Is There a Connection Between Diet and Preterm Labor in African American Women? An Analysis of Literature

by

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ABSTRACT

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Globally, an estimated 15 million babies are born too early every year, i.e., more than 1 in 10 babies, and of these (15 million) 1 million die. Preterm labor occurs when a baby is born before the 37th completed week of pregnancy. Black women are twice as likely to experience preterm labor than white women in the United States. Because this racial disparity is not well understood, the goal of the present study was to conduct an extensive literature analysis that focused on identifying a potential cause. Here, we propose that African American women are more likely to have different types of vaginal microbiomes compared to white women, in part, due to their differences in diets. Further, we propose that the differences in diets between the two groups of women could be due to the disparity in access to healthy foods, i.e., people in inner cities, who are predominantly African Americans, live in "food deserts", who are consuming mostly unhealthy foods with high-fat/high sugar and predominantly an animal-based diet. In contrast, a healthier diet with low-fat/low-sugar and mostly a plant-based diet is consumed primarily by white women living in more wealthy neighborhoods. Here, information about demographics and food deserts, the effects of diet on the vaginal microbiome, women health issues, such as bacterial vaginosis and preterm labor, as a consequence of diet, are collectively addressed and reviewed.

DEDICATION

To my parents and grandparents
For their continuous support and guidance

And In Memory of Ervin Hunter Sr., my grandfather,
without whom, I would not be here.

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1. INTRODUCTION

Premature (or preterm) birth - when a baby is born before the 37th completed week of pregnancy - is the leading obstetric problem impacting both mother and babies. ("Born Too Soon: Premature Birth in the U.S. Black Population", 2007). Every year in the United States, an estimated 15 million babies are born too early, of which a million die ("Preterm Labor", 2016). According to the March of Dimes report, 18.2% of black infants are born prematurely each year compared to only 9.3% of white infants ("Born Too Soon: Premature Birth in the U.S. Black Population", 2007). Preterm birth is the leading cause of infant death across all races during the first year of life in the United States but is double to triple among black infants ("Born Too Soon: Premature Birth in the U.S. Black Population", 2007).

Clearly, the racial disparity in birth outcomes for pregnant women and infants in the United States is highly concerning and needs to be addressed urgently because of the long term health implications and costs. For instance, preterm birth is predictive of developmental problems and adverse health outcomes later in life, such as respiratory and neurological disabilities ("Preterm birth", 2016). This public health crisis costs $26 billion annually for the care of premature babies in neonatal intensive care units ("Preterm birth", 2016).

The underlying causes of why black infants are more than twice as likely to be born preterm as white infants in the US are not well understood. The current work, therefore, focused on identifying potential causes likely to contribute to the racial disparity of preterm birth. Several researchers have suggested a wide range of factors, such as smoking and stress but, none have explored the effects of diet, specifically, an unhealthy high-fat/high-sugar (animal-based diet) versus a healthy low-fat/low-sugar (plant-based diet). Here, we perform a literature analysis and

based on this analysis, we propose four ideas that collectively may help explain why black women in the United States are twice as likely to have preterm birth rates that are significantly higher than white women: (1) It is well known that a large percentage of black women live in inner cities, and many inner cities are known to be "food deserts". As stated earlier, "food desert" is a term used to describe low-income African American neighborhoods with little or no access to healthy foods, such as fresh fruits and vegetables. Blacks living in "food deserts" are located near convenience stores and fast food restaurants that mainly sell cheap, high-fat, high-sugar, processed foods. These neighborhoods lack full-service super market stores, farmer's markets, and other vendors that sell fresh fruits and vegetables, which are mainly found closer to white, affluent neighborhoods (Treuhaft et al., 2009): (2) It is known that diet plays a major role in determining the type of human microbiome in the gut, which significantly impacts the health outcomes of the host. For instance, studies indicate that switching from a low-fat, plant polysaccharide-rich diet to a high-fat, high sugar "Western" diet can shift the type of microbiota as swift as within one single day, as well as change the representation of metabolic pathways in and alter gene expression in both the microbiome and their hosts (Turnbaugh et al., 2009): (3) We also know that the vaginal flora located in the lower genital tract is dynamic and is normally dominated and controlled by the microbe *Lactobacillus* (David et al., 2014). The presence of *Lactobacillus* is responsible for maintaining a low vaginal pH (normally less than 4.5) and is important for healthy pregnancy outcomes (Mirmonsef et al., 2014): (4) It is known that bacterial vaginosis is a condition in which *Lactobacillus* found within the female lower genital tract in the vagina are replaced by more virulent species (Roush, 1996). Therefore, the replacement of *Lactobacillus* with virulent species is associated with the induction of infections of the lower genital tract and subsequently to local and systemic inflammation that collectively lead to

preterm labor. Studies suggest that bacterial vaginosis roughly doubles the risk of preterm birth and may contribute to as much as 60% of the racial disparity in preterm delivery (Fiscella, 1996).

Given the literature noted above, since we know that the type of gut and vaginal microbiota can become negatively altered by an unhealthy high-fat/high-sugar and an animal-based diet, which in turn induces local and systemic inflammation, as well as other chronic diseases conditions that are associated with preterm labor, we propose that consuming an unhealthy high-fat/high-sugar (animal-based diet) may, in part, help explain the high rates of preterm labor in African Americans. In summary, an unhealthy high-fat/high-sugar (animal-based diet) foods induce the shift from good bacteria (*Lactobacillus)* to bad bacteria known to induce infections and chronic diseases that lead to preterm labor - more specifically, the higher rates of preterm labor in black woman than white women.

2. FOOD DESERTS

It is well known that "food deserts" are disproportionately heavily populated in low-income communities that are predominately black across the country, and that the food deserts have significant negative impacts on health (Treuhaft et al., 2010). In these (inner city) neighborhoods, access to nutritious, affordable and high quality health-promoting food is a challenge and out of reach (Treuhaft et al., 2010). Rather than full-service grocery stores, farmer's markets, and other vendors that sell fresh fruits, vegetables, and other healthy food, the black communities are rather bombarded in great abundance by convenience stores and fast food restaurants that mainly sell cheap, high-fat, high-sugar processed foods not offering any healthy options (Treuhaft et al., 2010).

The Policy Link and The Food Trust organizations reviewed and gathered more than 132 studies all consistently finding evidence that "food deserts" heavily populate low-income black communities. Their report provides all of the following information gathered from the 132 studies reviewed: Only 8 percent of African Americans live in an area with a supermarket, compared to 31 percent of whites; white areas have 3.2 times as many supermarkets as black areas; among the 132 studies, 21 found that food stores in lower-income neighborhoods and communities of color are less likely to stock healthy foods, more likely to offer lower quality items, and have higher prices compared to stores in higher-income or predominantly white communities. For instance, in Detroit's East Side neighborhood, African American women with lower incomes are less likely to shop at supermarkets (which are all located outside the neighborhood) and eat fruits and vegetables than white women with higher incomes; predominantly black zip codes have about half the number of chain supermarkets compared to predominantly white zip codes; and, produce quality is lower in predominantly black, low-income communities compared to affluent predominantly white communities (Treuhaft et al., 2010). Clearly, the white population - consume a healthier low-fat/low-sugar (plant based diet) because (1) they have better access to full-service grocery stores and farmer's markets that sell health-promoting or disease-combating foods, such as fresh fruits and vegetables and (2) they suffer less from diet-related diseases such as obesity, diabetes, and hypertension. On the other hand, the black population - including black women - consume an unhealthy high-fat/high-sugar (animal-based diet) because (1) they are located near fast food restaurants that mainly sell cheap high-fat/high-sugar processed foods and (2) they suffer more from diet-related disease such as obesity, diabetes, hypertension and preterm labor.

3. IMPACT OF DIET ON HUMAN MICROBIOME AND WOMEN HEALTH OUTCOMES

a) The Gut Microbiome

A microbiome is a community of microorganisms - such as bacteria - that inhabit a particular environment in or on the human body ("Microbiome", 2016). The intestinal microbiome is composed of microorganisms that inhabit the gut. It is known that the gut microbe plays a very important role in human health and disease. Understanding what constitutes a health-promoting (eubiotic) or disease-promoting (dysbiotic) microbial community has become the focus of several current studies (Gorvitovskaia et al., 2016), including the effects of diet on human gut microbiome. More specifically, the effects of an animal-based diet in contrast to a plant-based diet have been shown to alter certain bacterial species within the distal gut. The distal gut is the home to the largest number of microbes in the human body (Turnbaugh et al., 2009). One study created a well-defined, representative animal model of the human gut ecosystem by transplanting fresh or frozen adult human fecal microbial communities into germ-free C57BL/6J mice (Turnbaugh et al., 2009). The results indicated that switching from a low-fat, plant polysaccharide-rich diet to a high-fat, high-sugar "Western" diet shifted the structure of the microbiota within a single day, changed the representation of metabolic pathways in the microbiome, and altered microbiome gene expression (Turnbaugh et al., 2009). Another similar study noted that a high-fat/high-sugar 'Western' diet, altered the genetic composition and metabolic activity of our resident microorganism (the human gut microbiome) (David et al., 2014). This same study also specifically identified particular microorganisms present or not present depending on an animal-based diet (high-fat/high-sugar) or a plant-based diet (low-fat/low-sugar). The animal-based diet (high-fat/high-sugar) increased the abundance of bile-tolerant microorganisms (*Alistipes, Bilophila,* and *Bacteroides)* and decreased the levels of

Firmicutes that metabolize dietary plant polysaccharides (*Rosaburia, Eubacterium rectale* and *Ruminococcus bromii*) (David et al., 2014). The study even found that increases in the abundance and activity of *Bilophila wadsworthia* from the animal-based diet (high-fat/high-sugar) support a link between dietary fat, bile acids, and the outgrowth of microorganisms capable of triggering diseases, such as inflammatory bowel disease (David et al., 2014). Diets that are rich in animal protein and sugar (high-fat/high-sugar) alter the gut microbial communities from beneficial ones to ones that are now believed to contribute to the growing epidemics of chronic illnesses globally, including disorders such as obesity, inflammatory bowel disease and other chronic diseases (David et al., 2014). The study cited here (David et al., 2014) and others, support our hypothesis that diets rich in animal protein and sugar (high-fat/high-sugar) and devoid of health-promoting foods, can induce negative health outcomes, including preterm labor. Since there are other microbiomes that exist throughout the human body, such as the nose, the skin, the vagina and others, does diet affect the dynamics of their local microbiome, as described earlier in the gut and does this alteration impact health outcomes in the host? It is interesting to note that, overall, African American women have completely different vaginal microbiomes compared to white women, i.e., African American women tend to have more virulent vaginal microorganisms, while in contrast white women are more likely to have benign microorganisms (Mirmonsef et al., 2014). Since, as discussed earlier, the major determinant of gut microbiome is diet, we speculate that the racial difference in vaginal microbiome may also be attributed to the difference in diet.

b) The Vaginal Microbiome

The human vagina is inhabited by a range of microbes from a pool of over 50 species (Cribby et al., 2008). *Lactobacillus* is the dominate microorganism in the lower female genital

tract colonized within the vaginal microbiome (Antonio et al., 1999) and is the most common, particularly in healthy women (Cribby et al., 2008). *Lactobacillus* is a group of rod-shaped, gram-positive, non-spore forming bacteria located within the family Lactobacillaceae. Glycogen is the main energy source that *lactobacillus* uses and as a by-product, yields lactic acid. For this reason, vaginal pH decreases with increasing glycogen concentrations in the presence of *lactobacillus* (Mirmonsef et al., 2014). Estrogen is primarily responsible for mobilizing free glycogen in the vaginal epithelial cells (Fettweis et al., 2014). Accumulation of lactic acid lowers the normal pH of the vaginal tract to less than 5, which is significantly lower than the rest of the body, except the stomach. This low vaginal pH is beneficial in that it helps protect the vagina against its colonization by other virulent microbes (Mirmonsef et al., 2014). In addition, *lactobacillus* is known to produce anti-bacterial compounds, including lactocidin, acidolin, lactacin B and hydrogen peroxide (H_2O_2) (Hillier et al., 1993). H_2O_2 - producing *lactobacillus* are the most common and inhibit the growth of non-catalase-producing microorganism; the combination of hydrogen peroxide and a halide ion (such as chlorine) with peroxidase, which are abundant in the cervix and endometrium, ensures a potent anti- bacterial system (Eschenbach, 1993).

There are four species of *lactobacillus* that commonly colonize the vagina: *L. crispatus, L. jensenii, L. gasseri,* and *L. iners* (Mirmonsef et al., 2014). These different species of *lactobacillus* offer varying degrees of protection against vaginal pathogens. Colonization with *L. crispatus* and *L. jensenii* are considered to be the most beneficial against vaginal pathogens, while *L. gasseri,* and *L. iners* are thought to be the least protective against vaginal pathogens (Mirmonsef et al., 2014).

A study was conducted to characterize and contrast the vaginal microbial profiles in African American women versus American women of European ancestry. The Virginia Commonwealth University established the vaginal human microbiome project utilizing 16S rRNA gene sequence analysis to compare the microbiomes of vaginal samples from 104 African American women and 98 women of European ancestry. Results from the study indicated vaginal microbiomes significantly differ between African American women and white women and identified several taxa relevant to these differences (Fettweis et al., 2014). The study revealed that the *lactobacillus* species *L. crispatus,* one of the most potent in anti-bacterial activities, was the most common amongst European ancestry women, whereas, in contrast, *L. iners,* which is less potent, was the most common in African American women (Fettweis et al., 2014). In summary, these studies show that the vaginal microbiome of African American women is predominately colonized with the least protective lactobacillus species of *L. iners* (Petricevic et al., 2014) and the vaginal microbiome of white women is predominately colonized with the more protective lactobacillus species of *L. crispatus* (Antonio et al., 2009).

Another similar study examined the vaginal pH of black versus white women groups. The results of this study were consistent with the study cited earlier, i.e., black women were found to have a pH of 4.7 +/- 1.04 as compared to white women, with a lower pH of 4.2 +/- 0.3 (Ravel et al., 2010). The authors of the study concluded that (1) the racial difference in vaginal pH between African American women and white women could account for the significant differences in the bacterial communities and (2) since the pH of white women is more acidic than black women, it is more protective and more likely to kill invading pathogens than their counterparts.

c) Bacterial Vaginosis

As stated earlier, it is well established that the bacterial species *lactobacillus* dominates the vaginal microbiome. A deficiency in *lactobacilli* can upset the microbial balance in the vagina, frequently resulting in a disorder or syndrome called bacterial vaginosis (BV). BV is associated with a quantitative and qualitative shift from normally occurring lactobacilli to a mixed microflora dominated by anaerobic bacteria (Petricevic et al., 2014). Other definitions of bacterial vaginosis include: the absence of *lactobacilli* in the vagina (Reid et al., 2003), a condition in which the benign lactobacilli normally present in the vagina are replaced by more virulent species (Eschenbach, 1993) or, a condition characterized by a depletion of *lactobacilli* population and the presence of Gram-negative anaerobes, or in some cases Gram-positive cocci, and aerobic pathogens (Cribby et al., 2008).

BV has been linked to a number of complications of pregnancy, including preterm labor, amnionitis, postcesarean endometritis, histologic chorioamnionitis, and postabortion pelvic inflammatory disease (Hillier et al., 1993). These pregnancy complications are further supported by a report addressing that pregnant women with lower levels of *lactobacillus* and a higher abundance of the bacterial species *Gardnerella vaginalis* in the vagina had an increased risk of preterm labor (Blaszczak-Boxe, 2015). Other reports have indicated that BV results in the production of mucolytic enzymes that may breach maternal defenses, thus exposing the chorioamnion to other urogenital tract infections (Fiscella, 1996). Women with BV have different vaginal microbiomes than women without bacterial vaginosis. More specifically, women with BV show an increase in the concentration and variety of non-lactobacillus bacteria, including *Gardnerella vaginalis*; the concentration of these bacteria in the vagina are up to 1,000-fold higher in patients with BV than in patients with a *lactobacillus*-dominant flora

(Eschenbach, 1993). *Gardnerella vaginalis* is the pathogen responsible for the initiation of BV (Schwebke et al., 2014).

From a racial disparity perspective, African American women are twice as likely to be diagnosed with BV (Fettweis et al., 2014). Another study reports similar data indicating that BV is associated with a significantly higher risk among black women compared to white women and that such racial differences indicate that BV may contribute to as much as 60% of the racial disparity in preterm labor (Fiscella, 1996).

White women are more protected and are less likely to develop bacterial vaginosis, according to a study showing that an increased frequency of *L. crispatus*, which is commonly found in white women, was significantly linked to a lower prevalence of BV, thus preventing the growth of the BV-related micro-organisms, *G. vaginalis,* an anaerobic gram-negative rods (Antonio et al., 1999). Other related studies indicate that *L. crispatus* has been shown to have a fivefold decreased risk for developing BV (Fettweis et al., 2014). What is the impact, if any, between BV and diet?

d) Diet and Bacterial Vaginosis

The relationship between the quality of food and health is well established (Bahr, 2007). As discussed earlier, recent studies have also demonstrated a link between diet and the gut microbiome, and that Western diets negatively alter gut microbiome, which subsequently negatively impacts the health of the host (David et al., 2014). Interestingly, just as with the gut microbiome, most recently, several studies have found associations between BV and poor micronutrient status, including inadequate levels of vitamins A, C, E, and D and β-carotene, as well as low dietary intakes of folate, calcium and vitamin E (Thoma et al., 2011). The same

study previously assessed the association between macronutrient intake and BV in 1,520 predominately African American women 15–44 years of age and found an increased risk of BV among women with higher energy and total fat consumption (Thoma et al., 2011). A similar but separate study was also conducted aimed at evaluating the association between diet and the presence of BV in 1,521 women, of which 86% were African-America (Neggers et al., 2007). This study revealed that increased dietary fat intake is associated with an increasing risk of BV and severe BV, whereas, increased intake of phytonutrients, such as folate, vitamin A and calcium may decrease the risk of severe BV (Neggers et al., 2007). Collectively, these and data cited earlier, link BV to diet and for this reason we speculate that one of the main factor that could be contributing to higher rates in preterm labor in African American women than their white counterparts (Thoma et al., 2011) could likely be lack of access to plant-based foods due to "food deserts" in their communities.

4. DIET, MICROBIOME AND PRETERM LABOR

Preterm labor is a multifaceted and complicated disorder. However, we know that one of the major cause is infection and the subsequent inflammation (Agrawal et al., 2011). Infection could arise from the external environment or from virulent gut and or vaginal flora altered by unhealthy diets. Regardless of the source, the pathogenic microbes that infect the placenta and cervix will ultimately lead to fetal membrane rupture, cervical incompetence and uterine contraction. For instance, (a) the amniotic fluid of patients with preterm labor has higher rates of microbial colonization and levels of inflammatory cytokines than preterm patients not in labor and term patients in labor, (b) intrauterine or systemic administration of microbes or microbial products to pregnant animals can result in preterm labor and delivery (c) extrauterine maternal infection, such as pyelonephritis, pneumonia, and periodontal disease have been associated with

premature parturition, (d) subclinical intrauterine infections are associated with preterm labor and delivery and (e) patients with intra-amniotic infection or intrauterine inflammation (i.e. elevation of amniotic fluid cytokines and matrix-degrading enzymes) identified as early as the mid-trimester are at risk for subsequent preterm delivery(Agrawal et al., 2011).

A large Norwegian study makes a direct link between diet and preterm birth and diet. The results from the study found that pregnant women, who ate a prudent diet rich in vegetables, salad, fruit, berries and nuts were linked to a lower risk of preterm birth, especially women who were having their first baby (Lewis et al., 2014). In contrast, pregnant women, who ate a Western diet containing a lot of salty snacks, chocolate and sweets, cakes, French fries, white bread, ketchup, sugar sweetened drinks, processed meat products, and pasta had an increased risk for preterm labor. Researchers noted that their finding do not establish a causal link between diet and preterm birth (Lewis et al., 2014). Here, we propose a causal link between diet, virulent bacteria and preterm labor, i.e., unhealthy diet induces virulent and infectious bacteria in the flora of the gut and vagina, which will then either ascend to the uterus and cervix or is transported through circulation to inflammation and its associated complications cited earlier, and ultimately preterm labor.

5. CONCLUSION

African American women are twice as likely to experience preterm birth as white women. Examining the underlying cause of this racial disparity was the main focus of the current study. Factors, such as smoking and stress have been previously proposed as the main precursors that lead to preterm labor. Here, we propose another less explored factor, namely diet. We hope we have provided here some reasonable evidence that will initiate discussions and studies on the

role of diet in the racial health disparities in preterm labor rates that currently exists in the US. Admittedly, the proposed relationship is not conclusive and thus will require further investigations. The primary goal of the current literature analysis was to "connect the dots", bring attention to the issue and provoke discussion on the potential role of "food desserts" on the high rates of preterm labor in low income African Americans. Firstly, our proposal is strengthened by the fact that black South Africans, with lower socioeconomic status and are largely on a plant-based diet, have a preterm labor rate at 8% (Figure 1)(Mongale, 2012). This rate (8%) is not only significantly lower than African Americans but is also lower than the USA national average, as well as that of white American women (Murphy et al., 2015); Secondly, the rate of preterm labor in the Appalachia region, such as Western North Carolina, which is predominately white with a lower socio-economic status and likely unhealthy diet, is at 14.3%, which is almost double that of South Africa, greater than the rest of the state in North Carolina, as well as the national US preterm rate (Figures 1 and 2) (Evans, 2014). Lastly, preterm lab rates in Europe is almost half that of the white Americans, which could in part be due to the difference in diet ("Born Too Soon: Preterm Birth in Europe Trends, Causes and Prevention" , 2015). Obviously, preterm labor is a complex and multifaceted complication. However, there is need for future studies to test whether a plant-based diet could alter the vaginal flora in African American women living in "food desert" communities and importantly whether this could, long term, reduce the rate of preterm labor in these communities. If the outcome is positive, vaginal bacteria markers could become a useful way to determine whether an expecting mother is at risk, as well as determine whether they are on a healthy diet. Ultimately, we hope that this could potentially lower the rates of and minimize the negative outcomes associated with preterm labor in African American women.

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FIGURES AND TABLES

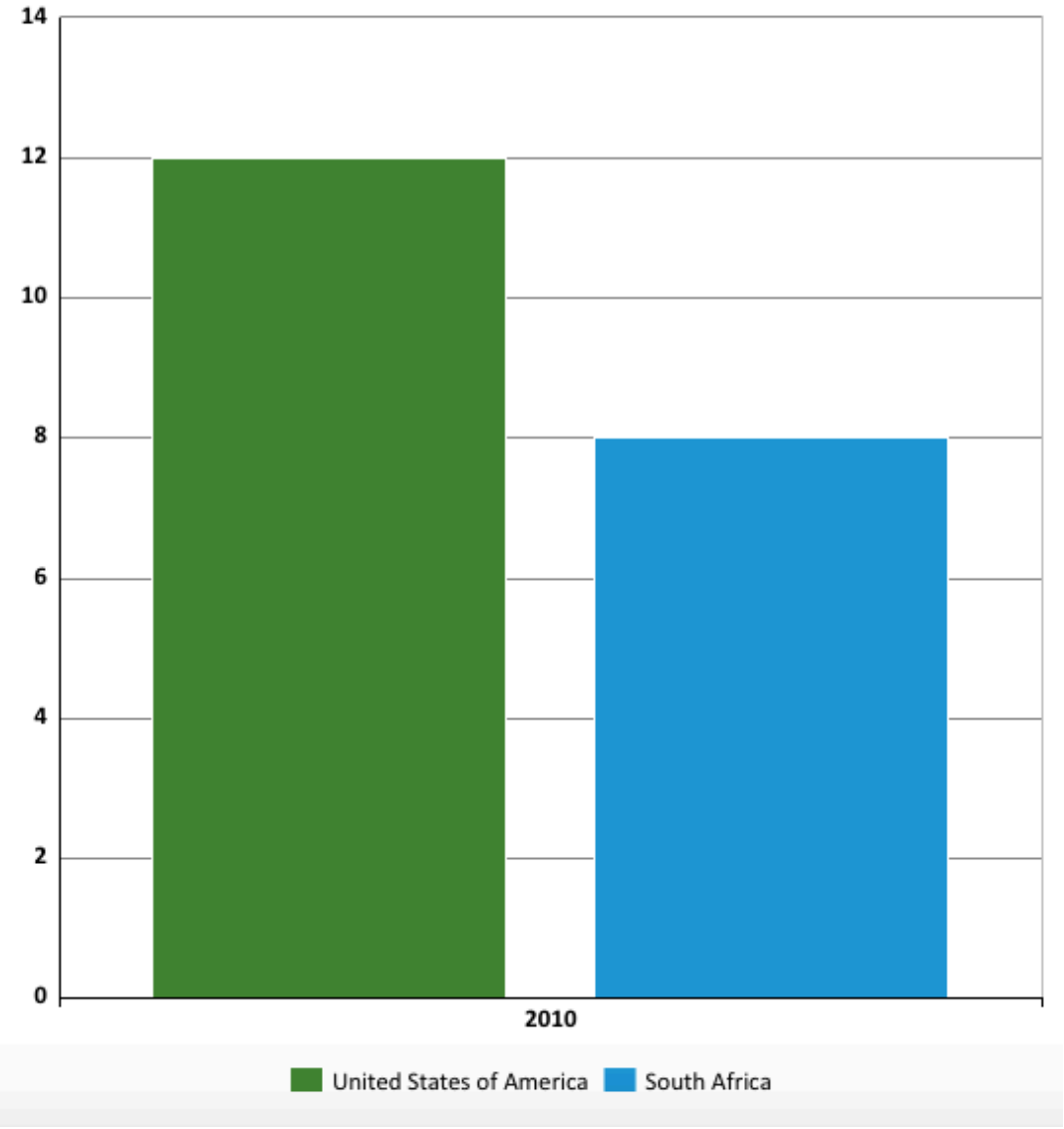

Figure 1. Comparison of preterm birth rate (per 100 live births) between the United States of America and South Africa in 2010.

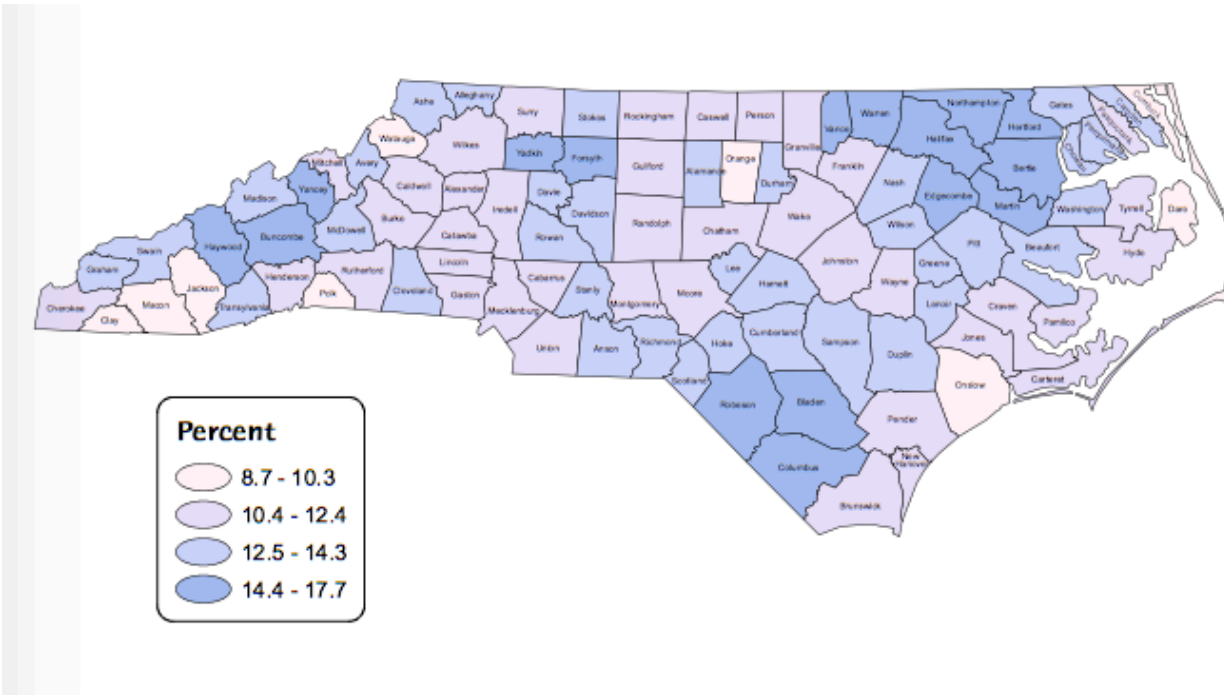

Figure 2. Preterm birth rates in North Carolina across counties between 2008 and 2012. Note that the high rates of preterm labor in the Western part of the state (Appalachia mountains), which is predominantly low income, is comparable to the large cities, where minority communities are more concentrated.