sex, Race, and Hispanic Origin for the U.S., States, and Counties: April 1, 2010 to July 1, 2018 for all states except Alaska. The data from Alaska came from the county health rankings which was provided by the county health rankings website (https://www.countyhealthrankings.org), as were the all remaining data. County health rankings gets its data from different sources as provided by the government as follows:

- 2016/2017 Behavioral Risk Factor Surveillance System
- 2016 U.S. Diabetes Surveillance System
- 2015 and 2017 USDA Food Environment Atlas, Map the Meal Gap from Feeding America
- Business Analyst, Delorme map data, ESRI, & U.S. Census Tigerline Files
- 2017 National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
- 2017 Small Area Health Insurance Estimates
- 2017 Area Health Resource File/American Medical Association
- 2019 CMS, National Provider Identification
- 2014-2018 American Community Survey, 5-year estimates

- 2014 and 2016 Uniform Crime Reporting – FBI

Some of the variables were recoded in order to create consistency in the analysis. The percent figure for percent foreign-born, smoker, physical inactivity, insufficient sleep and substance abuse were all subtracted from one in order to be interpreted as the following, respectively: U.S. Born, non-smoker, physical activity, sufficient sleep and abstinence from substance use.

After the data was compiled, principle components analysis (PCA) and ordinary least squares (OLS) regression were used for analysis. In order to run the PCA, the data variables were entered in to the analysis as follows to create each component. At first, all physical health variables heart disease, diabetes, obesity, chlamydia and HIV were gathered. The PCA determined that this group of variables should be separated into two separate components that were named "Chronic Disease", which included diabetes, heart disease, and obesity. The sexually transmitted diseases ("STD") component included chlamydia and HIV. Mental health variables included all mental illness and suicidal thoughts. The PCA showed that these two can be included in the same component named "Mental Illness".

Socio-economic factors of percent Black race, foreign born (FB) citizen, percent with some college, median income, single-parent headed household created two components: Household demographics (percent Black race, FB (which was converted to U.S. Born by subtracting 1 from the percentage) and single-parent headed household) and Household Economics (some college, median income).

Community characteristics access to exercise locations/facilities, access to primary care physicians, access to mental health providers, percent uninsured, rurality, food deprivation as calculated by 10 - Food Environment Index, Income Inequality as measured by the GINI coefficient and the violent crime rate were also included. Through the PCA, three components were created: Healthcare Access (access to exercise locations/facilities, access to primary care physicians, access to mental health providers); "Access_Barriers" (percent uninsured, rurality) and "Neighborhood Deprivation" (food deprivation, income inequality, and the violent crime rate). The final component was behavior which included all behavioral variables (percent non-smoker, alcohol and drug abstinence, physical activity, consumption of fruit and vegetables and sufficient sleep)

For each component, values were derived from regression scores that were calculated for each observation. The component data was placed into two (OLS) regression models for analysis. One model had PTB as the dependent variable and the second model had behavior as a dependent In order to do robustness checks of the models, LASSO regression was used.

3.4 Study Results

The original data included 3,141 counties of the U.S. After eliminating counties with missing data, the final sample included were 1,993 counties. The results of the OLS regression showed that counties with higher percentages of positive health behaviors had a negative relationship with PTB ($\beta = -0.529$, $p < 0.001$). Other components that had significant relationships with PTB were household demographics ($\beta=0.540$, $p < 0.001$), community deprivation ($\beta=0.318$, $p < 0.001$), healthcare access ($\beta=-0.192$, $p = 0.002$), and chronic disease ($\beta=0.220$, $p < 0.001$). Household Economics was shown to have a curvilinear relationship with PTB: At the first order, household economics had a positive relationship to PTB (β= 0.184, p = 0.008) while the square term also had a positive relationship (β= 0.115, p = 0.001). The cubed term had a negative relationship with PTB (β= -0.027, p = 0.012). STD, access barriers and mental health did not have a significant relationship with PTB. The R2 value was 0.48. (Table 3.1)

Table 3.1 OLS Regression – Dependent Variable = PTB

Variable	Parameter Estimate	Standard Error	t Value	Pr > |t|
Chronic Disease	0.22246	0.05308	4.19	<.0001
STD	0.04492	0.04604	0.98	0.3293
Household Demographics	0.53958	0.05689	9.48	<.0001
Household Economics	0.18358	0.06887	2.67	0.0077
Household Economics - Sq	0.1148	0.02995	3.83	0.0001
Household Economics - Cu	-0.02664	0.01059	-2.52	0.012
Healthcare Access	-0.19179	0.05052	-3.8	0.0002
Healthcare Access_Barrier	0.04963	0.05311	0.93	0.3502
Community Deprivation	0.31776	0.05081	6.25	<.0001
Mental Health	0.00285	0.03406	0.08	0.9332
Behavior	-0.52944	0.06178	-8.57	<.0001

We also ran a LASSO regression. This was used to confirm the results of the OLS regression. The results indicate that the addition of all variables except Healthcare Access_Barrier reduce the error in the model. (Table 3.2) and (Figure 3.1)

Table 3.2 LASSO Regression – Dependent Variable = PTB

Step	Effect Entered	Number Effects In	ASE*	Test ASE**	CV PRESS***
* Optimal Value of Criterion					
0	Intercept	1	3.9344	3.6706	5502.8835
1	Behavior	2	3.7508	3.5063	3449.1139
2	Household Demographics	3	2.333	2.2644	2921.2323
3	Community Deprivation	4	2.223	2.1674	2903.864
4	Chronic Disease	5	2.0744	2.0409	2882.0674
5	STD	6	2.0717	2.04	2885.1997
6	HealthCare Access	7	2.0439	2.0262	2872.1346
7	Household Economics Sq	8	2.0147	1.9986	2855.9614
8	Household Economics	9	2.0129	1.9977	2854.2591
9	Mental Health	10	2.0118	1.9978	2861.3497
10	Household Economics Cu	11	2.0019	1.9948	2852.4331*
11	HealthCare Access_Barrier	12	2.0005	1.9953	2856.8998
ASE = Average Standard Error (Train)					
***Test ASE = Average Standard Error (Test)*					
****CV PRESS = Prediction Error from the 10K Cross Validation*					

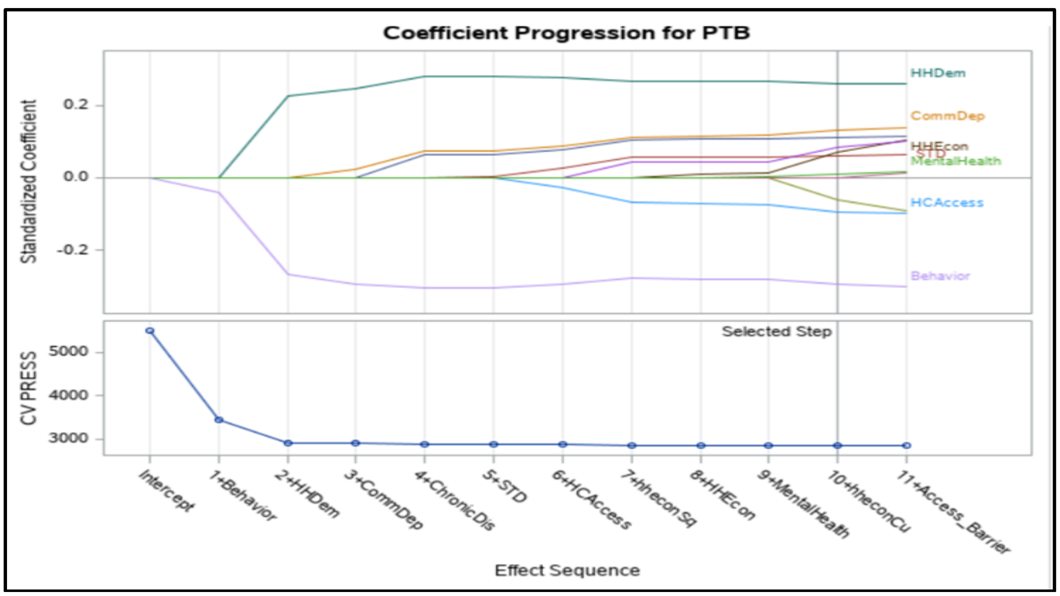

Figure 3.1 LASSO results for dependent variable = PTB.

The LASSO model parameter estimates indicated were similar to those of the OLS regression showing the behavior and household demographics were the strongest factors of PTB. (Table 3.3) The R2 value for the LASSO was 0.49.

Table 3.3 LASSO Parameter Estimates – Dependent Variable = PTB

Parameter	DF	Estimate
Intercept	1	9.977475
Chronic Disease	1	0.21413
STD	1	0.117016
Household Demographics	1	0.520142
Household Economics	1	0.136346
Household Economics Sq	1	0.08494
Household Economics Cu	1	-0.017731
HealthCare Access	1	-0.191203
Community Deprivation	1	0.249206
Mental Health	1	0.021406
Behavior	1	-0.574584

We did another OLS regression model to examine the characteristics that contribute to healthy behaviors (Table 3.4). Characteristics that had a positive relationship to healthy behaviors were household economics (β=0.452, $p < 0.001$) healthcare access_barrier (β=0.070, $p = 0.001$) and healthcare access (β=0.238, $p < 0.001$). Characteristics that reduced the engagement in healthy behaviors were household demographics (β=-0.254, $p < 0.001$) and neighborhood deprivation (β=- 0.119, $p < 0.001$). The R2 value was 0.58.

Table 3.4 OLS Regression Model – Dependent Variable = Healthy Behavior

Variable	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	-0.00359	0.01278	-0.28	0.779
Household Demographics	-0.2535	0.01884	-13.46	<.0001
Household Economics	0.45219	0.01889	23.94	<.0001
HealthCare Access	0.2385	0.01692	14.1	<.0001
HealthCare Access_Barrier	0.07065	0.01831	3.86	0.0001
Community Deprivation	-0.11946	0.01901	-6.28	<.0001

We also ran a LASSO regression. This was used to confirm the results of the OLS regression. The results indicate that the addition of all variables reduced the error in the model. (Table 3.5) and (Figure 3.2)

Table 3.5 LASSO Regression – Dependent Variable = Healthy Behavior

Step	Effect Entered	Number Effects In	ASE	Test ASE	CV PRESS
* Optimal Value of Criterion					
0	Intercept	1	0.9986	0.9563	1850.8067
1	Household Economics	2	0.6961	0.6612	971.6273
2	Household Demographics	3	0.5274	0.512	830.3595
3	HealthCare Access	4	0.499	0.4897	782.1472
4	Community Deprivation	5	0.4145	0.4345	770.0651
5	HealthCare Access_Barrier	6	0.4105	0.435	765.8222*

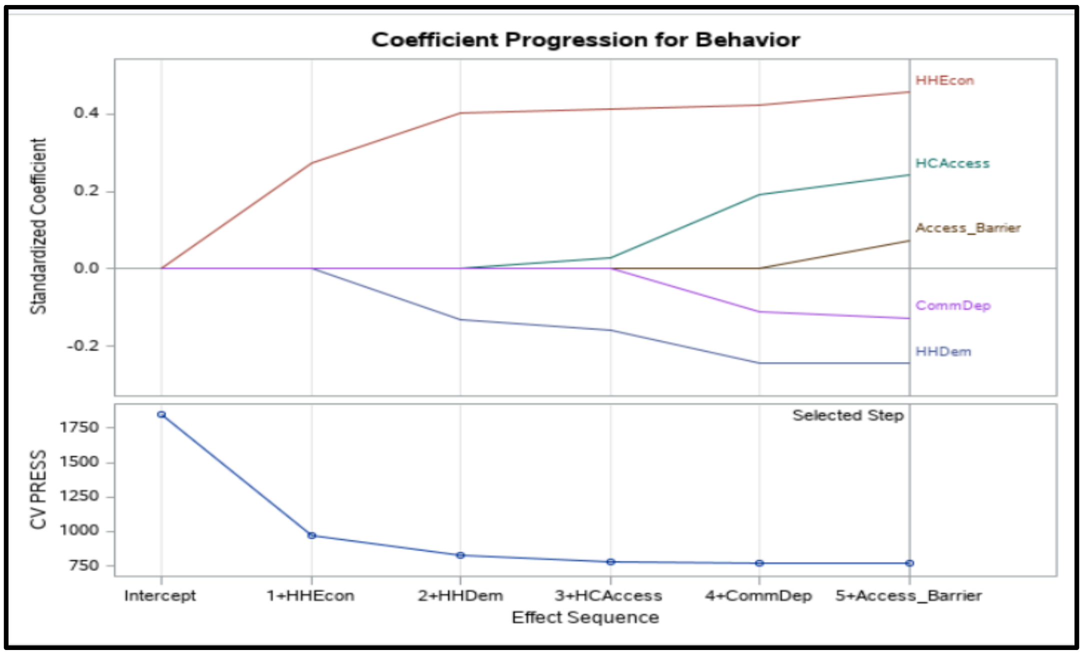

Figure 3.2 LASSO results for dependent variable = Behavior.

The LASSO model parameter estimates indicated were similar to those of the OLS regression showing the household economics and household demographics were the strongest factors of PTB. (Table 3.6) The R2 value for the LASSO was 0.59.

Table 3.6 LASSO Parameter Estimates – Dependent Variable = Healthy Behavior

Parameter	DF	Estimate
Intercept	1	0.008252
Household Demographics	1	-0.250457
Household Economics	1	0.464364
HealthCare Access	1	0.242974
HealthCare Access_Barrier	1	0.076775
Community Deprivation	1	-0.126541

3.5 Discussion

3.5.1 Summary of Data Analysis

The OLS analysis showed that healthy behaviors have a significant and negative effect on PTB ($\beta = -0.529$, $p < 0.001$). Results from the LASSO regression were similar to the OLS results by indicating that behavior was the most important factor in PTB and having a similar parameter estimate ($\beta = -0.575$).

Although there have not been studies that consolidated a combination of different healthy behaviors, our results are consistent with relationships of individual behaviors cited in literature. Smoking was found to increase the odds of PTB (Rajia et al., 2020; David A. Savitz & Murnane, 2010) while the consumption of alcohol was cited as being complicit in the rate of PTB (Tucker et al., 2015; Umer et al., 2020). Adverse health behaviors of drug abuse, lack of physical activity and lack of sleep and nutrient deficient diet al.so showed to increase the odds of PTB. (Haugen et al., 2008; Misra, Strobino, Stashinko, Nagey, & Nanda, 1998; Okun et al., 2011; Tucker et al., 2015).

Household economics was shown to have a negative curvilinear relationship with PTB that indicates that as income/education increases past a certain point, the rate of PTB decreases. This is consistent with the cited literature by Nkansah-Amankra et al. which found that those who had an income of $10,000 or less had 38% more PTB than those who made $40,000 or more.(Nkansah-Amankra et al., 2010) The OLS results of the model of behavior also provides additional evidence that household economic characteristics of geographical units (with this study examining U.S. counties) has a significant relationship with behavior (β=0.452, $p < 0.001$). The LASSO regression also found that household economics had the greatest effect on engagement on health behaviors. This indicates that as education/income increases, so does the engagement in healthy behaviors. This consistent with previous evidence that examined various behaviors.("Food Deserts in America (Infographic)," 2018; Humphreys, 2015; Jones, 2015; N. P. Patel et al., 2010; "Poorer people are less physically active," 2014; Volkow, 2017)

The results of this study indicate that when a health practitioner recommends a pregnant patient to engage in health promoting behaviors, one must look at his or her patient in her full life context realizing that opportunities to improve behavior may not be readily available.

3.5.2 Existing PTB Reduction Program Template/Health Behavior Change Programs

The template for programs that have missions that seek reduction in the rate of PTB look to address the following:

- Prevent spontaneous indicated late preterm/early term births
- Promote progesterone supplementation in high risk individuals as its estimated to potentially decrease PTB by 45%
- Make cervical cerclage available. Cervical cerclage is the surgical placement of a suture or tape around the cervix in an attempt to prevent dilatation and subsequent

preterm birth. Evidence indicates that this procedure could potentially decrease the rate of PTB by 20%

- Create programs and policy to reduce tobacco use in pregnant women. This would be accomplished through psychosocial interventions and nicotine replacement therapy which had been estimated to potential decrease PTB by 20%. Also, smoke free legislation decreased PTB by 10%

- Urge judicious use of fertility technology where only one egg is used at a time to reduce the number of multiple births which is a risk factor of PTB. Literature indicates that this will decrease the PTB rate by 63%

- Establish preterm birth prevention clinics.   The first large-scale attempt to determine the effectiveness of such a program was the West Los Angeles Preterm Birth Prevention Project. Eight prenatal county clinics in California were allocated at random to be experimental or control clinics. The intervention was based on providing additional education to the women and offering more clinic time. In the experimental group, there was a 19% reduction in the preterm birth rate when compared with that of the control clinics. This difference in rates was statistically significant when the number of patient risk factors was taken into account. In pregnancies of black women, the preterm birth rate was 15% in the experimental clinics and 22% in the control clinics.(Newnham et al., 2014)

Despite the success of this model for PTB rate reduction, the March of Dimes still gives the U.S. a prematurity grade of C and no state had an A grade (Oregon had an A – grade).("2019 March of Dimes Report Card," 2019) The gap in the programs are that they do not focus on improving behaviors of the pregnant women outside of smoking. Successful programs should employ an ecological model in their creation. The ecological formulation of a program would consider public policy, community, institutional and individual factors. There are existing behavioral improvement programs that have been successful in public health and have templates that can be used in the reduction in PTB.

3.5.3 Proposed Programs to Improve Health Behaviors

Creating a behavior-based program to decrease the rate of PTB would be beneficial to the health of a community in general. This can also create a savings in the healthcare system. Not only would they potentially reduce the cost of PTB which now stands at $26 billion at a minimum, but potentially decrease the costs of other chronic diseases as the adoptions would improve community health. A weakness in many PTB reduction strategies is that they only address the immediate issue if a woman is pregnant which does not take the life cycle factors that affect PTB into account. The creation of health behaviors must be cemented early in life in order for it to become habit in addition to programs while a woman is pregnant. To this end, there should be annual education for children and adults employing the health belief model. The health belief model is the basis of interventions to increase knowledge of health challenges, enhance perceptions of personal risk, encourage actions to reduce or eliminate the risk, and—in its later iteration—build a sense of self-efficacy to undertake the needed changes. While it focuses on the individual, the model recognizes and addresses the social context in which health behaviors take place.(Green, Murphy, & Gryboski, 2020)

Programs for children should be part of the curriculum in the school system and after school programs. There should be fundamentals taught concerning the effect of nutrition, physical exercise, drugs and alcohol on the body along with the effects of not engaging in the activities like chronic disease and issues with future pregnancies. For adults, annual education should become a requirement of eligibility into the Medicaid and SNAP programs or create incentive and financial credit programs for those who have a minimum percentage of attendance. This is based on evidence provided by researchers from New York University, Stanford University, and the University of Chicago. They found that the entry of new supermarkets has little impact on the eating habits of low-income households. Even when people in low-income neighborhoods do buy groceries from the new supermarkets, they tend to buy products of the same low nutritional value. They also found that when low-income people move from neighborhoods served by lower-quality stores to ones with healthier offerings, there is little effect on the consumption of nutrient dense food. The authors concluded that when it comes to food and nutrition, it’s not just that higher income Americans have more money. They benefit even more from higher levels of education and better information about the benefits of healthier eating.(Florida, 2018)

In addition to education, there should be an infrastructure that promotes healthy behaviors and provides opportunities for community members to apply what they have been taught. An example of this would be the contribution of state and federal government to either build or repurpose old buildings to use for physical exercise, avail areas for community gardens and credits to grocery store chains to have shops in underserved areas and food deserts. For drug and alcohol treatment, the respective state or local government should allocate funds to rehabilitation centers that do not accept Medicaid in order that they can allocate a certain percent of their availability to Medicaid patients. In addition to that, a part of the education for children aged 12 – 18 would be to have a field trip to these facilities so that those who are patients can talk to them about the negative impacts that drugs and alcohol had in their life. (Similar to the “Scared Straight” program). In addition, there should be more focus on mental illness where new community facilities have a social worker and psychologist on site so that the psychological needs can be fulfilled for the adults and children within the community. This would seek to be further education on reducing stress and help with depression and other psychological issues that attack those in deprived communities.

Although the above activities would be more costly to government, there would be great returns. An example of this possibility is drug treatment. Medical costs decreased by 30 percent on average between the year prior to medically assisted drug treatment (MAT) and the third year following treatment. These cost trends reflect a decline in expenditures in all types of health care settings including hospitals, emergency departments, and outpatient centers. It is estimated that for every dollar invested in methadone treatment, there is a $4 or $5 return. It has been found that MAT led to reduced hospital length of stay for pregnant women. The women in the MAT group had 10 days in the hospital while those who were non-MAT had 17 days in the hospital.(Medicaid.org, 2014)

3.5.4 Study Weaknesses

Some of the weaknesses of the study was that with the use of available county data, the full population data was used and not just the women. Regardless of these weaknesses, the results were consistent with theory and the previous literature. Another weakness was that there were some counties that had missing data and caused a reduction of the sample. Nevertheless, given that this was a positive study, there is an indication that the power of the study was sufficient.

3.6 Conclusion

This study reaffirmed the importance of healthy behaviors in the prevention of PTB. This work adds to the literature in that it does not look at behaviors in a vacuum, but sought to look at the behavior within social context by examining the barriers of engagement due to poverty and low economic status. This study examined existing programs and sought to present ideas that were missing in existing programs with the hopes of removing the barriers that those in poverty face in pursuing healthier lifestyle.

CHAPTER 4

PRETERM BIRTH: IS THERE AN OBESITY PARADOX BASED ON SOCIO-ECONOMIC STATUS?

4.1 Abstract

4.1.1 Introduction

According to the March of Dimes Global action report, preterm birth (PTB) rates are on the rise in most countries. It is now the single most important cause of neonatal deaths (babies under 28 days) and the second leading cause of death in children under age 5. The interaction effect of maternal body mass index (BMI) and socio-economic status (SES) on PTB has not been explored in literature. Given the fact that the rates of PTB is increasing in the U.S. and the world, it is important to examine factors that may contribute to its increased incidence. In this paper, the interaction effect of socio-economic status (SES) and body mass index (BMI) will be examined.

4.1.2 Methods

Data for this study was obtained from the Natality Data of the National Vital Statistics System within the National Center for Health Statistics. These files provide demographic and health data for births occurring during the calendar year. The records that were used in the study represented singleton births for mothers from years 2015 - 2018. The primary data points that we examined were PTB, BMI and SES. Our controlling variables included: age, weight gain, previous PTB, marital status, previous births, and smoking status during pregnancy, prenatal care, hypertension, diabetes and race.

4.1.3 Results

Our regression model for the overall sample showed that there was a significant relationship between BMI and PTB after considering all secondary factors. For every unit increase in BMI, there were decreased odds of PTB (OR = 0.968, 95% CI 0.966 – 0.97, $P<0.001$). The square term of BMI was also significant indicating that BMI has a curvilinear relationship.

There were other models for each social class. The model for HSES shows very limited effects of BMI and BMI squared. In contrast, the model for LSES indicated that BMI was a significant factor in PTB. For every increase in BMI, there was a decrease in the probability of PTB (OR = 0.929, 95% CI 0.926 – 0.933, $P < 0.001$). As with the overall sample, those who were LSES also had a curved relationship with PTB. As BMI increases the odds of PTB decreases until the BMI has a value of approximately 40-45 where the probability of PTB starts to increase.

4.1.4 Conclusion

Our study has found an obesity paradox in PTB for those women who are LSES. This has the potential to change the practice of prenatal care of normal weight women. It was also found that the relationship between BMI and PTB is not linear but curvilinear indicating that after a certain BMI is reached, the relationship between these two elements change from being inverse (as BMI increases, the odds of PTB decreases) to being a direct relationship. We also found that while weight is a significant factor in LSES women, it is not significant in HSES women. This may be due to the SES differences in access to foods and lifestyles that lead to healthier weights.

4.2 Background / Introduction

According to the March of Dimes Global action report, preterm birth (PTB) rates are on the rise in most countries. It is now the single most important cause of neonatal deaths (babies under 28 days) and the second leading cause of death in children under age 5. Preterm babies have more morbidities, greater risk of neonatal intensive care unit (NICU) admission, 20% greater risk of complications and 5% greater chance of developing an intellectual or developmental disability.(Dolezel, 2019) In 2018, the incidence of PTB in the U.S. increased for the fourth year in a row to 10.02%(B. E. Hamilton, Martin Joyce A., Osterman Michelle J.K. , M.H.S., Rossen, Lauren M. , 2019) with an estimated annual cost of $26.2 billion. (*Institute of Medicine (U.S.) Committee on Understanding Premature Birth and Assuring Healthy Outcomes*, 2007)

The effect of maternal body mass index (BMI) on the rate of preterm birth is inconclusive in the literature. Studies show that the rate of PTB increases as BMI increases.(L. Liu et al., 2019; McDonald et al., 2010) Khatibi et al. reported that maternal BMI greater than normal weight (BMI 18.5 – 24.9) was associated with an increased odds of PTB with adjusted odds ratio (aOR) ranging from 1.11 (95% confidence interval [CI], 1.03–1.20) for preobesity/overweight (BMI 25-29.9) to 2.00 (95% CI, 1.48–2.71) for grade-III obesity (BMI greater than 40).(Khatibi et al., 2012) There is also literature indicating high BMI is protective against PTB.(Kosa et al., 2011; Rainey, Che, & Meints, 2018; Sharifzadeh, Kashanian, Jouhari, & Sheikhansari, 2015) Hendler et al. reported decreased rates of PTB as BMI increases with those underweight (BMI less than 19) having 16.6% SPTB, normal weight (BMI 19-24.9) having 11.3%, overweight (BMI 25 –

29.9) having 8.1% and obese (greater than 30) a composited 6.2 rate.(Hendler et al., 2005)

The study of socio-economic status (SES) and PTB is diverse because of the many elements that comprise SES. There were studies that used the residential neighborhood to measure SES. Some of these studies found that this was a significant factor in PTB, with those living in more disadvantaged neighborhoods having higher odds.(Luo, Wilkins, & Kramer, 2006) In the meta-analysis by Ncube et al., it was found that there was 27% greater risk of PTB in disadvantaged neighborhoods when compared with less disadvantaged geographical areas.(Ncube et al., 2016) In contrast, Clayborne et al. found that upon adjusting for covariates, there was not a significant relationship between neighborhood SES and birth outcomes.(Clayborne, Giesbrecht, Bell, & Tomfohr-Madsen, 2017) There were other studies that used income as a measure of SES. Another study found that PTB rates per 1,000 were 104.6 for the affluent group, 108.9 for the upper-middle group, 115.8 for the lower-middle group, and 146.9 per 1,000 for the poverty group yielding a significant difference between the income classes based on U.S. census classifications.(D'Angela, Hesson, & Langen, 2018) Years of education has also been used as a measure of SES, with the finding that lower education was associated with higher PTB rates. In the study by Morgen et al., education was a stronger factor in PTB than income and employment status. Those who were less educated (less than 10 years of schooling) had a 22% greater hazard of PTB for those nulliparous and 56% greater hazard for those who were parous. (Morgen, Bjørk, Andersen, Mortensen, & Nybo Andersen, 2008)

While the intersection of weight and SES has not been addressed in the context of PTB, there is exhaustive literature on this topic. In Paeratakul et al., it was found that there was a relationship between SES and perception of being overweight (PSOW). Those who had higher income had a significantly higher PSOW than those of a lower income. Those with higher education had a 1.6 greater odds of PSOW than those of lower education.(Paeratakul, White, Williamson, Ryan, & Bray, 2002) Sobal et al. reported that in developing countries, there was strong inverse relationship among women. Obesity was six times more prevalent among women of lower SES (LSES) than among those of higher SES (HSES) while there was a direct relationship observed in developing (non-Western) countries. In developing countries, greater prevalence of obesity in individuals of HSES appears to be due to their social influence in obtaining more adequate food supplies, coupled perhaps with cultural values favoring fat body shapes. Obesity may be a sign of health and wealth in developing societies, the opposite of its meaning in developed countries.(Sobal & Stunkard, 1989) It has been suggested that LSES citizens of the U.S. may share similar characteristics with those living in developing countries. (Shaefer, Wu, & Edin, 2017)

Given the increasing rate of PTB in the U.S. and the world, it is important to examine factors that may contribute to its incidence. In this paper, the interaction effect of socio-economic status (SES) and body mass index (BMI) and its relationship with PTB was examined. While there are many studies that examine BMI and SES as separate issues, there are no studies that examine the interaction of these two factors in PTB. Studies also do not address how BMI affects the PTB rates of members of HSES and LSES populations.

4.3 Study Methods

This study was determined to be exempted from IRB review because there was no interaction or intervention with the subjects or their private identifiable data. Data for this study was obtained from the Natality Data from the National Vital Statistics System of the National Center for Health Statistics. The files provide demographic and health data for births occurring during the calendar year. The microdata included in this study are based on information abstracted from birth certificates filed in vital statistics offices of each state and the District of Columbia from the years of 2015 through 2018.

There was 15,611,133 birth records analyzed. Included in the study were records of mothers who had singleton births and who were between the ages of 25 – 44. This age range was chosen because we used education to determine SES and we wanted to be sure that we included those who could possibly complete at least a bachelor's degree. We excluded those who were over 44 because fertility declines to the point that getting pregnant naturally is unlikely for most women. Also, women greater than 44 have more of a risk for morbidities and we wanted to avoid confounding factors.("Having a baby after age 35: how aging affects fertility and pregnancy," 2018) We also excluded those with missing data such as undefined or unknown insurance, BMI, and other elements like education, race, smoking, prenatal care, marital status, previous PTB, gravity, parity, hypertension (HTN) and diabetes (DM).

The primary data points that we examined were PTB, BMI and SES. We looked at BMI as a continuous variable. There was not a PTB variable within a file, so gestational age at birth was used. PTB was coded as a "yes" if the gestational age at birth was less than 37 weeks and "no" if greater than or equal to 37 weeks. HSES was coded as “yes” if the subject had a bachelor’s degree or greater and private or self-pay insurance. LSES was coded as “yes” if the subject had a high school diploma or less and had Medicaid or self-pay insurance. Our controlling variables included: age, weight gain, previous PTB, marital status, previous births, and smoking status during pregnancy, prenatal care, hypertension, diabetes and race.

We used three logistic regression models. One model included the full data, the second that included only HSES women, the third including only LSES women. The dependent variable was PTB. The controlling variables served as the independent variables. BMI, age and weight gain were given square terms in order to examine whether there were curvilinear relationships with PTB. SAS 9.4 was used for analysis.

4.4 Study Results

After making the exclusions, there were 9,822,253 records used for the overall analysis. After accounting for education and insurance type, there were 3,734,177 who were coded as HSES and 2,118,132 who were coded as LSES as noted in Figure 4.1.

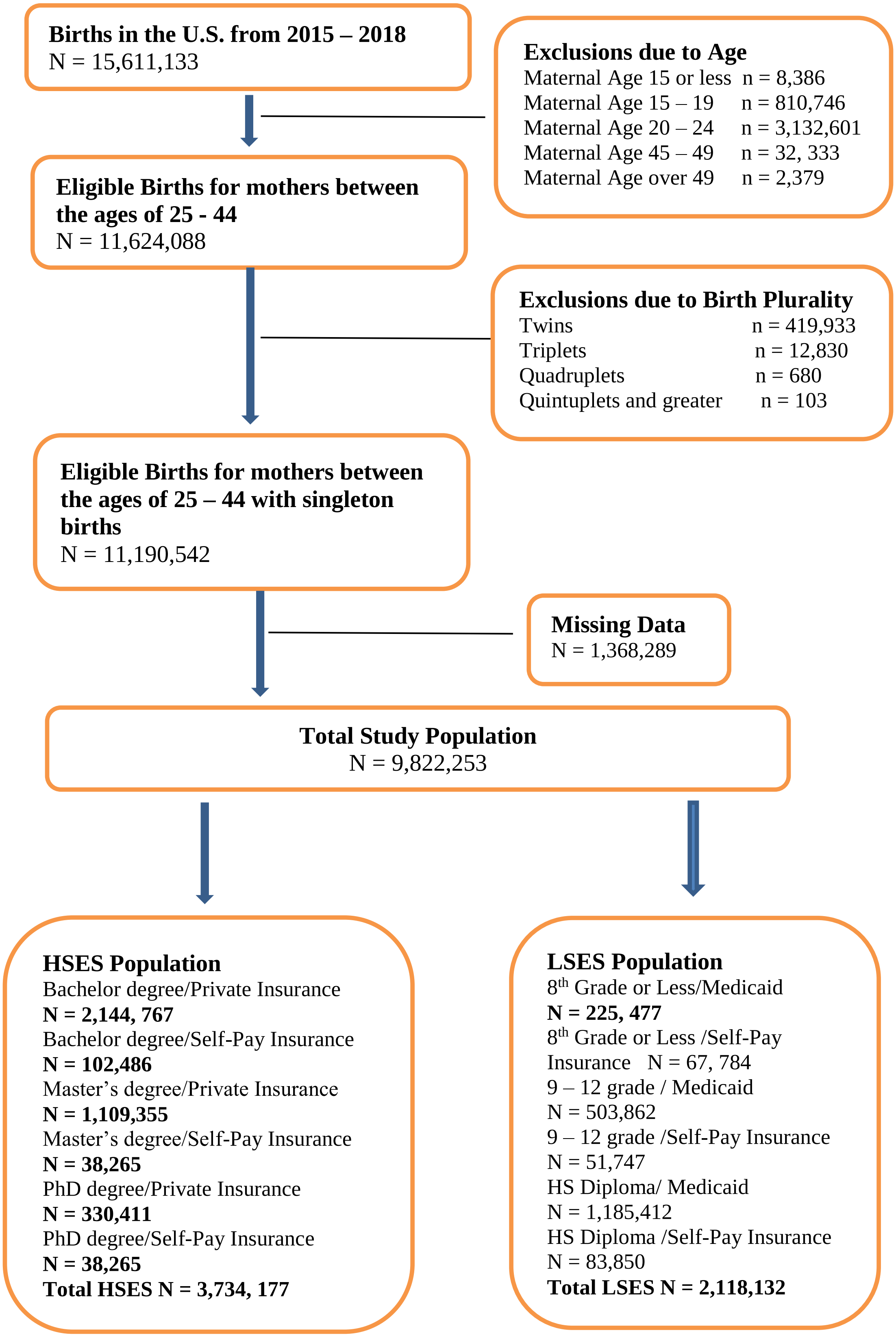

Figure 4.1 Diagram of study population

Baseline characteristics can be seen in Table 4.1 and 4.2. The average age in our overall, HSES and LSES sample was 31.21+/- 4.22, 32.30 +/- 3.92 and 30.34+/- 4.35, respectively. The average BMI in our overall sample was 27.01 +/- 6.64, 25.35 +/- 5.60 for those who were HSES and 28.18+/- 6.99 for those who were LSES. In our overall sample, 56% were White, 12% were Black and 32% were of other races. For those who were HSES, 70.8% were White, 5.9% were Black and 23.3% were of other races. For those who were LSES, 31.5% were White, 18.1% were Black and 50.4% were of other races. Other races included Hispanics, Non-Hispanic – American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander and multi-racial.

Table 4.1 Baseline Characteristics of Overall Population

Characteristic	N	Full Sample
Maternal Age (Mean/SD)	9,822,253	31.21 +/- 4.2
Maternal BMI (Mean/SD)	9,769,039	27.01 +/- 6.6
Maternal Education (n / %)	9,822,253	
HS Diploma or Less		2,887,219 (29.4%)
Some College		1,872,014 (19.1%)
Associates Degree		936,914 (9.5%)
Bachelor's Degree		2,554,789 (26%)
Master's Degree		1,219,291 (12.4%)
PhD Degree		352,026 (3.6%)
Insurance (n / %)	9,769,039	
Medicaid		3,472,472 (35.6%)
Self-Pay		436,830 (4.4%)
Private Insurance		5,589,737 (60%)
Pregnancy Weight Gain (Mean/SD)	9,822,253	29.41 +/- 14.6
Prior Preterm Birth (n / %)	9,769,039	339,449 (3.5%)
Single (n / %)	9,199,832	2, 672,031 (29%)
Previous Births (n / %)	9,769,039	7,356,299 (74.9%)
Smoked during Pregnancy (n / %)	9,769,039	777,676 (8%)
Prenatal Care (n / %)	9,769,039	9,711,010 (99%)
Pre-existing HTN (n / %)	9,769,039	198, 966 (2%)
Gestational HTN (n / %)	9,769,039	592,520 (6.1%)
Pre-existing DM (n / %)	9,769,039	96,001 (1%)
Gestational DM (n / %)	9,769,039	701, 063 (7.2%)
Race (n / %)	9,769,039	
White		5,468,219 (56.1%)
Black		1,185,466 (12.1%)
Other Races		3,115,354 (31.8%)

Table 4.2 Baseline Characteristics of HSES/LSES Population

Characteristic	N	HSES	N	LSES
Maternal Age (Mean/SD)	3,734,177	32.3 +/- 3.9	2,118,132	30.3 +/- 4.4
Maternal BMI (Mean/SD)	3,734,177	25.4 +/- 5.6	2,118,132	28.2 +/- 7
Maternal Education (n / %)	3,734,177		2,118,132	
HS Diploma or Less		[redacted]		2,118,132 (100%)
Some College		[redacted]		[redacted]
Associates Degree		[redacted]		[redacted]
Bachelor's Degree		2,247,253 (60.2%)		[redacted]
Master's Degree		1,147,620 (30.7%)		[redacted]
PhD Degree		339,304 (9.1%)		[redacted]
Insurance (n / %)	3,734,177		2,118,132	
Medicaid		[redacted]		1,914,751 (90.4%)
Self-Pay		149,644 (4%)		203,381 (9.6%)
Private Insurance		3,584,533 (96%)		[redacted]
Pregnancy Weight Gain (Mean/SD)	3,734,177	30.98 +/- 12.8	2,118,132	26.9 +/- 15.6
Prior Preterm Birth (n / %)	3,734,177	77, 749 (2.1%)	2,118,132	108,937 (5.1%)
Single (n / %)	3,497,301	237,934 (6.8%)	1,975,673	1,142,618 (57.8%)
Previous Births (n / %)	3,734,177	2,376,850 (63.7%)	2,118,132	1,887,238 (89.1%)
Smoked during Pregnancy (n / %)	3,734,177	48,227 (1.29%)	2,118,132	336,713 (15.9%)
Prenatal Care (n / %)	3,734,177	3,719,771(99.6%)	2,118,132	2,059,814 (97.3%)
Pre-existing HTN (n / %)	3,734,177	55,559 (1.5%)	2,118,132	50,307 (2.4%)
Gestational HTN (n / %)	3,734,177	209,225 (5.6%)	2,118,132	119,778 (5.7%)
Pre-existing DM (n / %)	3,734,177	22,435 (.6%)	2,118,132	30,122 (1.4%)
Gestational DM (n / %)	3,734,177	226,841 (6.1%)	2,118,132	175,047 (8.3%)
Race (n / %)	3,734,177		2,118,132	
White		2,643,353 (70.8%)		661,227 (31.5%)
Black		220,435 (5.9%)		383,702 (18.1%)
Other Races		870,389 (23.3%)		1,068,303 (50.4%)

In Table 4.3, our regression model for the overall sample showed that there was a significant relationship between BMI and PTB after considering all secondary factors. For every unit increase in BMI, there were decreased odds of PTB (OR = 0.968, 95% CI 0.966 – 0.97, P<0.001). The square term of BMI is also significant indicating that BMI has a curvilinear relationship.

Table 4.3 Logistic Regression for Overall Population

Predictor	β	P-Value	Odds Ratio	95% Confidence Interval
Constant	2.492	<0.001		
Age	- 0.063	<0.001	0.939	0.932 – 0.946
Age Squared	0.001	<0.001	1.001	1.001 – 1.001
BMI	-0.032	<0.001	0.968	0.966 – 0.97
BMI Squared	<0.000	<0.001	1.000	1.000 – 1.000
Weight (Wt.) Gain	-0.036	<0.001	0.965	0.965 – 0.966
Weight Gain	<0.000	<0.001	1.000	1.000 – 1.000
Prior PTB	0.683	<0.001	3.922	3.887 – 3.957
Single	0.111	<0.001	1.248	1.241 – 1.256
Previous Births	-0.100	<0.001	0.818	0.813 – 0.823
Smoked during Pregnancy	0.160	<0.001	1.378	1.367 – 1.390
Prenatal Care	-0.557	<0.001	0.329	0.323 – 0.334
Pre-existing HTN	0.522	<0.001	2.839	2.804 – 2.874
Gestational HTN	0.613	<0.001	3.41	3.384 – 3.436
Pre-existing DM	0.491	<0.001	2.67	2.626 – 2.715
Gestational DM	0.117	<0.001	1.264	1.253 – 1.275
Race				
Black vs White	0.199	<0.001	1.432	1.422 – 1.443
Other Races vs Whites	-0.038	<0.001	1.13	1.123 – 1.137

R^2 = 0.037 Max rescale R^2 = 0.090

Tests	X^{2a}	df[b]	P-Value
Overall Model Evaluation			
Likelihood Ratio Test	90,249.64	17	<0.001
Score Test	460,155.76	17	<0.001
Wald Test	372,135.80	17	<0.001
Goodness of fit test			
Hosmer & Lesmeshov	313.16	8	<0.001

[a]X^2=Chi Square
[b]df = degrees of freedom

The regression models for the two SES's are seen in Table 4.4 and 4.5. For those who are HSES, the Wald statistic indicates BMI was not a significant predictor for PTB. In contrast, the BMI for those who were LSES, was a significant factor in PTB. For every increase in BMI, there was a decrease in the probability of PTB (OR = 0.929, 95% CI 0.926 – 0.933, P < 0.001). As with the overall sample, those who were LSES also had a curved relationship with PTB. In figure 4.2, illustrates that for LSES women, BMI increases the odds of PTB decreases until the BMI has a value of approximately 40-45 where the probability of PTB starts to increase.

Table 4.4 Logistic Regression for HSES Population

Predictor	β	P-Value	Odds Ratio	95% Confidence Interval
Constant	2.417	<0.001		
Age	- 0.103	<0.001	0.902	0.889 – 0.916
Age Squared	0.002	<0.001	1.002	1.002 – 1.002
BMI	-0.003	0.239	1.003	0.998 – 1.008
BMI Squared	<0.001	<0.001	1.000	1.000 – 1.000
Weight (Wt.) Gain	-0.042	<0.001	0.958	0.957 – 0.959
Weight Gain	<0.001	<0.001	1.000	1.000 – 1.000
Prior PTB	0.753	<0.001	4.504	4.418 – 4.592
Single	0.096	<0.001	1.212	1.192 – 1.233
Previous Births	-0.165	<0.001	0.718	0.711 – 0.725
Smoked during Pregnancy	0.116	<0.001	1.26	1.216 – 1.305
Prenatal Care	-0.418	<0.001	0.433	0.412 – 0.455
Pre-existing HTN	0.517	<0.001	2.810	2.740 – 2.881
Gestational HTN	0.632	<0.001	3.543	3.495 – 3.592
Pre-existing DM	0.441	<0.001	2.418	2.329 – 2.511
Gestational DM	0.087	<0.001	1.189	1.170 – 1.209
Race				
Black vs White	0.192	<0.001	1.414	1.390 – 1.438
Other Races vs Whites	-0.038	<0.001	1.124	1.112 – 1.137

R^2 = 0.026 *Max rescale R^2 = 0.072*

Tests

	X^2[a]	df[b]	P-Value
Overall Model Evaluation			
Likelihood Ratio Test	91,875.49	17	<0.001
Score Test	122,163.33	17	<0.001
Wald Test	101,812.73	17	<0.001
Goodness of fit test			
Hosmer & Lesmeshov	1,329.09	8	<0.001

[a]X^2=Chi Square
[b]df = degrees of freedom

Table 4.5 Logistic Regression for LSES Population

Predictor	β	P-Value	Odds Ratio	95% Confidence Interval
Constant	1.908	<.0001	[redacted]	
Age	0.011	0.1502	1.011	0.996 – 1.025
Age Squared	<0.001	0.081	1.000	1.000 – 1.000
BMI	-0.074	<.0001	0.929	0.926 – 0.933
BMI Squared	<0.001	<.0001	1.001	1.001 – 1.001
Weight (Wt.) Gain	-0.032	<.0001	0.958	0.957 – 0.959
Weight Gain	<0.001	<.0001	1.000	1.000 – 1.000
Prior PTB	0.624	<.0001	3.485	3.432 – 3.538
Single	0.091	<.0001	1.200	1.188– 1.213
Previous Births	-0.069	<.0001	0.871	0.857 – 0.885
Smoked during Pregnancy	0.146	<0.001	1.34	1.322 – 1.358
Prenatal Care	-0.543	<0.001	0.337	0.330 – 0.345
Pre-existing HTN	0.503	<0.001	2.736	2.648 – 2.807
Gestational HTN	0.580	<0.001	3.189	3.139 – 3.239
Pre-existing DM	0.502	<0.001	2.727	2.648 – 2.807
Gestational DM	0.131	<0.001	1.299	1.278 – 1.321
Race				
Black vs White	0.186	<0.001	1.326	1.307 – 1.345
Other Races vs Whites	-0.089	<0.001	1.008	0.995 –1.020

R^2 = 0.045   *Max rescale R^2 = 0.096*

Tests	X^{2a}	df^b	P-Value
Overall Model Evaluation			
Likelihood Ratio Test	90,249.64	17	<0.001
Score Test	113,981.33	17	<0.001
Wald Test	93,693.35	17	<0.001
Goodness of fit test			
Hosmer & Lesmeshov	718.76	8	<0.001

[a]X^2=Chi Square
[b]df = degrees of freedom

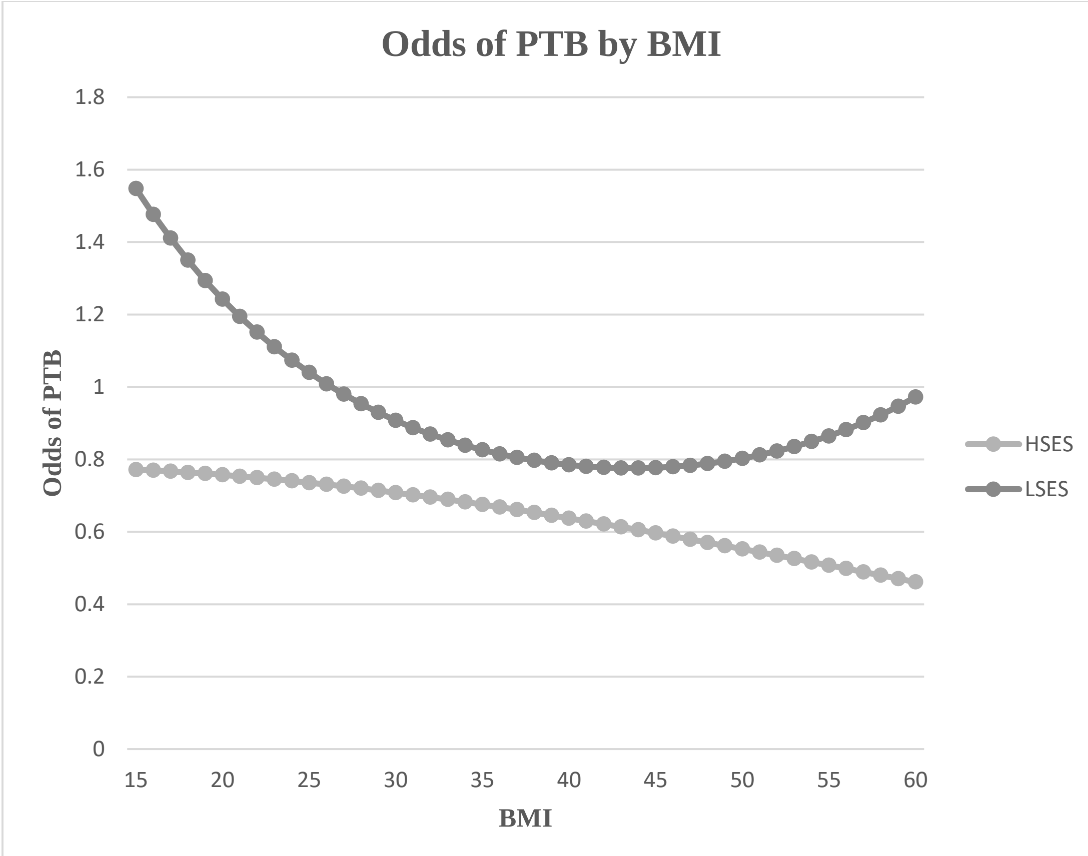

Figure 4.2 BMI Curves for HSES and LSES - Curves derived from logit formula: logb p/1 – p = β0 + βBMIX + βBMISqX2 (β0 = constant + all variables*mean or percentage values). Odds were derived from logit by taking the exponent of the logit result. Probability = 1/1+odds.

4.5 Discussion

The results indicate an obesity paradox in PTB for mothers who are LSES. An obesity paradox is a phenomenon where obesity is shown to be protective and associated with better outcomes than being normal weight. This has been demonstrated in other areas of medicine and epidemiology. In a study by Hainer, there was evidence of an obesity paradox with peripheral arterial disease, where the overall mortality rates decreased with increasing BMI. Those who were of normal weight had a mortality of 50% which was greater than the rates for those who were overweight and obese who had rates of 40%

and 31%, respectively.(Hainer & Aldhoon-Hainerová, 2013) Flegal et al. found that for all-cause mortality, Grade 1 obesity overall was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality than being normal weight. This study did find that obesity grade 2 and 3 were associated with higher all-cause mortality demonstrating a similar curvilinear pattern that was seen in this study. (Flegal, Kit, Orpana, & Graubard, 2013)

Sharifzadeh et al. found that PTB had a negative correlation with maternal BMI ($r = -0.124$, $p = 0.004$). This study also found that within their sample, those who were underweight had a PTB rate of 42.9% while those who were overweight and obese had rates of 5.1% and 5%, respectively.(Sharifzadeh et al., 2015) In another study completed by Kosa et al., when they categorized BMI, the only category that had significantly increased odds of PTB was the underweight group. This group had 2.11 greater odds of PTB using normal weight as a reference.(Kosa et al., 2011)

In general literature there is not a consensus concerning maternal weight and PTB. There are several studies that had findings contrary to this study. According to the meta-analysis, MacDonald et al. had results that indicated that the risk of preterm birth appeared significantly higher in overweight and obese women (1.24, 1.13 to 1.37).(McDonald et al., 2010) Khatibi et al. also found that increased body mass index was associated with an increased risk of PTB with adjusted odds ratio (aOR) ranging from 1.11 (95% confidence interval [CI], 1.03–1.20) for preobesity to 2.00 (95% CI, 1.48 –2.71) for grade-III.(Khatibi et al., 2012) One thing that can account for the disconnect is that many studies examine BMI as a linear phenomenon. In our study, we found that BMI (as well as age and weight gain) does not have a linear relationship with PTB, but rather a curvilinear one where the linear relationship changes after a certain point. In our study, we found that for LSES women, when BMI increases up to 40 – 45, odds of PTB decreases. Once a BMI that is greater than 45 is reached, the rate of PTB begins to increase.

Another finding was that BMI was a significant factor for LSES women and not for HSES women. While the difference that was found has not been explored for PTB, there have been studies that examined weight differences between the SES's. Paeratakul et al. examined the perception of weight based on SES and found that those with a higher income (greater than 350% higher than poverty rate) had a higher percentage perception of being overweight than those who were of a lower income (50.2% vs 44.2%) p = 0.002. They also found that those with higher education (HS graduate and above) had 1.6 greater odds of having a perception of being than those with a lower education.(Paeratakul et al., 2002) Results of this study indicate that those who have a higher perception of being overweight may work harder to lose weight. This finding is consistent with a meta-analysis by Sobal et al., who found that women of a HSES diet more often than do women of LSES and tend to be more committed to the view that slimness is desirable making them personally motivated to attain slim figures.(Sobal & Stunkard, 1989)

Given the differences in perceptions of weight, BMI may not be significant in HSES women. This may be secondary HSES women working toward an ideal of slimness. This is facilitated by their access to resources including expensive foods that are perceived as aids to dieting and more leisure time and greater opportunity for recreational exercise. Also, HSES women have access to high quality health care that can help offset the BMI effect.   LSES women who are of lower BMI may be food insecure while those who are obese have greater access to food, thus giving them the nutrition needed to have a non-PTB baby.

4.5.1 Clinical Implications

Although study results showed evidence that obesity is protective against PTB in LSES women, this should not infer that there should be less care given to this population. In our data, we found that those who are obese (BMI greater than 30) have almost 5 times greater odds of having pre-existing HTN, 2.5 times greater odds of having gestational HTN, 4.5 times greater odds of having pre-existing DM and 2.8 times greater odds of having gestational DM than those who are of normal weight. These are issues that require extra supervision for the mother and the child.

In conjunction with care for those who are LSES and obese, there should be extra attention paid to those who are under and normal weight particularly if they are LSES. Given that nutritional status before pregnancy can have an effect on pregnancy outcomes, where possible, family planning should be provided. During the planning, nutrition and lifestyle should be discussed. This should also be done in conjunction with a social worker who can aptly address issues of food security or other health problems. During the early stages of pregnancy, there should be closer attention paid to nutritional status through blood screening for anemia and vitamin deficiencies. This may help improve maternal and fetal well-being.

Another issue identified in the data is that LSES women have almost 15 times greater odds of smoking than HSES women. LSES women who were underweight and normal weight had a higher percentage of smoking (18%) than those who were overweight and obese (14%). Although smoking is linked to many maternal and fetal issues, it contributes to a host of problems for those who are underweight and of normal BMI including reducing the appetite and thus exacerbate any nutritional deficits. For those who smoke, there should be encouragement and counseling to participate in smoking cessation programs.

In general, pregnant women of normal weight may be regarded as healthier and not high risk. Regardless, the above recommendations could potentially help reduce the rate of PTB within this sector of the pregnant population.

4.5.2 Strengths and Limitations of the Study

The major strength of our study was the sample size the wealth of data that we were able to obtain. We were able to get a full population of the births in the U.S. from the last 4 years and obtain over 15 million records. This data was very reliable as it was from the National Vital Statistics System of the National Center for Health Statistics. This organization received birth data from all 50 states and Washington, DC.

Some limitations of the study were that there was no variable to distinguish whether the incidence of PTB was spontaneous or induced. There was no specific PTB variable, it had to be derived from the data on gestational age. There was also a lack of data for income and occupation for the person in each record. This led U.S. to use education and insurance status to determine our SES. While this was an indirect way to determine the SES, these elements are commonly used in other studies as a measure of SES.

4.6 Conclusion

Our study has found an obesity paradox in PTB for those women who are LSES. This has the potential to change the practice of prenatal care of normal weight women. It was also found that the relationship between BMI and PTB is not linear but curvilinear indicating that after a certain BMI is reached, the relationship between these two elements change from being inverse (as BMI increases, the odds of PTB decreases) to being a direct relationship (as BMI increases), the odds of PTB start to increase. We also found that while weight is a significant factor in LSES women, it is not significant in HSES women. This can be due to the SES differences in access to foods and lifestyles that lead to healthier weights.

CHAPTER 5

A RE-EXAMINATION OF THE RELATIONSHIP BETWEEN RACE AND PRETERM BIRTH

5.1 Abstract

5.1.1 Introduction

In an editorial “**Beyond nature versus nurture: race matters, but how?**” Terplan made a call to “*thoroughly consider the implications of race in their research or assess other factors that might confound apparent associations of outcomes with race* .” By examining race as an independent and complimentary factor in spontaneous preterm birth (SPTB), this work seeks to provide evidence that the relationship between race and SPTB is effected by interactions with other social and health determinants.

5.1.2 Methods

This is a retrospective cohort study sources by the 2018 U.S. Natality File which is provided by the National Vital Statistics System within the National Center for Health Statistics. Statistical methods used for this study were two logistic regression models, random forest and gradient boosting machine where SPTB is the dependent variable.

5.1.3 Results

The first model ran treated race as an independent variable. This model showed that being Black increased odds of SPTB (aOR 1.27, 95% CI 1.22 – 1.32, $P < 0.001$) when compared to White women. The second model we ran examined the interaction effect of race and other variables. It was that the introduction of interaction terms took away the independent significant relationship between SPTB and race ($p < 0.001$ to $p = 0.272$) For members of the Black race, interactions with the following factors increased odds of SPTB: number of prenatal visits (aOR 1.034, 95% CI 1.024 – 1.045, $p < 0.001$); previous birth/pregnancy (aOR 1.154, 95% CI 1.046 – 1.273, $P = 0.004$); marital status

being single (aOR 1.265, 95% CI 1.151 – 1.390, $P < 0.001$); and metabolic issues (aOR 1.133, 95% CI 1.026 – 1.251, $P = 0.013$).

5.1.4 Conclusion

The results of this study provides evidence that despite the PTB rate being far higher than for Whites, being Black in and of itself is not a risk factor in PTB. It is the living in an environment of social disadvantage that causes illness that creates greater risk for SPTB among other birth outcomes.

5.2 Background/Introduction

Racial disparities in preterm birth (PTB) are well-documented. According to the National Center for Health Statistics final natality data; the U.S. preterm birth (PTB) rates were highest for black infants (13.8%), followed by American Indian/Alaska Natives (11.6%), Hispanics (9.6%), Whites (9.1%) and Asian/Pacific Islanders (8.7%).("March of Dimes Peristats," 2020) The differentials between Black and White women have also been observed in Canada and Europe. McKinnon et al. used the Canadian Live Birth, Infant Death and Stillbirth Database and the 2006 Canadian census data. They found Black mothers had an 8.9% PTB rate and White mothers had a 5.9% rate (RR 1.49, 95% CI 1.32 – 1.66).(McKinnon et al., 2016) In a study of European women by Patel et al., the researchers Black women had greater odds of PTB then White (aOR 1.33, 95% CI 1.15 – 1.56).(R. R. Patel et al., 2004)

The disparity between Black and White women does not seem to decrease leading to investigators initiating studies to determine the causes. Desisto et al. did a Oaxaca decomposition analysis that found that factors that contributed to the differences was that Black women were more likely to have hypertension and diabetes, have birth paid for by

Medicaid and were less likely to be married.(DeSisto et al., 2018) There have also been epigenetic explanations that have been cited. According to Purisch et al., Macones et al. found that carriers of the *TNF-2* allele had a twofold greater risk of spontaneous preterm birth. Despite similar carrier frequencies for the allele, the relationship between *TNF*-2 and spontaneous preterm birth was stronger in African Americans (OR = 2.5, 95% CI: 1.4–4.5) than in Caucasians (OR = 1.6, 95% CI: 0.5–5.2). This study also found that TNF-2 may have a gene-environment interaction that is important in determining risk.(Purisch & Gyamfi-Bannerman, 2017)

Many studies indicate that many of the factors that may cause Black women within the U.S. to have higher rates of PTB is related to the surrounding environment as opposed to something intrinsic. This leads to the question of whether being Black is an independent risk factor just because they have higher rates.

When examining race as a construct, a 2002 Stanford study lead by Rosenberg et al. examined the question of human diversity by looking at the distribution across seven major geographical regions of 4,000 genetic alleles. The investigators found that over 92% of alleles were found in two or more regions while almost half of the alleles studied were present in all seven major geographical regions. The observation that the vast majority of the alleles were shared over multiple regions, or even throughout the entire world, points to the fundamental similarity of all people around the world. If separate racial or ethnic groups actually existed, we would expect to find “trademark” alleles and other genetic features that are characteristic of a single group but not present in any others. (7.4% of all the alleles were found in one group).(Chou)

In examining race and health, Kaufman et al. conducted a genetic study examining cardiovascular disease, diabetes etc. The investigators found that only 3% of racial disparities are due to genetics thus leaving 97% due to social origin.(Kaufman, Rushani, & Cooper, 2018)

If being a member of the Black race (of African descent) was an independent factor, then it would stand to reason that all members would have elevated risk of PTB. There are several studies that have shown differences between Black women who were born in the U.S. and those born outside of the U.S. (Africa and Caribbean) One study was by Elo et al. which found that U.S. Born Black women had greater odds of preterm than those who were foreign born (OR 1.37, 95% CI 1.32 – 1.42) and close to two times greater odds than Black women from sub-Saharan Africa (OR 1.79, 95% CI 1.69 – 1.90). This study showed that women from some sub-Saharan Africa nations had lower rates than White U.S. born women. (Elo, Vang, & Culhane, 2014) Collins et al. did a study where they examined U.S. and foreign born Black and White women. The investigators found that foreign born Black women were the only group of women who had increases in the rate of low birth weight children in the third generation (40% greater than generation 2) and a decrease in birthweight (57 grams less than generation 2)(J. W. Collins, Jr., Wu, & David, 2002)

In an editorial "*Beyond nature versus nurture: race matters, but how?",* Terplan stated "*Although federal requirements serve to promote racial inclusiveness in research, this tallying does not come with the additional requirement that authors thoroughly consider the implications of race in their research or assess other factors that might confound apparent associations of outcomes with race. This deficit, unfortunately, has led to an abundance of racial associations with a corresponding paucity of causation* *assessments".(Terplan, 2007)*

This paper will seek to respond to the call to "*thoroughly consider the implications of race in their research or assess other factors that might confound apparent associations of outcomes with race.*" It will expand the conversation to race by examining it as an independent and complimentary factor in PTB. This will provide evidence that race is societal factor that is effected by interactions with other social and health determinants.

5.3 Study Methods

The data was be retrieved from the 2018 U.S. Natality files. This data is provided by the National Vital Statistics System within the National Center for Health Statistics. The file was retrieved from the National Bureau of Economic Research website (nber.org). These files provided demographic and health data for births occurring during the calendar year. Once data was collected, those who are included were be as follows:

- Identified as non-Hispanic Black and non-Hispanic White
- Aged 20 – 35
- Singleton births
- Those with either Private or Medicaid Insurance

We then created a socio-economic status (SES) variable. Those who were considered higher SES (HSES) were those who have a minimum college education and private insurance. Those who were considered lower SES (LSES) were those who have a maximum high school diploma and are enrolled in Medicaid. Those who did not fit this criteria were excluded from analysis. This left us. with a file that had 7% PTB. We further excluded those who had medically indicated in order that we would only include those with spontaneous PTB (SPTB). Given the low percentage of PTB in the file, we balanced the data by creating a file of those with SPTB and another file with the same number of randomly selected controls who did not have a SPTB. We then consolidated a file that had all the data that would be included in analysis.

Statistical analysis was completed using the logistic regression models with 10-fold validation, random forest and gradient boosting machine (GBM) The dependent variable was be SPTB (Yes or No) and the independent variables included race, SES, other demographics, prior medical history and social history. Race was coded so that "White" and SES was coded so that "HSES" and they served as the respective reference. For the logistic model, we ran one model assuming that race was an independent factor and another model where race is examined independently and in interaction terms. Random Forest and GBM were also run for the model with race as an independent and part of an interaction term. Three models were run to verify the initial results indicating that the independent race variable was not as important as some of its interaction SAS 9.4 and R was used for analysis.

5.4 Study Results

The full file included 3,801,534 records. After making exclusions and balancing of the data, the final file had 100,886 records. White women accounted for 82% of the data while Black women accounted for 18%. Seventy one percent of the sample were considered HSES while 29% would be considered LSES. The mean age for the mothers in the study was 31.6 (+/- 4.2) years of age. The average age of White women was 31.8

(+/- 4.1) years of age and 31 (+/- 4.5) years of age for Black women. The mothers who were HSES has an average age of 32.4 (+/- 4) while LSES women had an average age of 30 (+/- 4.2) at the birth of their children.

Of all the Black women in our data, we found that 57% had PTB while there was a 42% rate of PTB for White women. For those who were HSES, the rate of PTB was 40% while the rate for those who were LSES was 56%.

The first model that we ran treated the race as an independent variable. This model showed that race was a significant factor in SPTB. The results indicated that members of the Black race had greater odds of SPTB than members of the White race (aOR 1.27, 95% CI 1.22 – 1.32, P < 0.001). The model had an area under the curve (AUC) of 0.73. When a 10-fold cross-validation was run, the AUC ranged from 0.729 to 0.731 indicating that the folds were consistent with the full model results. The model predicted SPTB with a sensitivity of 48% and a specificity of 82%. (Table 5.1)

The second model we ran examined the interaction effect of race and other variables had with SPTB and if these factors remained an independent significant factor. What we found was that the introduction of interaction terms took away the independent significant relationships that race (p < 0.001 to p = 0.213) had with SPTB. The model showed that many of the interaction terms were more significant than the independent term. For members of the Black race, interactions with number of prenatal visits (aOR 1.034, 95% CI 1.024 – 1.045, p < 0.001); previous birth/pregnancy (aOR 1.154, 95% CI 1.046 – 1.273, P = 0.004); marital status being single (aOR 1.265, 95% CI 1.151 – 1.390, P < 0.001); and metabolic issues (aOR 1.133, 95% CI 1.026 – 1.251, p = 0.013) were more significant than race as an independent factor. (Table 5.1) The AUC for the model was 0.734 and the 10k fold range was 0.733 – 0.735. The model predicted SPTB with a sensitivity of 51% and a specificity of 81%.

Table 5.1 Models for SPTB with and without Interaction Terms

	Model 1				Model 2			
		95% Confidence Intervals		Pvalue		95% Confidence Intervals		Pvalue
Effect	Odds Ratio	Lower	Upper		Odds Ratio	Lower	Upper	
Maternal Age	0.893	0.854	0.934	<.0001	0.9	0.858	0.943	<.0001
Maternal Age Sq	1.002	1.002	1.003	<.0001	1.002	1.001	1.003	<.0001
Age*Race					0.996	0.986	1.005	0.3779
Age*SES					0.995	0.986	1.003	0.2115
BMI	0.968	0.956	0.979	<.0001	0.966	0.955	0.978	<.0001
BMI Sq	1.000	1.000	1.001	<.0001	1.001	1	1.001	<.0001
BMI*Race					1.001	0.996	1.007	0.6251
BMI*SES					0.98	0.975	0.985	<.0001
Weight Gain	0.972	0.969	0.975	<.0001	0.97	0.967	0.973	<.0001
Weight Gain Sq	1.000	1.000	1.000	<.0001	1	1	1	<.0001
Weight Gain * Race					1.003	1	1.005	0.03
Weight Gain * SES					1.004	1.002	1.007	0.0001
Number of PreNatal Visits	0.677	0.668	0.686	<.0001	0.633	0.624	0.642	<.0001
Number of PreNatal Visits Sq	1.01	1.009	1.01	<.0001	1.011	1.01	1.011	<.0001
Number PreNatal Visits * Race					1.034	1.024	1.045	<.0001
Number PreNatal Visits * SES					1.097	1.088	1.107	<.0001
SES	1.213	1.159	1.269	<.0001	0.738	0.537	1.016	0.0629
Race	1.269	1.218	1.323	<.0001	0.791	0.546	1.144	0.213
Race*SES					0.788	0.71	0.875	<.0001
Gravity/Parity	0.856	0.829	0.883	<.0001	0.813	0.784	0.844	<.0001
Gravity/Parity * Race					1.154	1.046	1.273	0.0042
Gravity/Parity * SES					1.182	1.08	1.293	0.0003
Marital Status - Single	1.132	1.084	1.182	<.0001	1.031	0.959	1.109	0.4101
Marital Status - Single * Race					1.265	1.151	1.39	<.0001
Marital Status - Single * SES					1.031	0.944	1.127	0.4916
Smoker	1.155	1.093	1.22	<.0001	1.241	1.076	1.431	0.0031
Smoker * Race					1.058	0.926	1.208	0.4087
Smoker * SES					0.898	0.768	1.05	0.1791
Metabolic Disease	2.28	2.198	2.365	<.0001	2.163	2.066	2.265	<.0001
Metabolic Disease * Race					1.133	1.026	1.251	0.0132
Metabolic Disease * SES					1.072	0.983	1.169	0.1155
Sexually Transmitted Disease	0.949	0.831	1.084	0.4408	0.963	0.846	1.097	0.5728
	AUC = 0.73				*AUC = 0.734*			
	Sensitivity = 0.48				*Sensitivity = 0.51*			
	Specificity = 0.82				*Specificity = 0.81*			

5.4.1 Comparison of Models

In addition to the logistic regression models, random forest and GBM models were run where we were able to assess the importance of the race variable and then also compare the confusion matrices that assess the performance of each of these models.

The logistic regression variable importance summary is in Figure 5.1. This figure shows that the factors that contributed to the model were number of prenatal visits, number of prenatal visits squared, metabolic disease, the interaction between SES and number of prenatal care visits and weight gain. As is consistent in the model, race interactions (with number of prenatal care visits and marital status) show to be more important than the independent race variable.

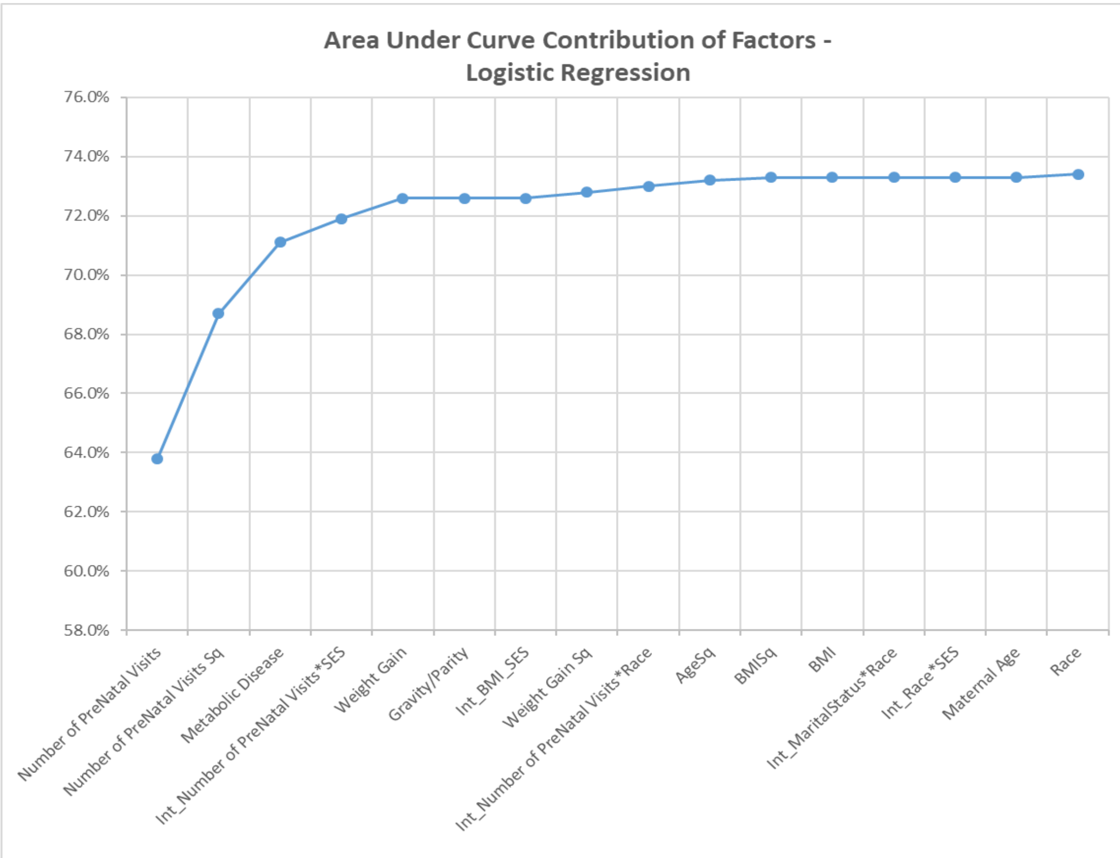

Figure 5.1 Logistic regression variable importance chart. Variable importance was derived by determining which variables contribute the greatest increase to the area under the curve.

We also ran a random forest where we assumed that the “variables to try” was 5 and the train test split was 60%/40%. Figure 5.2 shows the order of variable importance. All the variables within the figure are those with a “out of bag” (test data) GINI with greater than 0. This is due to the fact that any variable with a GINI value at zero or less than zero make no contribution to the model. The results are similar to that of the logistic regression in that number of prenatal visits, number of prenatal visits squared, metabolic disease, the interaction between SES and number of prenatal care visits were shown to have the greatest impact in PTB. This figure also showed that race interaction with metabolic disease was more important than the independent race variable.

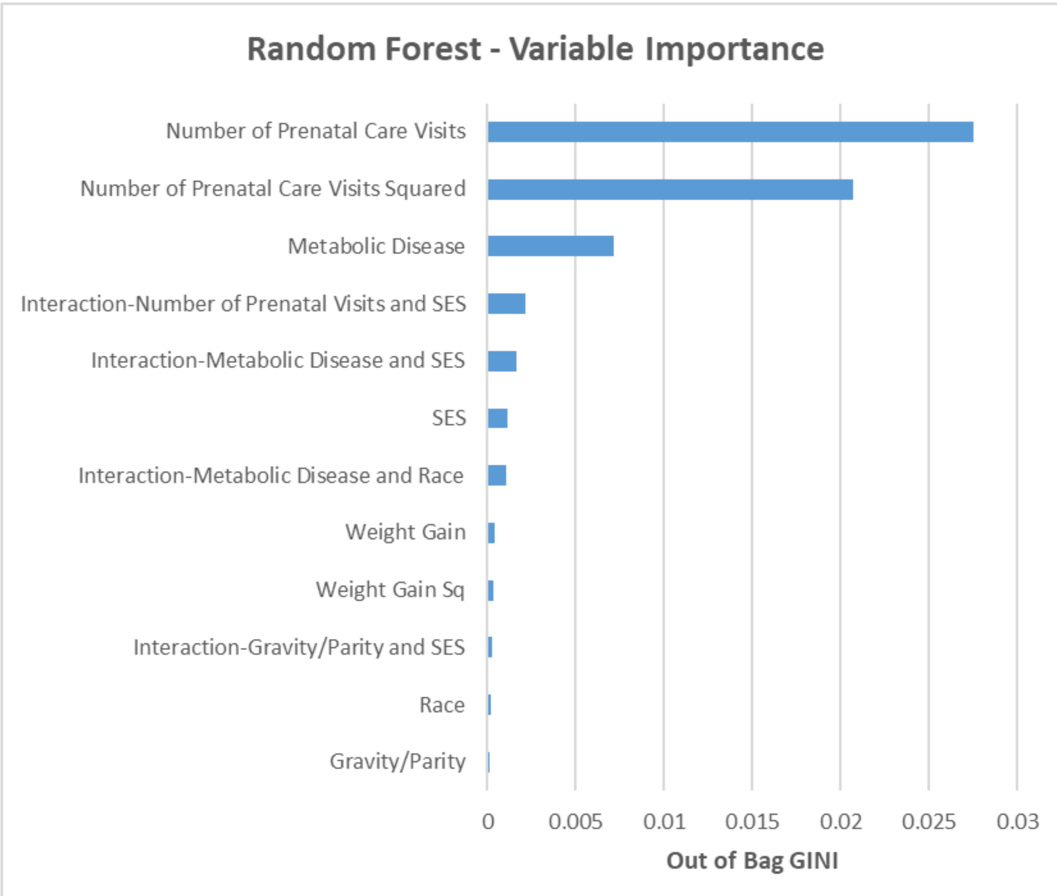

Figure 5.2 Random Forest – variable importance chart. Ran model using vars to try= 5, train/test split of 40%/ 60%.

We also ran a GBM where we assumed a train test split was 60%/40%. Figure 5.3 shows the order of variable importance. The results are similar to that of the logistic regression and random forest in that number of prenatal visits and metabolic disease were shown to have the greatest impact in PTB. This figure also showed that all of the race interactions were more important than the independent race variable.

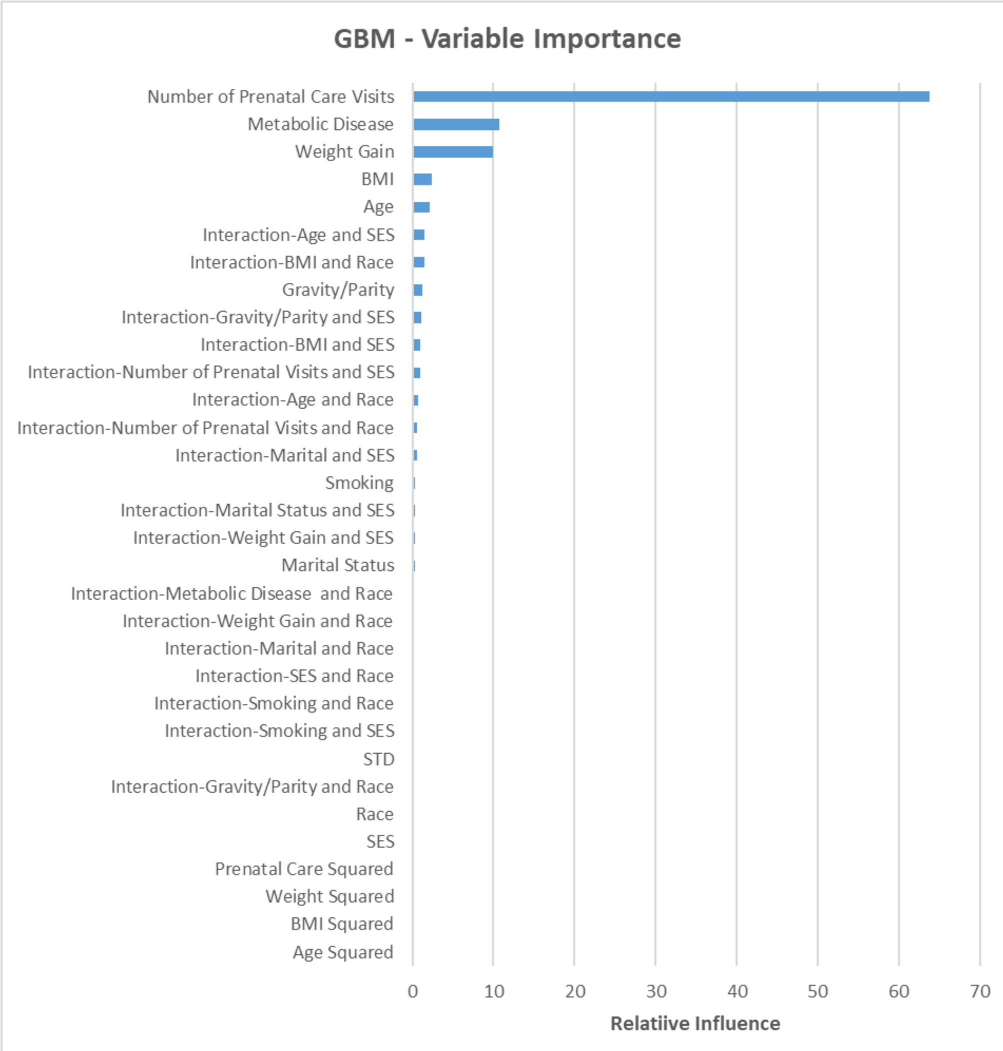

Figure 5.3 GBM Variable importance chart

The confusion matrices for these three models showed that area under the curve (AUC) were similar for their train and test data. Logistic regression model had an AUC of 72.6% and 73% for the training and testing data, respectively. The random forest had an AUC of 74.5% and 71.7% for their training and testing data, respectively. The training and testing AUC for GBM was 73.2% and 73.3%, respectively. There were slight deviations in the sensitivity and specificity for the models. The most sensitive model was the GBM while the logistic regression model has the highest specificity (Table 5.2.).

Table 5.2 Confusion Matrices

	Logistic Regression		Random Forest		Gradient Boosting	
	Training	Testing	Training	Testing	Training	Testing
AUC	72.6%	73.0%	74.5%	71.7%	73.2%	73.3%
Sensitity	51.0%	51.3%	70.8%	69.2%	71.4%	71.7%
Specificity	80.0%	80.3%	66.8%	63.1%	61.8%	61.8%

5.5 Discussion

This paper is a response to call of the editorial by Terplan which stated that research should "*thoroughly consider the implications of race in their research or assess other factors that might confound apparent associations of outcomes with race*". Terplan also suggested that although the federal government does require race to be included as factor in research, it does not go far enough. The editorial stated that because of this limitation, authors are not required to "*consider the implications of race (or SES) in their research or assess other factors that might confound apparent associations of outcomes with race (or SES). This deficit, unfortunately, has led to an abundance of racial associations with a corresponding paucity of causation assessments"*

The results of the paper provides evidence that Terplan's assessment is correct. When the model was run with race as an independent factor, it was shown to have a significant association with SPTB. When the race was interacted with other factors, it was no longer significant in determining the odds of SPTB. The addition of the interaction terms eliminated the independent relationship of race ($p < 0.001$ to $p = 0.272$). The random forest analysis and GBM results also showed that the effect of the independent race factor was eclipsed by the interaction terms that include race.

This provides evidence of the statement, "disparities have little to do with being Black in and of itself, but what it *means* to be Black in society". This is evident in the interactions that were more significant than race as an independent term. The interaction of Black race and number of prenatal visits showed increased odds of SPTB for every unit increase in the number of prenatal visits attended (aOR 1.039, 95% CI 1.023 – 1.056, $p < 0.001$). This finding provides further evidence of the "Weathering Hypothesis". This was initially proposed by Geronimus et al. and postulated that the health of African-American women may begin to deteriorate in earlier adulthood than their White counterparts as a physical consequence of cumulative social and economic disadvantage. In this specific study that was examining birth outcomes based on age, they found that while White mothers who were in their 20's had a birth advantage over teenagers while Black teenage mothers had birth advantages over all other ages.(Geronimus, 1992) When looking at the independent prenatal visits variable, it is notable that it is protective against SPTB (up to a certain number of visits) whereas for those who are Black, there is increased. One could conclude that the reason why we see opposing relationships is that Black women may be initiating prenatal care with more risk than their White counterparts.

The interaction of being Black and having previous pregnancies showed that there is an increased odds of SPTB (aOR 1.145, 95% CI 1.009 – 1.300, $P = 0.035$). This relationship is also opposite of the relationship of the independent previous pregnancy factor (aOR 0.815, 95% CI 0.785 – 0.846, $P < 0.001$) which has a protective relationship with SPTB. The reason for the positive interaction is possibly due to the pregnancy history of Black women. According to the file, in 2018, Black women had 54% greater odds of experiencing a prior PTB. Generally those who experience prior PTB had 4.6 times greater odds of SPTB in their current pregnancy. The interaction between Black race and metabolic issues as marked by a prior history or current/gestational diabetes and/or hypertension increased the odds of PTB (aOR 1.143, 95% CI 1.034 – 1.262, P = 0.009).   This is consistent with Berger et al. who found that those who had diabetes and HTN had 3 times greater odds of SPTB. (Berger et al., 2020)

The findings of this study can be encouraging for because being a member of a certain race is immutable. If an immutable characteristic is a risk factor, then that would create a problem that cannot be fixed.   But if that characteristic is affected by other factors that can change, then work can be done to reduce the incidences of SPTB and reduce its cost to society. The factors that have significant interactions with being a member of the Black race are related to health. Given these results, the initiation of health programs would is a solution that has been shown to be successful. An example of this is the CDC REACH (Racial and Ethnic Approaches to Community Health) program that seeks to reduce disparities between the races and ethnicities. They do this though providing grants to non-profits and local governments whose mission and purpose is to reduce the disparities in the burden of chronic diseases like hypertension, heart disease, Type 2 diabetes, and obesity through culturally tailored interventions to address preventable risk behaviors (i.e., tobacco use, poor nutrition, and physical inactivity). From the years of 2014-2018, this program has provided 2.9 million people with improved access to healthy foods and beverages, over 332,000 benefited from smoke-free intervention and 830,000 were given access to local chronic disease programs that are linked to clinics. While these are great programs, the rate of PTB for Black women are still 50% greater than their White counterparts(CDC, 2019a).

The missing link may not be the prevalence of programs, but the presence of Black medical staff. According to the Association of American Medical Colleges (AAMC), 5% of active physicians identified as Black or African American. Considering that Black people comprise of 13.9% as per the 2019 census estimates, these number are out of balance.("Diversity in Medicine: Facts and Figures 2019," 2019) This is more apparent when comparing the White population share (60.3% in the U.S.) to the percentage of practicing physicians who identify as White (56.2%). Some of the reasons why having a Black physician be advantageous to Black patients are that Black physicians may be able to provide higher quality of care to Black patients. There have been studies that have found that when Black men had Black physicians, these men were more likely to get invasive, preventative services and care. Alan et al. found that Black doctors wrote more additional notes on their Black cardiovascular patients than the non-Black doctors. They also found that they spent more time with their patients because their patients agreed to have more life-saving screenings. These findings suggested that the Black-white disparity in cardiovascular mortality can be reduced by 10%.(Alsan, Garrick, & Graziani, 2019) It was also found that racial concordance between patient and physician also impacted the level of trust within the relationship. In Saha et al., they had the sample watch several d one of 16 vignettes depicting a physician reviewing cardiac catheterization results and recommending coronary artery bypass graft (CABG) surgery. Vignettes differed on physicians' race, gender, age, and communication style. They found that the Black patients gave the Black physicians higher scores on all attributes and were more willing to undergo CABG as necessary. (Saha & Beach, 2020) These studies indicate that there should be a greater push to train and recruit Black physicians to counteract potential implicit bias and to promote healthy compliance and trust by their Black patients.

A strength of this study was the large sample that was taken from all births in 2018. Another strength of this study was the fact that we were able to delineate those who had spontaneous PTB birth and medically indicated PTB. This was important to make this distinction because the one is biologically determined while the other is determined by a physician based on guidelines provided. This study was also made strong by the examination of the interaction of race with other factors. This is something that has not been done in disparity studies and was in response to a need expressed by Terplan. Some weaknesses of the study was that the preterm birth variable was not in the file and had to be created. Another weakness of the study was that there was not data on the file that could be used as a measure for implicit bias. While literature has indicated that implicit bias is dangerous to Black women who are pregnant, it would have been strong to have variables that could measure the impact of bias on the PTB rates.

5.6 Conclusion

The results of this study provides evidence that despite the SPTB rate being far higher than for Whites, being Black in and of itself is not a risk factor in PTB. It is the living in an environment of social disadvantage that causes illness that creates greater risk for PTB among other birth outcomes.

CHAPTER 6

COST EFFECTIVENESS ANALYSIS: PRETERM BIRTH AND BIRTHING FACILITIES

6.1 Abstract

According to the March of Dimes Global action report, preterm birth (PTB) rates are on the rise in most countries. It is now the single most important cause of neonatal deaths (babies under 28 days) and the second leading cause of death in children under age 5. There is evidence that the use of midwifes and non-hospital births (community births) can potentially be a missing link in the reduction of PTB while reducing the cost of care. In this study we did a cost effectiveness analysis examining which was most cost effective location of birth in the U.S. with respect to PTB: standard hospital, free-standing birth centers or home births. We used TreeAge Pro for analysis that provided decision trees and probabilistic sensitivity analysis. It was found that free-standing birth centers were most cost effective with the lowest cost of birth and the lowest rate of PTB. It is the hope that this analysis would motivate Medicaid administrators to promote that use of birthing centers by rethinking how much coverage they provide for care at these facilities.

6.2 Background / Introduction

According to the March of Dimes Global action report, PTB rates are on the rise in most countries. It is now the single most important cause of neonatal deaths (babies under 28 days) and the second leading cause of death in children under age 5. Preterm babies have more morbidities, greater risk of neonatal intensive care unit (NICU) admission, 20%

greater risk of complications and 5% greater chance of developing an intellectual or developmental disability.(Dolezel, 2019) In 2019, the incidence of PTB in the U.S. increased for the fourth year in a row to 10.02%.(B. E. Hamilton, Martin Joyce A., Osterman Michelle J.K. , M.H.S., Rossen, Lauren M. , 2019) This translated to a total cost of $26 billion dollars to the healthcare system and society at-large. There is evidence that the use of midwifes and non-hospital births (community births) can potentially be a missing link in the reduction of PTB while reducing the cost of care.

The use of midwifery services has been shown to have outcomes that are comparable to standard pregnancy care. There are three types of midwives:

- Certified Nurse Midwife (CNM)
- Certified Midwife (CM)
- Certified Professional Midwife (CPM).

These certifications differ in level of education required and their credentialing organizations. CNM and CM's are required to have a minimum of a master's degree and are under the credentialing authority of the American Midwifery Certification Board. CNM's are authorized to practice in all states while CM's are authorized to practice in five states. CPM's are required to graduate from an approved midwifery education accreditation council (MEAC) program or school and are credentialed by the North American Registry of Midwives (NARM). They are authorized to practice in 34 states. The Midwifery Model of Care is defined by three actions:

- Identify - Recognize the woman as a unique individual in the context of her family and community
- Advocate – supports and protects the physiologic process of labor and birth

- Empower – established the woman as an active partner in her own care. (Improving Maternal Health Access, Coverage, and Outcomes in Medicaid A Resource for State Medicaid Agencies and Medicaid Managed Care Organizations, 2020)

Outside of hospitals, midwives also practice in free standing birthing clinics (FSBC) and preside over home births. FSBC's are non-hospital facilities organized to provide family-centered maternity care for women judged to be at low-risk for obstetrical complications. Its model of care includes the primary health provider that delivers prenatal care and stays with the woman during labor from the time of admission through the immediate postpartum period. Given that the concept of FSBC's were developed by CNM's, the FSBC shares in their philosophy of care which views childbirth as a natural healthy process and promotes wellness and positive attitudes. The FSBC program aims at giving the woman confidence in her ability to give birth and balancing the use of human touch and technology. This alternative model of prenatal and childbirth care does not rely on the routine use of expensive technological care.(Patricia W. Stone, Zwanziger, Walker, & Buenting, 2000)

Licensure for FSBCs is provided by individual states. Accreditation for a center is based on carefully defined national standards developed by the Commission for the Accreditation of Birth Centers. Freestanding birth centers must maintaint transfer agreements with hospital(s) nearby for patients requiring specific medical interventions in the hospital setting.(Patricia W. Stone et al., 2000) As of 2020, there are currently more than 384 freestanding birth centers in the U.S. in 37 states and DC. This represents growth of 97% since 2010. (AABC, 2021)

In the early 1900's, home births accounted for the vast majority of births with only 5% happening in hospital settings. By 1935, the rate of births in hospitals increased to 75%. Between 1920 to 1932, as more middle class women started to have hospital births, the rate of maternal mortality increased from 600 to 630 per 100,000. Between 1915 and 1929, neonatal deaths from birth injuries and nursery-based nosocomial infections increased by more than 40%. The rates of morbidity and mortality in hospital births started to decrease with the advent of blood banking in the 1940's and availability of antibiotics in the 1950's. Despite the decrease in mortality and morbidity, there was a growing concern about the increased level of interventions in the hospitals like enemas, immobilization in labor, no oral intake, episiotomy, forceps delivery and cesarean delivery that lead to the search of alternatives to hospital deliveries. In the 1970's and 1980's, there was a reemergence in home births. There was a 20% in the rates from 2004 to 2008. It increased another 59% from 2008 to 2012. (Caughey & Cheyney, 2019) In the year 2019, there were 38,506 home births as per the CDC Wonder database.

Surveys of mothers to be indicate that reasons for the steady increase in non-hospital births were the following:

- Safety
- Avoidance of unnecessary medical interventions common in hospital births
- Previous negative hospital experience
- More control
- Comfortable, familiar environment.

Another dominant theme was women's trust in the birth process. Women equated medical intervention with reduced safety and trusted their bodies' inherent ability to give birth without interference.(Boucher, Bennett, McFarlin, & Freeze, 2009; Hazen, 2017) The COVID-19 pandemic also increased the interest in community births. Changes to birth practices, which included the use of additional personal protective equipment, strict protocols about birth room occupation (eg, limiting the presence of partners and other attendants), and discouraging skin to skin contact at birth made many mother's to be seek other alternatives to hospital births.(Callander, Bull, McInnes, & Toohill, 2021)

The usage of community birthing options with midwives tend to vary based on their geographic location. In the U.S., community births accounts for less than 2% of all births.(MacDorman & Declercq, 2019) Medical societies in Europe encourage the usage of midwifery services. In 2014, Britain's National Institute for Health and Care Excellence (NICE) recommended that healthy women with uncomplicated pregnancies give birth under the supervision of midwives rather than physicians. (Y. T. Yang, Attanasio, & Kozhimannil, 2016) In Netherlands, home births accounted for 30% of births in 2000. In 2012, 85% of women in the Netherlands started their care with a community midwife; the other 15% of women, most of whom had a significant history of medical or obstetric complications, received care from a secondary or tertiary care obstetrician. (Caughey & Cheyney, 2019)

There are many cited benefits of midwife care and community (non-hospital) births. Recent studies indicate that midwife-led models of care produce fewer instances of antenatal hospitalization, instrumental birth, and cesarean delivery Also, births with midwife-led care result in shorter hospital stays, higher patient satisfaction, and significantly lower costs of care.(Y. T. Yang et al., 2016). There are several studies that have confirmed these results.(Hutton, Reitsma, & Kaufman, 2009; Janssen et al., 2009;

van der Kooy et al., 2011) In Blix et al., it was found that when compared to hospital births, home births had reduced risk of assisted vaginal delivery (OR 0.32; 95% CI 0.20-0.48), epidural analgesia (OR 0.21; CI 0.14-0.33) and dystocia (OR 0.40; CI 0.27-0.59). Multiparas who planned home births had reduced risks for operative vaginal delivery (OR 0.26; CI 0.12-0.56), epidural analgesia (OR 0.08; CI 0.04-0.16), episiotomy (OR 0.48; CI 0.31-0.75), anal sphincter tears (OR 0.29; CI 0.12-0.70), dystocia (OR 0.10; CI 0.06-0.17) and postpartum hemorrhage (OR 0.27; CI 0.17-0.41). This study found no difference in Apgar scores or perinatal death.(E. Blix, Huitfeldt, Øian, Straume, & Kumle, 2012)

Community births are also associated with reduced costs of births. In a paper by Stone et al., they found that the total cost of prenatal care, delivery and post-natal care provided by FSBC’s was $6,087 while the hospital costs were estimated to be S6,803. The sensitivity analysis found that FSBC would be more cost effective if there was an increase in volume.(Patricia W. Stone et al., 2000) Another study by Anderson et al. found that the average cost of an uncomplicated vaginal birth was 68% less than that in the hospital.(R. E. Anderson & Anderson, 1999) In another study, it was found that if all low risk women had home births in Australia, cesarean rates would have reduced from 13.4% to 2.7%, 860 fewer inpatient bed days and 10.1 fewer hours of women's intensive care unit time per 1000 births. If all women gave birth in birth centers, cesarean rates would have reduced to 6.7%, 760 inpatient bed days would have been saved along with 5.6 hours of women's intensive care unit time per 1000 births.(Callander et al., 2021)

There are also risks that are associated with home and FSBC births. In one study, it was found that the overall risk of neonatal death was significantly higher in planned home births (12.1 neonatal death/10,000 deliveries; P<.001) compared with hospital births by certified nurse midwives (3.08 neonatal death/10,000 deliveries) or physicians (5.09 neonatal death/10,000 deliveries). Neonatal mortality rates were increased significantly at planned home births, with the following individual risk factors: breech presentation (neonatal mortality rate, 127.52/10.000 births), nulliparous pregnant women (neonatal mortality rate, 22.5/10,000), previous cesarean delivery (18.91/10,000 births), and a gestational age ≥41 weeks (neonatal mortality rate, 17.17/10,000 births).(Grünebaum, McCullough, Sapra, Arabin, & Chervenak, 2017) Another study by Snowden et al. also found a higher rate of perinatal in non-hospital setting (3.9 vs 1.8 deaths per 1,000).(Snowden et al., 2015) These findings were not conclusive as there were studies that did not find significant differences in the rate of perinatal death. (E. Blix et al., 2012; de Jonge et al., 2009; van der Kooy et al., 2011)

There is evidence that the rate of PTB is lower in non-hospital community birth settings. In a Canadian study conducted by McRae et al., the authors found that odds of PTB were lower for antenatal midwifery versus general practitioner's (aOR 0.74, 95% CI 0.63 to 0.86) and obstetrician's patients (aOR 0.53, 95% CI 0.45 to 0.62).(McRae et al., 2018) In another study completed in Australia, similar results were found. They compared a program where they had enhanced midwife services ("Birthing on Country" Service) to the standard of care. They found that those who used the service had a preterm birth rate of 6.9% in comparison to the 11.6% rate for those who used standard care. (Kildea et al., 2019) Strong Start for Mothers and Newborns Initiative is a program that uses enhanced prenatal care models of centering or group prenatal care, maternity care home, and birth center care. Those who engaged in the Strong Start program had an overall rate of PTB of 4.4% which is less than half of the national average at the time (9.9%). This program also had a narrower disparity of PTB between White and Black women. The PTB rate for White women was 4.2% (which was less than their national rate (9%)). The rate was 5.4 for Black women in the program which was less than half of their national rate (13.8%). They estimated that the Strong Start program could reduce the Medicaid costs of PTB by $24.25 million per 10,000 births.(Alliman et al., 2019)

A cost effectiveness analysis of giving birth in the U.S. in different birth locations with respect to the preterm birth rates was completed for this study. It is the hope that Medicaid and health care insurance carriers will use these numbers in order to provide justification for more financial coverage of non –hospital births for low risk pregnant women.

6.3 Methods

6.3.1 Data Sources and Inclusion

The birth data came from the U.S. Natality file from 2019. This file is sourced from the National Vital Statistics System of the National Center for Health Statistics. It was provided for public use from the National Bureau of Economic Research (*www.nber.org*). This file provided data on the number of births in the U.S., the birth attendants (physician or midwives), location of birth (hospital (referred to as standard of care (SOC), home or birthing center), gestational age at birth, mode of delivery (vaginal or caesarian section) and age of the mother.

We also used gestational age to create a variable for PTB. Those who had a gestational age of less than 37 weeks were coded as PTB. Once this variable was created, we were able to derive the PTB rate for each of the birth locations. We also used the CDC Wonder website to obtain birth data stratified by each state.

In order to account for the differences in the medical authority between physicians and midwifes and to follow the American College of Obstetrics and Gynecology (ACOG) listing of contraindication for non-hospital births, we removed records representing babies with the following:

- Birth abnormality or congenital disease
- Caesarian sections (current and previous)
- Maternal morbidity (defined by the incidence of maternal transfusions, perinatal laceration, ruptured uterus, unplanned hysterectomy and admission into ICU)
- Additional instrumentation like forceps or vacuums
- Non-cephalic positioning
- Multiple births.

6.3.2 Risk Stratification

After removing these records, variables were created to account for risk characteristics for PTB that are still eligible for midwifery care. Those who were considered to have a weight risk were those who were underweight (BMI < 18.5) and morbidly obese (BMI >=40). The age risk are those who were under age 17 and over the age of 34. The final risk category were those with the following medical issues:

- HTN (pre-existing and gestational)
- DM (pre-existing and gestational)
- Eclampsia (Included as hypertension)

• Previous PTB

• Fertility Assistance

A risk variable was created as a dichotomy where those with no reported risk were coded as “0” and those with at least one risk factor was coded at a “1”. Once this variable was created, we gathered information on the percentage of preterm births within the remaining sample based on different risk groups.

With the risk group, physician recommendation was taken into account. While there above risks are not contraindicated as per the ACOG, many physicians may choose to advise their patients with these risks to go to standard of care. In order to take this under consideration, we modeled these risks as independent variables to determine if any of these create such a risk of PTB that many physician would choose to care those with these risks. The dependent variable we used was PTB. We ran the logistic regression and found the variables the greatest effect were Previous PTB, DM and HTN because they had the greatest value for the Wald Statistic and made the greatest contribution to the model area under the curve (AUC). (Table 6.1, Figure 6.1). Given this strong relationship, those with these risks were excluded from analysis.

Table 6.1 Logistic model – Dependent Variable = PTB

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
PrPTB	1	1	0.73	0.01	13,140.98	<.0001
Diabetes	1	1	0.21	0.01	1,072.28	<.0001
Hypertension	1	1	0.64	0.02	664.59	<.0001
Underweight	1	1	0.16	0.01	351.40	<.0001
Age - 17 years or younger	1	1	0.24	0.02	159.19	<.0001
Morbid Obesity	1	1	0.10	0.01	157.42	<.0001
Assisted Fertility	1	1	0.04	0.02	6.47	0.011
Age - 35 years and greater	1	1	0.00	0.00	0.07	0.7936

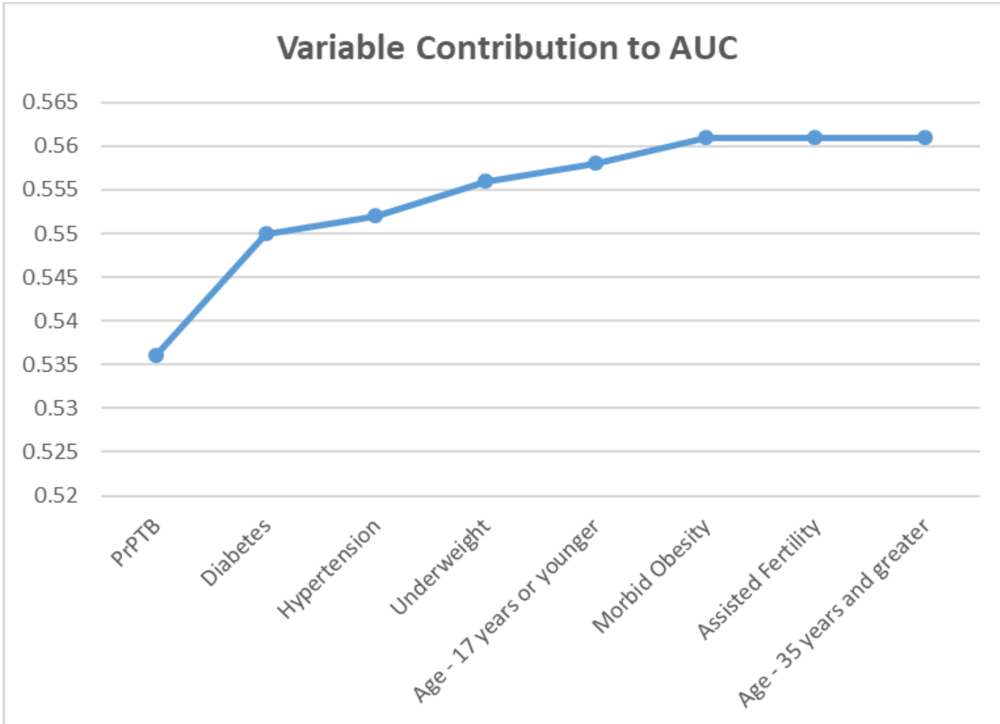

Figure 6.1 Chart of variable contribution to model AUC. It is seen that after the hypertension variable, the contribution to the model AUC flattens indicating that while these variables are significant, there effect on PTB is marginal.

6.3.3 Cost Data – Prenatal Care

The average and standard deviation of prenatal care cost was originally sourced from the paper by Stone et al. (Patricia W. Stone et al., 2000) This paper provided the cost of prenatal care for those who use FSBC (which means they use midwives) and standard hospital care (which means care from a physician). It was assumed that the costs for FSBC would be the same for home births because they are both using midwives. Because this paper provided costs from the year 2000, we applied the CPI adjustment to account for 2019 costs. In order to get the final figure for standard of care (SOC), FSBC and home births; I took a sample of each birth facility. I then created random numbers using figures that were within two standard deviations of the adjusted mean. Once all numbers were assigned, we took the mean of the random numbers to get the final figures that were entered into the cost effectiveness analysis.

6.3.4 Cost Data – Full Term Birth

Cost for routine vaginal term births at hospitals was provided by the article "The cost of giving birth in each state" which was provided by CBS News. (*https://www.cbsnews.com/pictures/cost-giving-birth-in-united-states/*). The source of their data was the Hospital Pricing Specialists who collected raw price-tag data from nearly 4,500 hospitals across the country. The cost of FSBC was derived by taking the figures from the hospital costs and the paper by Stone et al. (Stone, 2000). This paper reported that FSBC costs were 10.5% less than hospitals. I applied this difference to the hospital costs to obtain the FSBC figure. The cost of home births were derived by taking the hospital cost figures and using data provided by the article "Giving birth at home is cheaper than at hospitals, study says, but is it safe?" from the Washington Post which reported that on average home births cost just under $3,000 less than hospital births.

6.3.5 Cost of PTB

The cost of PTB was provided by the report by Norman J Waitzman, PhD and Ali Jalali, PhD.(Waitzman, 2016) The figures in the report were the cost of medical care, delivery, special education, early intervention services and production losses. We only included the cost of late PTB (32 – 36 6/7 weeks gestation) as figures showed that earlier gestational ages would be referred to hospitals because of the severity of complications.

The report provided the data by state. We took the mean costs of all states. The natality file was used to get the number of premature births for each birthing location.

An adjustment that had to be made was to account for transfers to the hospital. These births were considered to be hospital births with no recording of the transfer origin (to be explained in next section). We used the number of late PTB's within hospitals, FSBC and home births multiplied by the average costs. We added the totals for each birth facility and divided that total by the total number of preterm births overall to get a weighted average cost of PTB.

6.3.6 Accounting and Costs of Transfers

As stated above, transfers to the hospitals were considered to be hospital births in regardless of the birth origin. In an effort to avoid over-counting hospital birth and PTB data, we made an adjustment. We took the total of maternal and infant transfers and subtracted the number of records that had transfers of mothers and children. We took that number and subtracted it from the number of hospital births and added to the number of FSBC and home births.

We distributed the number of transfers between FSBC and the home births by calculating the percent distribution of these two birth locations. The percent distribution was calculated by adding all the non-hospital births (which was the denominator) and then dividing the number of FSBC/home births by this number. Once the proportion was calculated, we multiplied this figure to the total number of transfers. We then added the product to the number of FSBC and home births. We also followed this process when we made an adjustment to account for the number of PTB's that were transferred to the hospital.

The cost of transferring from the FSBC or home was sourced by the website "Cost Helper Health" - https://health.costhelper.com/ambulance.html. The percentage transfer rates for FSBC was sourced from Rooks et al.(Rooks, Weatherby, & Ernst, 1992) The rates of transfers from home births were sourced from Blix et al.(Ellen Blix, Kumle, Kjærgaard, Øian, & Lindgren, 2014)

6.3.7 Disability Adjusted Life Years (DALY's)

In addition to monetary costs, we also used a measure, disability-adjusted life years (DALYs). This figure was used to account the burden of diseases, injuries and risk factors on human populations. The DALY's measure is grounded on cogent economic and ethical principles. It is used to guide policies toward delivering more cost-effective and equitable health care. .(Murray & Acharya, 1997) The DALY that I used for PTB was 5.1 which was sourced by a paper by Blencowe et al. (Blencowe et al., 2013)

6.3.8 Data Analysis Methods

Decision trees were created using TreeAge Pro (Williamstown, MA) to complete the cost effectiveness analysis of using different birth facilities. We also ran a probabilistic sensitivity analysis (PSA) where we ran 10,000 Monte Carlo simulations. We also figured the cost savings assuming a shift between hospital, FSBC and home births.

6.4 Results

6.4.1 Full Sample

There were a total of 3,757,582 births that were within the 2019 U.S. Natality file. After the exclusions were made, there were 1,835,045 left on the file. (Figure 6.2)

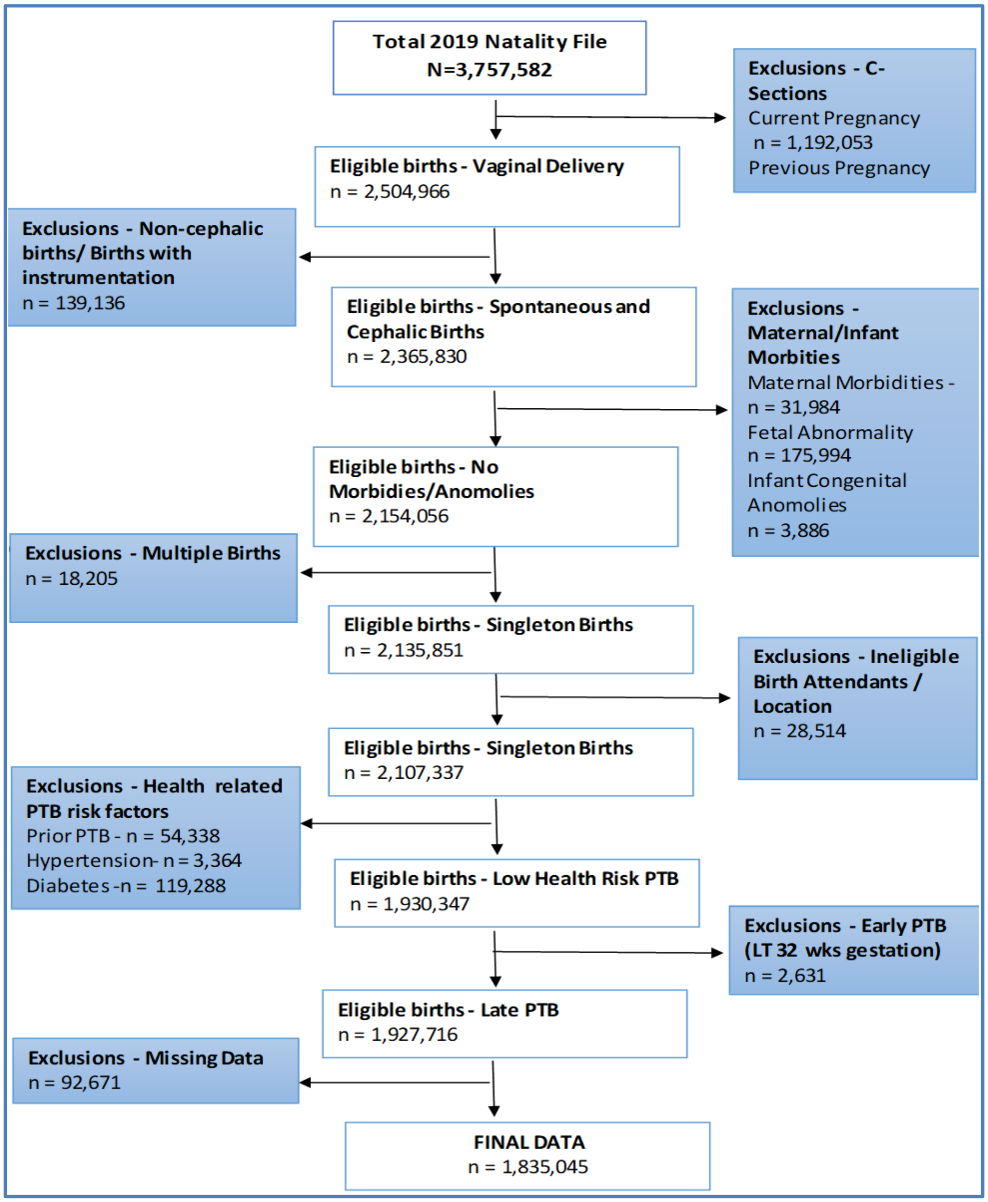

Figure 6.2 Chart of Inclusion/Exclusion Criteria for study. Ineligible birth attendants were those that were not MD, DO's nor midwifes. Ineligible locations are those outside of hospitals, FSBC's and intended home births.

Approximately 78% of those in the data had no reported risk factors for PTB. Within this group, the rate of late PTB was 3.6%. It is estimated that births at FSBC's accounted for less than 1% of all births (0.91%) while home births accounted for 1%. Standard hospital care accounted for the remaining births.

There were costs that were included in the analysis which remained static regardless of level of risk. The cost of late PTB's were estimated to be $30,618 for each hospital birth, $28,181 for each FSBC birth and $28,344 for each home birth. The cost of term births was estimated to be $17, 254 for births in hospitals (standard of care), $15,438 for those who gave birth in FSBC and $14,283 for home births. The estimated cost of prenatal care was $1,759, $3016, and 2,973 per birth for standard of care, FSBC and home births, respectively. The estimated cost of transfers were $4549, and $8,740 per birth for FSBC and home births, respectively. The rate of transfers from FSBC used in the decision tree was 16% and 30% for home births.

6.4.2 Cost Effectiveness Analysis - No Risk

For those with no recorded risk, the preterm birth rates were 3.5% for those who engaged in (SOC), 2.4% for those who gave birth at FSBC's and 2.9% for those who had home births. When placed in the model, the total cost of preterm birth was calculated by adding together the cost of prenatal care, transfers (where appropriate) and the product of the cost of PTB and the DALY's. The total cost of term births was calculated by adding the average cost of term births to the cost of prenatal care and transfers (where appropriate). It was found that the most cost effective birth location was FSBC with an overall cost of approximately $22,261. The cost of home birth and SOC were $23,849 and $26,944, respectively. (Figure 6.3)

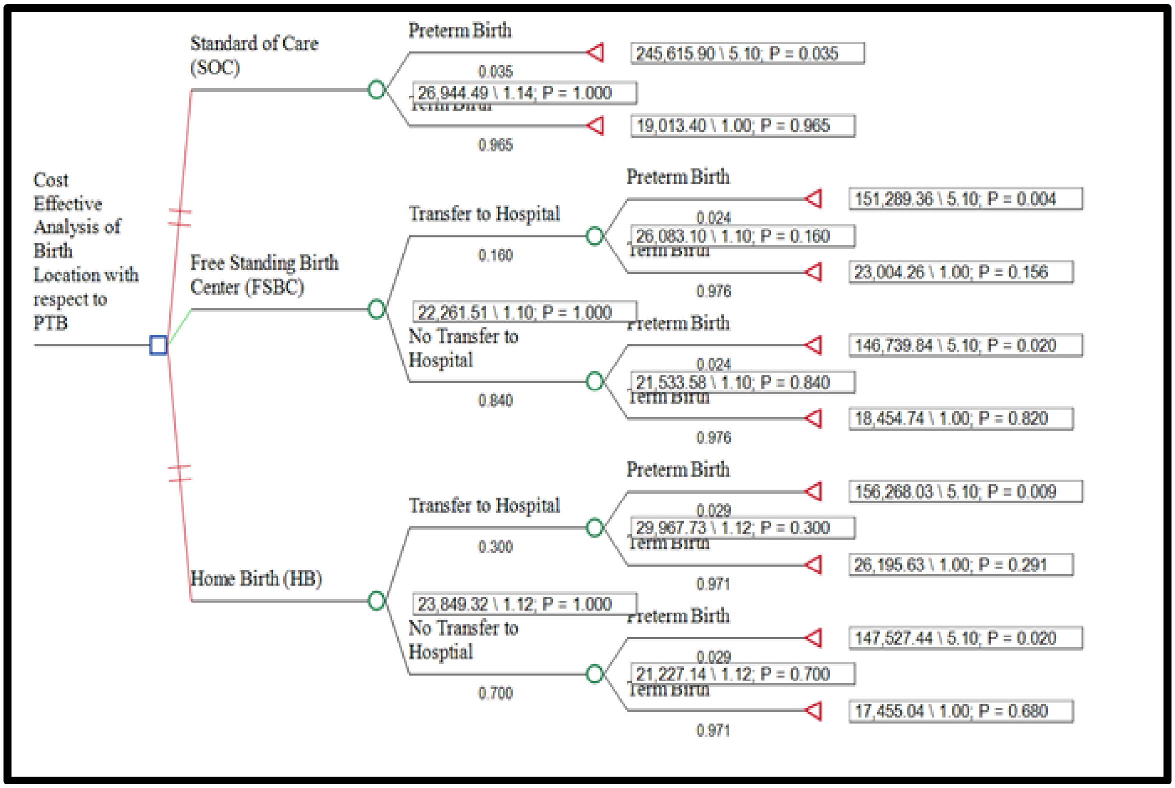

Figure 6.3 Decision Tree for those who have no reported risk. This result indicates that FSBC are the most cost effective method to give birth. This was determined by the cost per birth and the fact that it has the lowest rate of PTB.

This result was confirmed by the PSA which showed that 43% of the Monte Carlo iterations showed that FSBC was the most cost effective when the willingness to pay was set to $3,500 and 42% when the willingness to pay was $8,000. (Figure 6.4) The amounts that were used for willingness to pay were taken from Howell et al. (Howell, Palmer, Benatar, & Garrett, 2014) figures for Medicaid expenditures with a CPI adjustment for the year 2019.

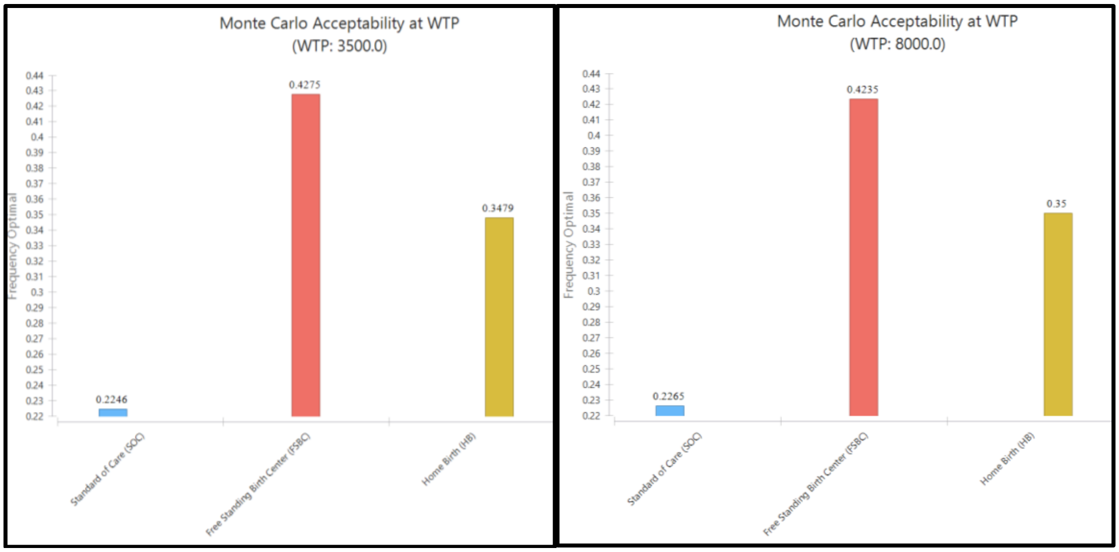

Figure 6.4 Monte Carlo PSA results. 10,000 iterations run. WTP = willingness to pay. Gamma distribution was used for the cost estimates while beta distribution was used for the percentages of PTB.

6.4.3 Cost Effectiveness Analysis - Risk

For those with at least one recorded risk, the preterm birth rates were 3.9% for those who engaged in SOC, 2.1% for those who gave birth at FSBC's and 2.4% for those who had home births. It was also found that the most cost effective birth location was FSBC with an overall cost of $21,877. The cost of home birth and SOC were $23,199 and $27,851 per birth, respectively. (Figure 6.5)

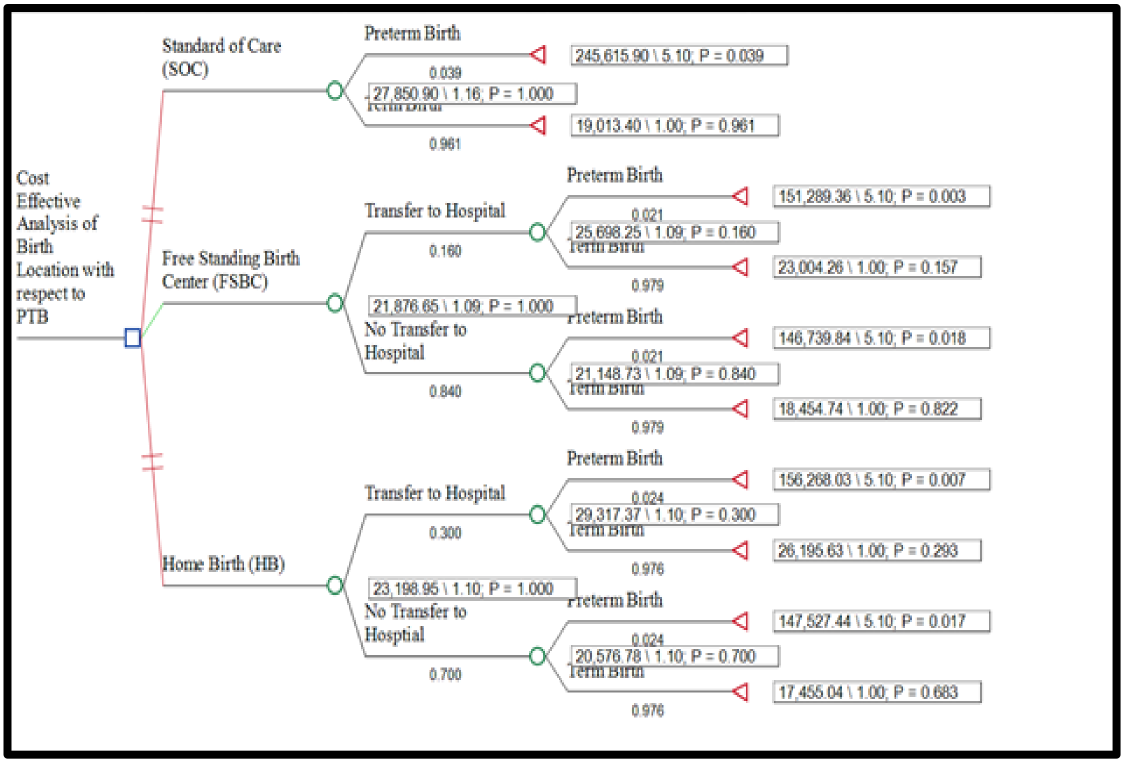

Figure 6.5 Decision Tree for those who have minimal risk. This result indicates that FSBC are the most cost effective method to give birth. This was determined by the cost per birth and the fact that it has the lowest rate of PTB.

This result was confirmed by the PSA which showed that 46% of the Monte Carlo iterations showed that FSBC was the most cost effective when the willingness to pay was set to $3,500 and $8,000. (Figure 6.6)

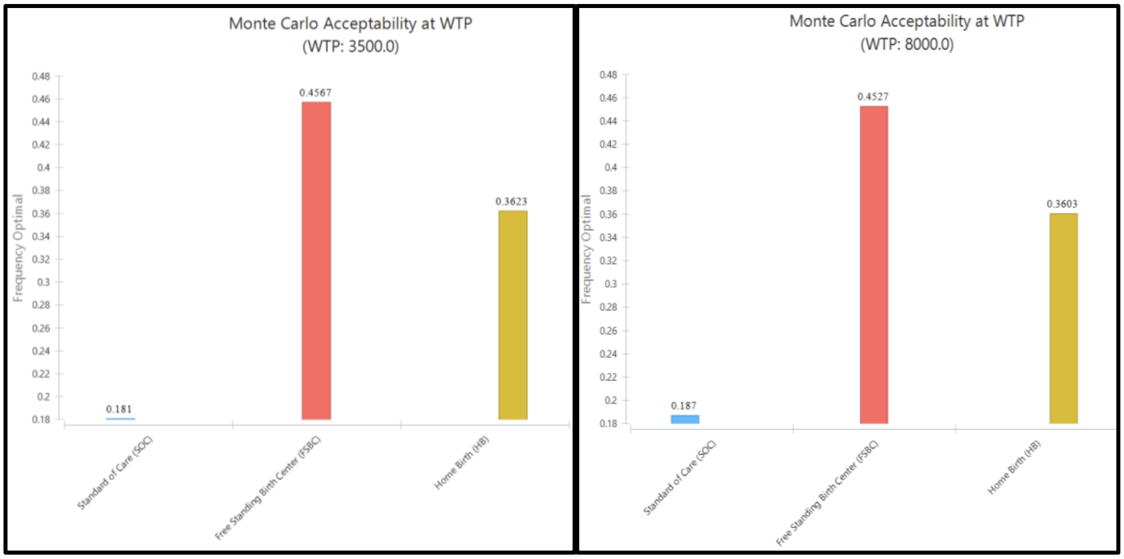

Figure 6.6 Monte Carlo PSA results. 10,000 iterations run. WTP = willingness to pay. Gamma distribution was used for the cost estimates while beta distribution was used for the percentages of PTB.

6.4.4 Cost Effectiveness Analysis – Combination of Risk and No Risk Populations

When the risk and no risk group were combined, the preterm birth rates were 3.6% for those who engaged in standard of care (SOC), 2.3% for those who gave birth at FSBC's and 2.8% for those who had home births. The most cost effective birth location was FSBC with an overall cost of $22,133. The cost of home birth and SOC were $23,719 and $24,014 per birth, respectively. (Figure 6.7)

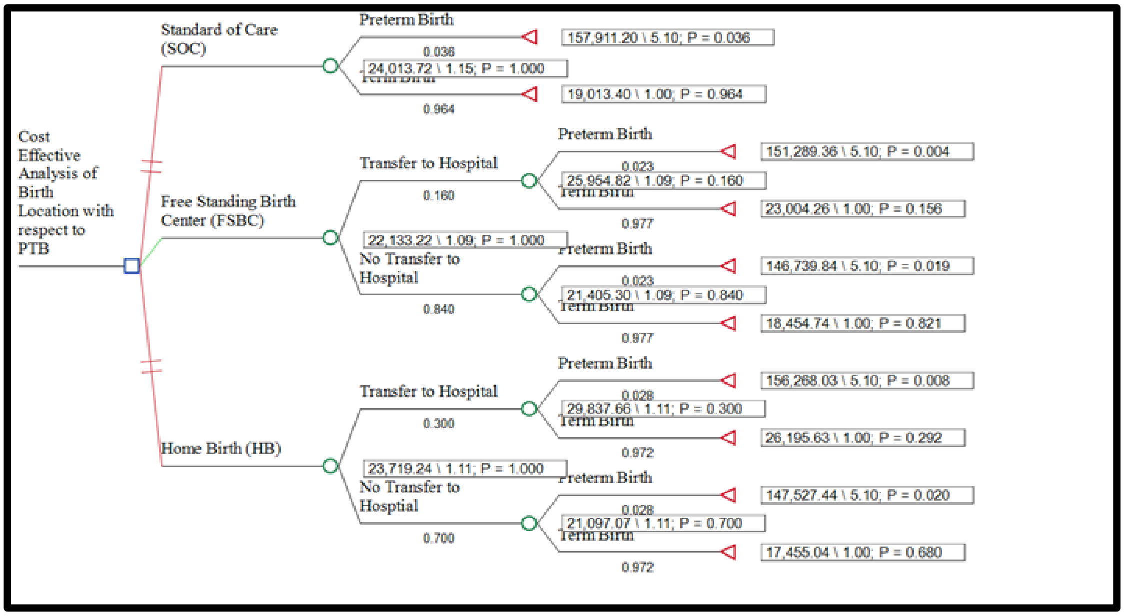

Figure 6.7 Decision Tree for full sample. This result indicates that FSBC are the most cost effective method to give birth. This was determined by the cost per birth and the fact that it has the lowest rate of PTB.

This result was confirmed by the PSA which showed similar that FSBC was most cost effective in 43% of the iterations for the willingness to pay of $3,500 and $8,000 (Figure 6.8)

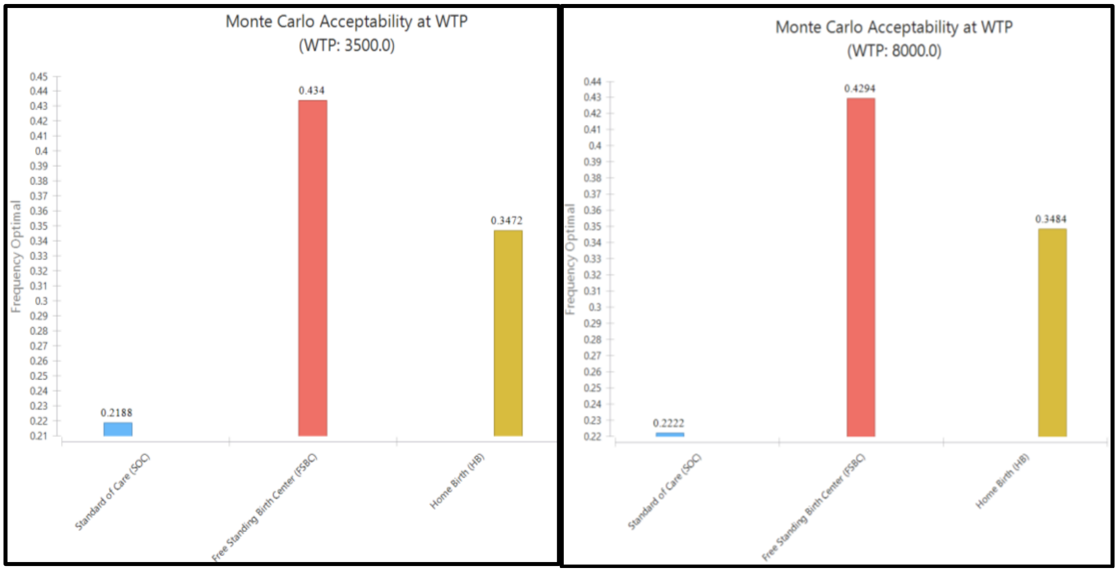

Figure 6.8 Monte Carlo PSA results. 10,000 iterations run. WTP = willingness to pay. Gamma distribution was used for the cost estimates while beta distribution was used for the percentages of PTB.

6.4.5 Cost Effectiveness Analysis – Medicaid Recipients

We did a sub-analysis where we examined Medicaid patients with minimal to no risk. The preterm birth rates were 4.3% for those who engaged in standard of care (SOC), 2% for those who gave birth at FSBC's (as per literature)(Alliman et al., 2019; Benatar, Garrett, Howell, & Palmer, 2013) and 2.3% for those who had home births.(MacDorman & Declercq, 2019) The most cost effective birth location for Medicaid patients was FSBC with an overall cost of $21,748. The cost of home birth and SOC were $23,069 and $28,757 per birth, respectively. (Figure 6.9)

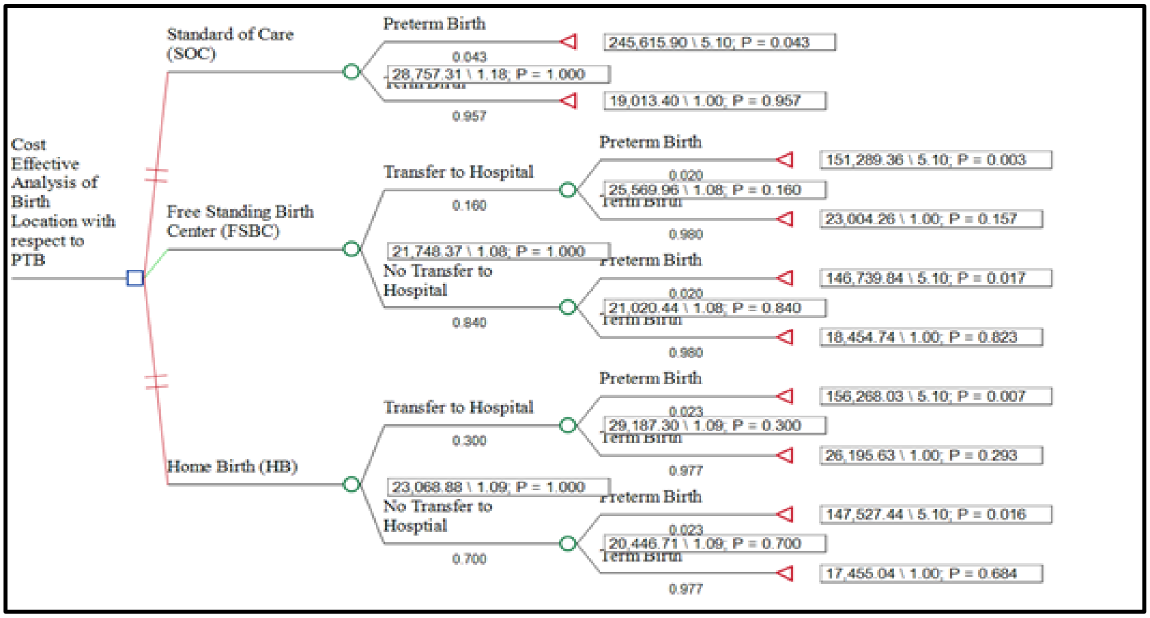

Figure 6.9 Decision Tree for Medicaid sub-sample. This result indicates that FSBC are the most cost effective method to give birth. This was determined by the cost per birth and the fact that it has the lowest rate of PTB.

This result was confirmed by the PSA which showed that FSBC was most cost effective in 45% of the iterations for the willingness to pay of $3,500 and 44% for the willingness to pay of $8,000 (Figure 6.10)

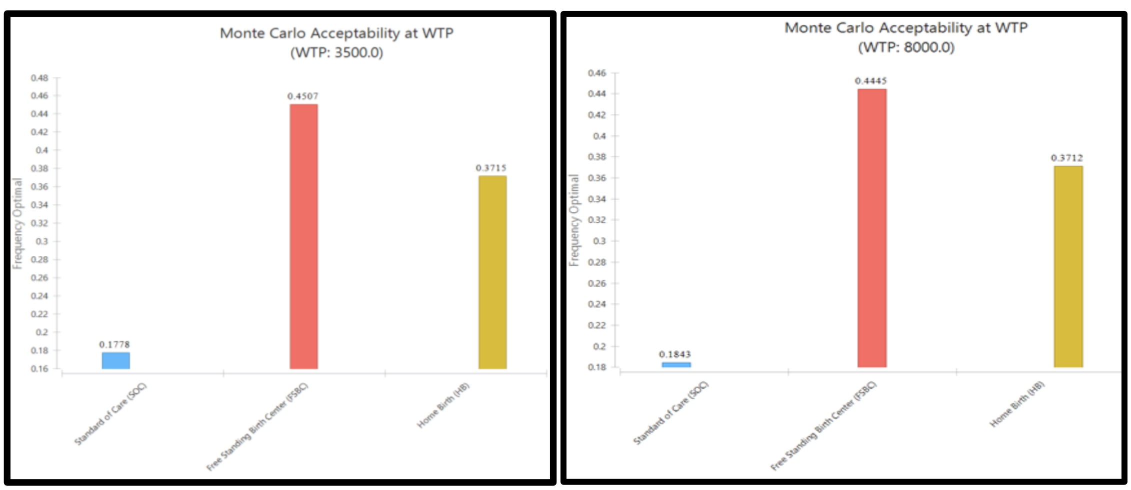

Figure 6.10 Monte Carlo PSA results for Medicaid patients. 10,000 iterations run. WTP = willingness to pay. Gamma distribution was used for the cost estimates while beta distribution was used for the percentages of PTB.

6.4.6 Cost Savings

When examining the full sample (those with and without risks), it was found that if there was a 10% shift from hospitals to FSBC's, there would be a $337 million dollars national savings in the cost of births. There could potentially be a reduction in the cost of PTB's by 3.8% which would equate to $391 million dollars savings in current costs and disability adjusted life years. For Medicaid patients, 10% shift from hospitals to FSBC would have a $534 million dollar savings in all birth costs and $571 million dollar cost savings in PTB.

In the paper by Howell et al., they stated that Medicaid covered $6,468 for hospital vaginal births (which equated to a rounded $8,000 in 2019 dollars) and $3,187 for birthing center vaginal births (which equated to a rounded $3,500 in 2019 dollars).(Howell et al., 2014). When I applied these numbers, it was estimated that Medicaid spends close to $6.1 billion dollars in coverage for low to no risk births. If there was a 10% shift away from hospitals to FSBC's at the same coverage levels, they could potentially save 5.6% of their expenditures for birth. This would create a savings of $343 million dollars.

Unfortunately, such a percentage move would be very difficult particularly for Medicaid recipients because birthing centers may be cost prohibitive due to the marginal coverage provided for birthing center care. Given this, there was an additional analysis done to examine if Medicaid were to increase their coverage of birthing centers to match what they provide for SOC. When this was done, it was estimated that the cost of birth to Medicaid would marginally increase their expenditures by $16 million (due to the low volume of birthing center births). The cost savings of birth and preterm would far exceed the increase in cost of covering FSBC at the same level of standard hospital care.

6.5 Discussion

The purpose of this study was to examine if the lower rates of PTB of community births translated to cost effectiveness of going outside of standard hospital facilities for birth. What was found was that FSBC's are the most cost effective location to give birth for women with none to minimal risk and community births (FSBC and home births) are less expensive than standard hospital care. This is consistent with many papers that have addressed this issue. (R. E. Anderson & Anderson, 1999; Howell et al., 2014; P. W. Stone & Walker, 1995) We also found that the rates of PTB were marginally reduced in the community settings when compared to hospital. This is consistent with what was found in literature as well.(Alliman et al., 2019; Kildea et al., 2019; McRae et al., 2018).

The rate of PTB in the U.S. is still the highest among high income nations. This high rate is partially attributable to racial disparities in PTB between Black women and other races. There are studies that have shown that when Black women gain access to birthing center care, they have rates of PTB that is considerably lower than standard hospital care. This is seen in Alliman et al., where they found that the PTB rate for Black women in the program was 5.4% which was less than half of their national rate (13.8%).(Alliman et al., 2019) This was also seen Benatar et al. This study examined the birth outcomes of women in Washington DC who were cared for at the Family Heath and Birth Center (FHBC). They found an overall decrease in PTB when compared to usual care (7.9% vs 11%, respectively). This reduced rate was also found with Black women

(8.6% vs 11.8%). The cited reasons for the general improved outcomes in these programs were that highly individualized prenatal care delivered in a culturally relevant and comfortable environment would have a positive effect on a population of women having children. The findings suggest that this setting (birthing center), when compared with traditional care, has indeed led to improved birth outcomes for higher need infants and mothers touched by the FHBC—the enabling factor.(Benatar et al., 2013)

Given the positive results of using FSBC's, there are still difficulties that Medicaid recipients who desire to use this service encounter. Many midwives who work in free standing clinics have issues with getting payments from Medicaid. This is due to state adoptions of managed Medicaid coverage that does most business though management care organizations (MCO's) who will not do business with birth clinics due to lack of volume. This in turn makes it cost prohibitive for Medicaid patients to take advantage of benefits of birthing centers because of the high out of pocket costs. (Courtot, Hill, Cross-Barnet, & Markell, 2020).

It is the hope the this cost effectiveness analysis, along with several completed before would possibly motivate Medicaid to make access to birthing centers easier by requiring the MCO's to allocate a certain amount of their business to birthing centers and also increasing the coverage to match that of hospitals for women who have none or minimal documented risk. Our analysis shows that at their present estimated coverage, if there was 10% decrease in hospital births for low to no risk women and they switched to FSBC, they could save $343 million dollars in expenditures. If they increased their coverage to match their hospital coverage, while expenditures would increase by $16 million dollars, this figure is low when comparing to the possibility of saving the healthcare system $534 million dollars for births and $571 million dollars for PTB's.

6.5.1 Strengths and Weaknesses of the Study

The strengths of this study is the data. We were able to get data for all births in the U.S. for the year 2019. Because of the access to the data, we were able to account for risk groups and make that a consideration in our study. This enabled us to not include data points who may have had high risks or had contraindications thus reducing bias. We also accounted for transfers in an effort not to over count PTB incidences in hospitals.

While the inclusion of transfers was a strength, the reporting on the natality file was a weaknesses because there was no data on the origin of the transfer. The file considered all transfers hospital births which may have skewed the numbers to the SOC disadvantage. This necessitated an educated guess based on the percentage of non-hospital births. Another weakness of the study was the lack of publically available cost data. There were a lot of adjustment necessary to make sure that we got the most accurate pricing based on papers and a diversity of sources.

6.6 Conclusion

FSBC's were shown to be the most cost effective option foe location of birth. This was due to it having the lowest rates of PTB. There should be more support in making this option available to all low risk women. One of the ways this can be done is through Medicaid administration rethinking its coverage model. This could potentially save the health care system hundreds of millions of dollars.

CHAPTER 7

CONCLUSION

Preterm Birth is an issue that has been studied. Despite the knowledge that has been compiled, the rates of PTB have not significantly reduced. One reason may be due to the fact that PTB is a result of every aspect of a woman's life outside of the physical body. The purpose of this work was to examine the effect of some of the elements of women's life. The work observed the domains of mental health status, healthy behaviors, and social determinants in addition to physical health.

This work had several papers with that confirmed the importance of examining pregnant women as multidimensional beings. The paper in Chapter 3 found that the composite of healthy behaviors has a very significant impact on the rate of PTB along with household demographics, community deprivation and community access. It also found that engagement in healthy behaviors is driven by the economic status of an individual. It is the hope that if a medical practitioner were to examine this study, they would consider a patients social context when making behavioral change recommendations.

Chapter 4 not only confirmed the importance of BMI in predicting PTB, but it also indicated that the effect of BMI is strengthened when combined with a women's SES. It was specifically found that BMI has an effect for those who were LSES and not for those who are HSES. This study also found that for LSES women, BMI has a curvilinear relationship to PTB indicating that there is an optimal BMI that has the lowest risk for PTB. Once the BMI is above this point, the risk of PTB increases. This study also found that there is an obesity paradox in PTB where those who are overweight or mildly obese have better rates of PTB than those who are of normal weight. This is important because obstetricians who work with lower social status patients can pay closer attention when caring for their normal to underweight patients by additional monitoring of their nutritional intake and consultation with social workers.

Chapter 5 examined race. Black women have the highest rates of PTB in the U.S. Europe and Canada. It was the hypothesis of this work that being Black in and of itself is not a risk factor or PTB and that the reason Black women have high rates is due to social disadvantage. The study confirmed this hypothesis as race was shown to be insignificant once interaction terms with social and medical variables were added to the model. This paper indicates that the legacy of slavery, Jim Crow laws and continual racial strife has effected Black women that has compromised their reproduction health.

Chapter 6 assessed the cost effectiveness of birth locations outside of standard hospital care with the use of midwives. This was motivated by literature that showed that alternatives like FSBC's and home births have reduced rates of PTB. Our study found that FSBC were the most effective location for low risk pregnant women. It is the hope that this knowledge would motivate insurance companies and Medicaid to provide more coverage to those who wish to use FSBC.

This work provides evidence that examining PTB requires one to look into a person's full life spectrum and life cycle. One is not just their body but their environment, family and experiences which are all connected.

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