Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

______________________________ _______________

Callie McLean Date

An activity space approach to understanding how average distance traveled is associated with vaginal microbiome composition and preterm birth rates among pregnant African American women in Atlanta

By

Callie McLean
MPH

Epidemiology

____
Michael Kramer, PhD
Committee Chair

An activity space approach to understanding how average distance traveled is associated with vaginal microbiome composition and preterm birth rates among pregnant African American women in Atlanta

By

Callie McLean

B.S.,
University of South Carolina Honors College
2019

Thesis Committee Chair: Michael Kramer, PhD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
[Master of Public Health/Master of Science in Public Health]
in Epidemiology
2022

Abstract

An activity space approach to understanding how average distance traveled is associated with vaginal microbiome composition and preterm birth rates among pregnant African American women in Atlanta

By Callie McLean

Background: Preterm births, defined as deliveries before 37 weeks of gestational age, account for 10% of births in the United States and increase risk of many adverse health outcomes for both the mother and child. Evidence suggests that stress impacts risk for preterm birth. The vaginal microbiome protects the vaginal and reproductive systems, but factors like stress can affect the composition and risk of preterm birth. This study tests the hypothesis that having to travel further to important locations contributes to changes in vaginal microbiome that contribute to increased risk of preterm birth. The locations are defined as work, school, and doctor's offices.

Methods: A prospective investigation of the association between activity space travel to anchor locations and vaginal microbiome community state type, as well as preterm birth. Data are from the Emory University African American Microbiome in Pregnancy Cohort Study and the Sesame Street Study. Sociodemographic information, vaginal swabs, activity space data, and birth outcomes were collected from 71 pregnant African American women living in metropolitan Atlanta, Georgia. Statistical analyses were run in R.

Results: Of 121 women sampled, 71 women (59%) had provided vaginal microbiome samples, activity space data, and had completed all questionnaires. During the study, 45 women (63.4%) carried their baby to full term and 15 women (21.1%) had non-iners Lactodominant vaginal microbiome composition. An odds ratio of 1.03 (0.558, 1.90) was calculated for average distance traveled outside the residence and gestational age at birth outcome and an odds ratio of 1.03 (0.809, 1.31) was calculated for average distance traveled outside the residence and vaginal microbiome composition.

Conclusions: This study is one of the first to use activity space data to investigate the effect of distance traveled on vaginal microbiome composition and preterm birth outcomes. The data suggest no statistically significant associations between average distance traveled outside the residence while pregnant and birth status outcome and vaginal microbiome composition.

An activity space approach to understanding how average distance traveled is associated with vaginal microbiome composition and preterm birth rates among pregnant African American women in Atlanta

By

Callie McLean

B.S.,
University of South Carolina
2019

Thesis Committee Chair: Michael Kramer, PhD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
[Master of Public Health or Master of Science in Public Health]
in Epidemiology
2022

Table of Contents:

1. Introduction

Epidemiology of Preterm Birth

The United States is one of the most developed countries in the world, yet has higher preterm birth and infant mortality rates than its comparable peers. There are approximately 15 million preterm births annually worldwide and, in 2017, one out of every 10 live births in the United States was classified as preterm (Purisch & Gyamfi-Bannerman, 2017). In 2008, preterm births were associated with 75% of perinatal mortality in the United States (Goldenberg et al., 2008). In 2018, the infant mortality rate was 5.67 per 1000 live births (Ely & Driscoll, 2021). Racial disparities exist within these rates, meaning there are even higher rates in select populations (Schaaf et al., 2012). These rates are alarming and previous research into the mechanisms behind this problem has not been able to comprehensively explain why the United States has such high numbers. There are many factors that need to be investigated further and addressed before these rates will be reduced.

Past research into the epidemiology of preterm births has defined preterm birth, analyzed historical trends, identified causal pathways, risk factors, consequences, and racial, ethnic, and geographic disparities (Purisch & Gyamfi-Bannerman, 2017; Goldenberg et al., 2008). Preterm birth is classified as any delivery before 37 weeks of gestational age. There are several different sub-classifications of preterm birth, all with their own rates and complications. Early or very preterm births are classified as occurring before 32 weeks of gestational age, moderate preterm births are classified as occurring between 32 and 34 weeks of gestational age, and late preterm birth are classified as occurring between 34 and 37 weeks of gestational age. The majority of preterm births (71.4% in 2015) are classified as late preterm, but early preterm births still account for a sizable amount of all preterm births (16.4% in 2015) and have the worst health outcomes. Babies that are born preterm are at risk for complications like cerebral palsy, poor eyesight, lung and muscle underdevelopment, respiratory distress syndrome, and sepsis among many other adverse health outcomes (Purisch & Gyamfi-Bannerman, 2017). It is paramount for pediatric health to reduce early preterm birth rates.

Preterm births can also be classified as spontaneous or iatrogenic (indicated) preterm births. Iatrogenic preterm births occur when there are medical conditions that would endanger the mother and fetus. Examples of these conditions include preeclampsia, gestational or uncontrolled diabetes, and placental abnormalities. Physicians purposely deliver babies early in these situations to protect the health of both the mother and the child. These are planned deliveries, usually cesarian, that are conducted with a curated team of health professionals and medical devices designed to maximize the chance of a positive health outcome. However, there is still a risk for both the mother and the child. Indicated preterm births account for one third of preterm births (Purisch & Gyamfi-Bannerman, 2017). Spontaneous preterm births account for approximately two thirds of preterm births. Spontaneous preterm births occur when women suddenly start labor before 37 weeks of gestational age. These deliveries are not planned and do not have the same precautions as indicated preterm births. These births can be very dangerous for both the mother and child and there is a high chance of complications. There are many common risk factors that have been identified for spontaneous preterm births. Women that have had previous preterm births, multiple pregnancies, consecutive pregnancies with little time in between, short cervical lengths, uterine abnormalities, low maternal body mass, or vascular disease are all at increased risk of spontaneous preterm births (Purisch & Gyamfi-Bannerman, 2017; Goldenberg et al., 2008). However, approximately half of women who experience preterm births have none of these risk factors, so research has been done to try to identify what additional factors may contribute to preterm births (Wadhwa et al., 2001). There is still much to be learned about these factors.

Stress and Preterm Birth

Maternal stress is a factor that has been researched more in recent decades. There are a few proposed physiological causal pathways related to maternal stress for spontaneous preterm births. One pathway is a neuroendocrine pathway. When a woman is pregnant, a fetus develops inside the uterus and is attached to a placenta. The placenta supplies the fetus with oxygen and nutrients and serves as a connection between the mother and the fetus. The neuroendocrine pathway helps regulate homeostasis, metabolism, energy, osmolarity, and blood pressure, among other functions. These functions help the fetus develop and grow throughout the pregnancy. When a fetus is fully developed and ready to be delivered, usually after 39 weeks of gestation, the pathway will activate parturition (labor). One hypothesis is that maternal stress would prompt these maternal-placental-fetal endocrine systems to activate parturition early, resulting in preterm birth. Another proposed pathway is an immune/inflammatory pathway. The hypothesis is that maternal stress would weaken immunity and increase risk of infection. Infection has been shown to activate parturition in an attempt to protect both the mother and the child. There is another hypothesis that there is a multiplicative effect of stress and infection due to the pathways cross-regulating each other (Wadhwa et al., 2001). It is clear that stress affects pregnancy and labor, but it is not yet known what threshold of stress helps trigger preterm birth.

There are still questions on how best to quantify and classify stress and how different types of stress may impact risk of preterm birth. It is important to consider when stress occurred, how long it occurred, what type of stress was experienced, and how severe the stress was. These can be difficult to measure as stress can be relative for each individual. Chronic stress is known to be associated with adverse health outcomes in general. Corticotrophin-releasing hormone (CRH) is important in stress response. One theory about the effects of chronic stress on preterm births is that chronic stress disrupts the CRH-cortisol feedback loop that helps regulate stress responses, resulting in hypothalamic-pituitary-adrenal axis (HPA) dysfunction during pregnancy. This would help trigger parturition. Another theory is that chronic stress alters the immune and inflammatory responses of the body, making pregnant women more susceptible to infections and preterm births. A third theory posits that chronic sympathetic activation, or sustained increased heart rate or blood pressure, changes the mother's vascular tone. Vascular dysfunction is a known risk factor of preterm birth. Racial disparities have been found in studies involving all of these theories (Kramer et al., 2011). Stress affects all pregnant women, but it affects some populations of pregnant women unequally.

Racial Disparities in Preterm Births

One trend in preterm births that has remained consistent through time is significant racial disparities. Studies have found African American women have a 60% excess risk for moderate preterm births compared to White women (Kramer et al., 2011). As stated before, very preterm births are births that occur before 32 weeks of gestation. Although this kind of preterm birth only accounted for 2% of all live births in the United States in 2011, it accounted for a third of all infant deaths. The rates are even more alarming when they are stratified by race. African American women are two to three times more likely to have a very preterm birth than their non-Hispanic white counterparts (Kramer & Hogue, 2009). This disparity persists even when adjusted for education, access to health care, socioeconomic data, and other behavioral factors.

Women in minority groups overall have experienced an increase in preterm births. This is concerning given the advancements in medicine.

Studies that have found great genetic variability in preterm birth rates within races reject hypotheses that these disparities are due to genetic differences between races alone (Wadhwa et al., 2001). Data show that immigrants of sub-Saharan Africa who delivered their babies in the United States had preterm birth rates comparable to native born White women. However, daughters of those same immigrants experienced higher preterm birth rates than their mothers. Conversely, preterm birth rates were lower for daughters of White immigrants compared to their mothers. Living in the United States has a protective effect on preterm birth rates for children of White immigrants, but a harmful effect on preterm birth rates for children of African immigrants. This suggests that there is a systemic stressor, racism, that is affecting Black women in the United States (Kramer et al., 2011). Further research into the compound effect of racism and other risk factors on preterm birth rates is being conducted.

Vaginal Microbiome

Researchers are becoming more interested in a different factor, the composition of the vaginal microbiome. Research is being conducted on both the composition and the factors that could affect this composition. The vaginal microbiome is a complex ecosystem that helps regulate bacteria and PH levels in the reproductive and urinary tracts and fights against infections. It has a delicate composition of microbiota that allows it to function seamlessly. Disruptions in this composition can result in infection, inflammation, and may also be a risk factor for preterm births. Historically, researchers have believed that a microbiome dominated by the *Lactobacillus* genus with very little microbiota diversity was associated with a healthy pregnancy and reproductive tract. The *Lactobacillus* genus is a lactic acid producing species that can also produce hydrogen peroxide, metabolites, and bacteriocins. Bacteriocins are bacteria produced peptides that can kill bacterial strains that pose a threat to the immune system. Therefore, the *Lactobacillus* species is believed to have a protective effect on the vaginal microbiome (Huang et al., 2014).

A study done using data from the Multi-Omic Microbiome Study: Pregnancy Initiative (MOMS-PI) analyzed vaginal samples from an ethnically diverse cohort of pregnant women who experienced spontaneous preterm birth and pregnant women who carried to term. The results of this study revealed that women who carried to term were more likely to have *Lactobacillus crispatus* dominated microbiomes than women who experienced spontaneous preterm births. Women who experienced preterm births had increased microbiota diversity in their vaginal samples compared to samples of women who carried to term. Their samples showed higher counts of *Megaspharea* type I and TM7-H1 (or BVAB-TM7), which have been associated with poor vaginal health in previous studies (Fettweis et al., 2019). There have been studies, however, that have shown lower levels of *Lactobacillus* species and higher levels of anaerobic bacteria in healthy women that carried their pregnancies to term.

Additionally, there are differences in concentrations across different ethnicities and races. Studies have found that while an overwhelming majority (80-90%) of both Asian and White women tend to have *Lactobacillus* dominant microbiomes, a lower proportion (60%) of Hispanic and African American women have the same vaginal microbiome composition. African American women tend to have a higher proportion of anaerobic microbiota, more diverse microbiota, and a composition more similar to standard diagnostic criterion for bacterial vaginosis (BV). BV is generally defined as a vaginal infection or bacterial imbalance. It is considered a risk factor for preterm birth. These results suggest that some ethnicities are predisposed to have a more diverse microbiome as well as higher risk of preterm birth. They also suggest that genetic factors impact the composition of the vaginal microbiome as well as vaginal and reproductive tract health (Huang et al., 2014). The combined effects of genetic factors and social determinants of health is a gap in the research that needs more investigation.

The vaginal microbiome is extremely complex and the mechanisms it uses to regulate and maintain itself is not completely understood. The composition of the microbiome can be affected by age, stage of menstrual cycle, diet, medication, contraception, sexual activity, and external or environmental factors. When the composition of the microbiome is altered, it makes women more susceptible to illness. In pregnant women, it can make them more susceptible to preterm birth and complications (Fettweis et al., 2019). There is a gap in the research on how social determinants of health, lived experiences, and other environmental factors can impact the vaginal microbiome and, consequently, preterm birth rates.

Activity Space Analyses

I am interested in an activity space analysis that investigates if the distance pregnant women travel to different anchors from their home is associated with changes in the vaginal microbiome. These anchors are defined as their work, school, and doctors' offices. These locations were chosen for their significance in every day life and pregnancy. Work and school is frequented on a regular basis. During pregnancy, a women will likely attend many appointments at doctor's offices. An activity space analysis investigates how someone moves and interacts with their environment. Activity space is defined as the places someone frequents outside of their place of residence. Standard deviational ellipses (SDE) are usually used to represent an activity space. These studies can use different methods like Global Positioning System (GPS) and Geographic Information System (GIS) to track participants' movements throughout their days

(Sherman et al., 2005; Zenk et al., 2011). Activity space studies are important because they consider the effect of environments outside of the home. This is an environment that is largely unexplored. Locations were categorized into different groups, including work, school, doctor-related, and more transient locations like shops and restaurants. Stress is a risk factor of preterm birth and has been shown to affect vaginal microbiome composition. Women that have to travel further may have increased stress compared to their peers who travel less far. There are many possible mechanisms. Traveling further could be indicative of having less support or a weaker support system, which could increase stress for the woman. It could also mean more time spent in transit and traffic, which could increase stress. Traveling further to work, school, and the doctor could also mean the women have to wake up earlier and are getting less sleep. There are many possible sources of stress related to traveling further. Activity space data collected for each pregnant woman in the study can be compared with vaginal, anal, and oral microbiome samples taken during their pregnancies. This allows for comparison of microbiome composition with specific travel and movements. Activity space data can also be paired with birth status outcomes. This allows for causal pathways to be explored by pairing different data collections.

Aims and Questions

The aim of this study is to take an activity space approach to understand how distance to anchors is associated with vaginal microbiome composition and preterm birth among African American women living in Atlanta. There are many associated questions with this aim. One question that will be explored is whether being further from anchors is associated with Iners dominant or diverse microbiome composition. A higher level of *Lactobacillus* genus microbiota or non-iners Lactodominance is found in women who carry to term (Huang et al., 2014). There is still much unknown about the factors that affect vaginal microbiome composition. This study will explore a possible causal pathway and give insight into any precautions or steps that can be taken to promote ideal vaginal microbiome composition. A second question is whether being further away from anchors is associated with higher rates of preterm birth. There are several known causes of preterm birth, but not all preterm births are explained by these known factors or pathways (Purisch & Gyamfi-Bannerman, 2017; Goldenberg et al., 2008; Wadhwa et al., 2001). This study aims to help close this knowledge gap by exploring a new possible causal pathway. Findings could help inform guidance and recommendations for pregnant women.

2. Methods

Population

A prospective cohort design was used for the Emory University African American Microbiome in Pregnancy Cohort Study, which began in 2017. The study followed African American women living in Atlanta for the duration of their pregnancy. Investigators collected vaginal microbiome samples, demographic data, data on preterm birth risk factors, data on social determinants of health, and birth outcome data. A subset of this population was sampled for the simultaneous Sesame Street Study, another prospective cohort study.

The Sesame Street Study recruited pregnant women from the Emory University African American Microbiome in Pregnancy Cohort Study. This study recruited African American pregnant women between the ages of 18 and 40 years from Grady Memorial Hospital and Emory University Hospital Midtown in Metropolitan Atlanta. Women were recruited if they presented for their first prenatal visit at one of these hospitals between 8 and 14 weeks of gestation. This was verified by their clinical record and/or ultrasound. These hospitals were chosen due to the fact that, together, they have a wide reach over various income levels and one is public and the other is private. Biological samples and questionnaires were collected at both prenatal visits and again between 24 and 30 weeks of gestation. Clinical data was collected post-delivery. Participants could not be expecting multiple children and they were required to be able to competently speak and write English. Participants could also not have any chronic medical conditions or be on any chronic prescriptions, which was verified by clinical records. Participants were also required to live within 20 miles of the laboratory.

The Emory University African American Microbiome in Pregnancy Cohort Study’s goal was to recruit at least 540 women to have a robust sample of women to collect data from. The

Sesame Street Study includes 121 women who were selected to provide activity space data. This study is ongoing and there are currently 71 women in this subset who also have microbiome data processed by the lab.

Measures of outcomes

There are two outcomes in this study: gestational age at birth and vaginal microbiome community state type. Gestational age at birth outcomes were classified as full term, medically indicated early term birth, medically indicated preterm birth, spontaneous early term birth, spontaneous preterm birth, or fetal loss. Preterm births are classified as any delivery before 37 weeks of gestational age and early term births are a subclassification defined as any delivery before 32 weeks of gestational age. A fetal loss is defined as an intrauterine loss of fetus after 20 weeks of gestational age. Medically indicated early or preterm births are planned deliveries before 37 weeks of gestational age due to medical conditions that endanger the life of the mother and/or fetus. Spontaneous early or preterm births are deliveries before 37 weeks of gestational age that are not planned. This study dichotomized births as carried to full term and not carried to full term, with every outcome but full term being categorized as not carried to full term. Birth outcomes were collected from medical records. This was done using a standardized chart abstraction tool (Dunlop et al., 2021).

Vaginal microbiome composition was categorized as "Non-iners Lactodominant" and "Iners Dominant or Diverse". Vaginal microbiome sample type classification was determined by composition of different bacteria like *Lactobacillus*. Samples that were identified as community state type I, community state type II, or community state type V were classified as "Non-iners Lactodominant". This composition was considered favorable based on evidence from past microbiome studies. Samples that were identified as community state type III, community state type IV-A, community state type IV-B, or community state type IV-C were classified as "Iners Dominant or Diverse". Five vaginal swabs were self-collected from each woman. Participants were given detailed instructions on how to collect vaginal swabs and immediately handed samples to a research coordinator upon completion. Previous studies support that self-collected vaginal swabs have comparable validity to physician-collected swabs. The first two swabs, Sterile Catch-All™ Sample Collection Swabs, were frozen on dry ice and stored upright in MoBio bead tubes at -80°C until researchers were able to measure the vaginal microbiome and extract DNA. Samples were sequenced using V3-V4 region of the16 rRNA gene. A third swab determined the vaginal pH using pH strips. The fourth swab was used for later classification of vaginal cytokines and was also stored at -80°C. The fifth and final swab was used to determine presence of BV. The swab was tested in the Emory Clinical Microbiology laboratory using the Nugent criteria after being rolled onto a glass microscope slide (Dunlop et al., 2021).

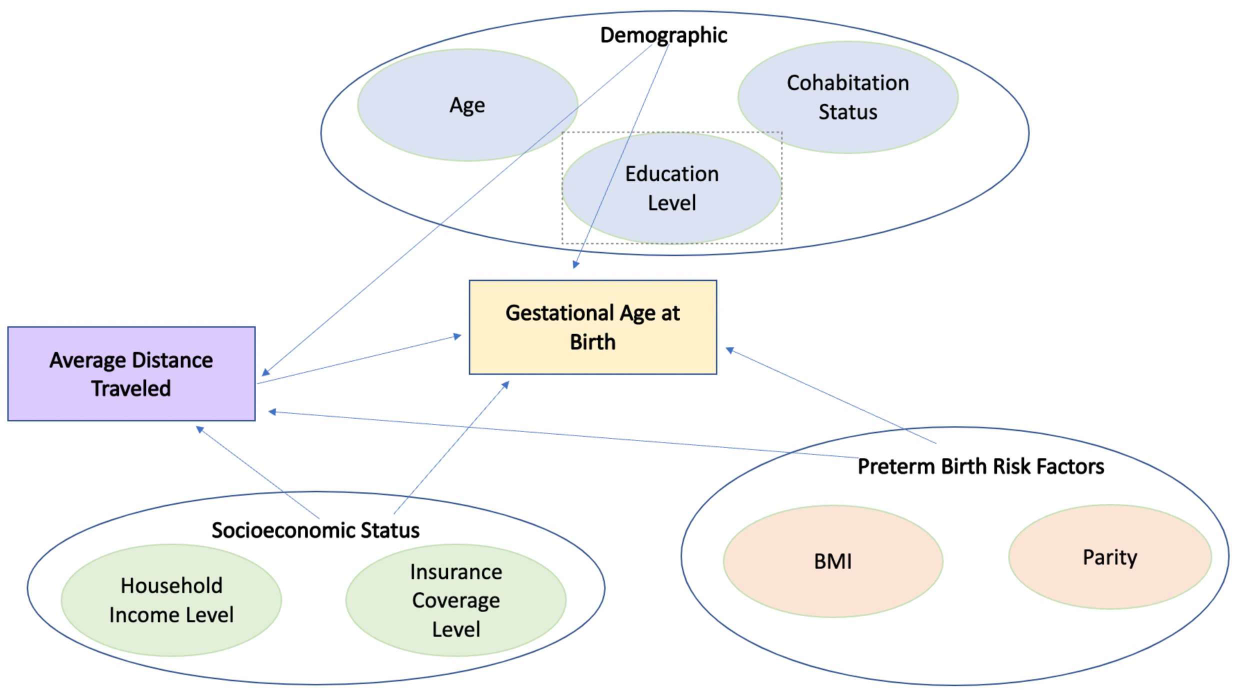
Measures of Exposure

The exposure in this study is the average distance the women traveled to work, school, and their doctors during their pregnancy. Locations were categorized into groups based on type of place. Distance traveled was calculated using longitude and latitude coordinates of activity space data provided by participants on the two questionnaires administered. Each woman's residence was used as their starting point for calculations. The gmapsdistance package in R was used to calculate distance traveled to each category of location by street network. Distance traveled was then averaged using the calculated distances from the three categories for each woman.

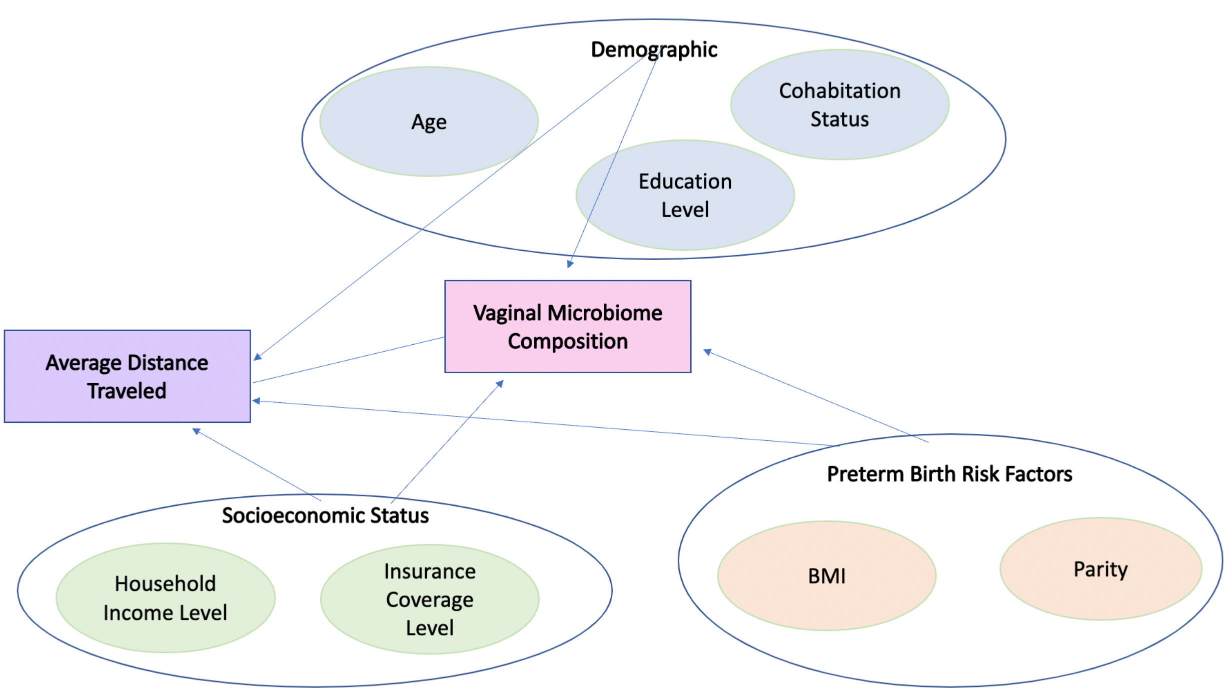
Covariates

Potential confounders are preterm birth risk factors, demographic information, and variables contributing to socioeconomic status. Demographic variables included age, cohabitation status, and education level. These demographic variables were selected because they are related to both outcomes as well as the exposure. Age and education level could affect whether the women is traveling to work or school and could impact how far they have to travel. Cohabitation status, categorized by whether the woman was living with her partner, could affect a woman's working status, their access to transportation, or if they have help with tasks like driving any children to school. Variables contributing to socioeconomic status include household income level and insurance coverage level. These socioeconomic variables were chosen because they also relate to both outcomes and the exposure. Household income, categorized using income levels, could affect working status, access to transportation, and selection of schools and doctors. Insurance coverage level, categorized by coverage type, could affect attendance of doctors visits. Preterm birth risk factors include how many children each participant has and body mass index at the first prenatal visit. These risk factors were chosen because they also relate to both outcomes and the exposure. Number of children could affect availability for doctors' appointments, traveling to school, and working status. Body mass index at the first prenatal visit could be affected by time spent traveling and ability to exercise and eat along recommended guidelines. Data on these covariates were collected from questionnaires participants completed as well as abstracted from medical charts. REDCap management software was used to enter and manage data from medical charts, questionnaires, and lab tests (Dunlop et al., 2021).

Dag 1. Causal Pathway of Average Distance Traveled and Preterm Birth



Dag 2. Causal Pathway of Average Distance Traveled and Vaginal Microbiome Type



Addressing bias

Several efforts were made to address and minimize bias. To minimize selection bias, the two hospitals selected represent public and private hospitals and treat patients from a wide range of socioeconomic backgrounds. The Sesame Street subset is a random subset of the Emory University African American Microbiome in Pregnancy Cohort Study, also minimizing selection bias. Distance traveled was averaged across each woman to minimize self-report bias and measurement error. Locations were categorized to aid in calculation and reduce measurement error. Potential confounders were adjusted for.

Data Analysis

Poisson regression analyses were run on models using a generalized estimating equation (GEE) to evaluate the relationship between average distance traveled and gestational age at birth as well as average distance traveled and vaginal microbiome composition. Analyses were run on the unadjusted model as well as models adjusting for demographic factors, demographic and socioeconomic factors, and demographic, socioeconomic, and preterm birth risk factors. Estimates were exponentiated to obtain prevalence ratios and confidence intervals were calculated. Histograms were produced to show the relationships between the outcome variables and average distance traveled categorized by natural clustering

Any missing data was addressed through complete case analysis. Women that did yet have microbiome data lab processed were not included in these calculations.

3. Results

There were 121 women sampled in the Sesame Street Study. At the time of this analysis, 71 women (59%) had provided vaginal microbiome samples, activity space data, and had completed all questionnaires. Each woman was followed from her first prenatal appointment at 8-14 weeks of gestation until a birth status outcome was achieved. During the study, 45 women (63.4%) carried their baby to full term and 15 women (21.1%) had non-iners Lactodominant vaginal microbiome composition. The mean age of the study population was 25.6 years and ages ranged from 18 to 35 years. The average education level was 2.45 on a scale where the maximum was 4 and the average income level was –0.188 on a scale where the maximum was 0.584. The categorization of average distance traveled at the median was decided by natural clustering of distances visualized in plots. Summary statistics can be seen in Table 1.

Table 1. Summary of gestational age at birth outcomes, vaginal microbiome composition, and demographic, socioeconomic, and preterm birth risk factors by average distance traveled outside the residence

	Shorter (less than 45 10 km units) (N=36)	Longer (greater than 45 10 km units) (N=35)	Overall (N=71)
Gestational Age at Birth Outcome			
Carried to Term	23 (63.9%)	22 (62.9%)	45 (63.4%)
Not Carried to Term	13 (36.1%)	13 (37.1%)	26 (36.6%)
Vaginal Microbiome Composition			
Iners Dominant or Diverse	28.00 (77.80%)	28.00 (80.00%)	56 (78.90%)
Non-iners Lactodominant	8.00 (22.20%)	7 (20.00%)	15 (21.10%)
Age	26.10 (4.26)	25.10 (5.02)	25.6 (4.65)
Education Level	2.56 (1.00)	2.34 (0.97)	2.45 (0.98)
Cohabitation Status	0.53 (0.51)	0.49 (0.51)	0.51 (0.50)
Insurance Coverage Level	1.94 (0.72)	1.89 (0.80)	1.92 (0.75)
Household Income Level	-0.22 (0.22)	-0.16 (0.24)	-0.19 (0.226)
Parity	0.67 (0.48)	0.60 (0.50)	0.63 (0.49)
First Prental BMI Level	2.81 (1.01)	2.91 (0.95)	2.86 (0.98)

Table 1 shows how average gestational age at birth outcomes, vaginal microbiome types, demographic variables, socioeconomic variables, and preterm birth risk factors are distributed across categories of average distance traveled outside the residence by women during their pregnancy (in 10 km units)

Values are percentages for gestational age at birth outcome and vaginal microbiome composition and mean (standard deviation) for all other variables

Recognizing the natural clustering of average distances traveled, Figures 1 and 2 show the distribution of different categories of gestational age at birth outcomes and vaginal microbiome types across categories of average distance traveled. The categories were 'Shorter (less than 45 10 m units)', and 'Longer (greater than 45 10 km units)'. The groups were relatively equal in size. Both categories of average distance traveled had almost identical distributions of gestational age at birth outcome. Likewise, both categories of average distance traveled had a relatively similar distribution of vaginal microbiome composition outcomes. Both outcomes of interest, not carrying the baby to full term and non-iners Lactodominant vaginal microbiome composition, were the more rare outcomes in this sample, as visualized in Figures 1 and 2.

Figure 1.

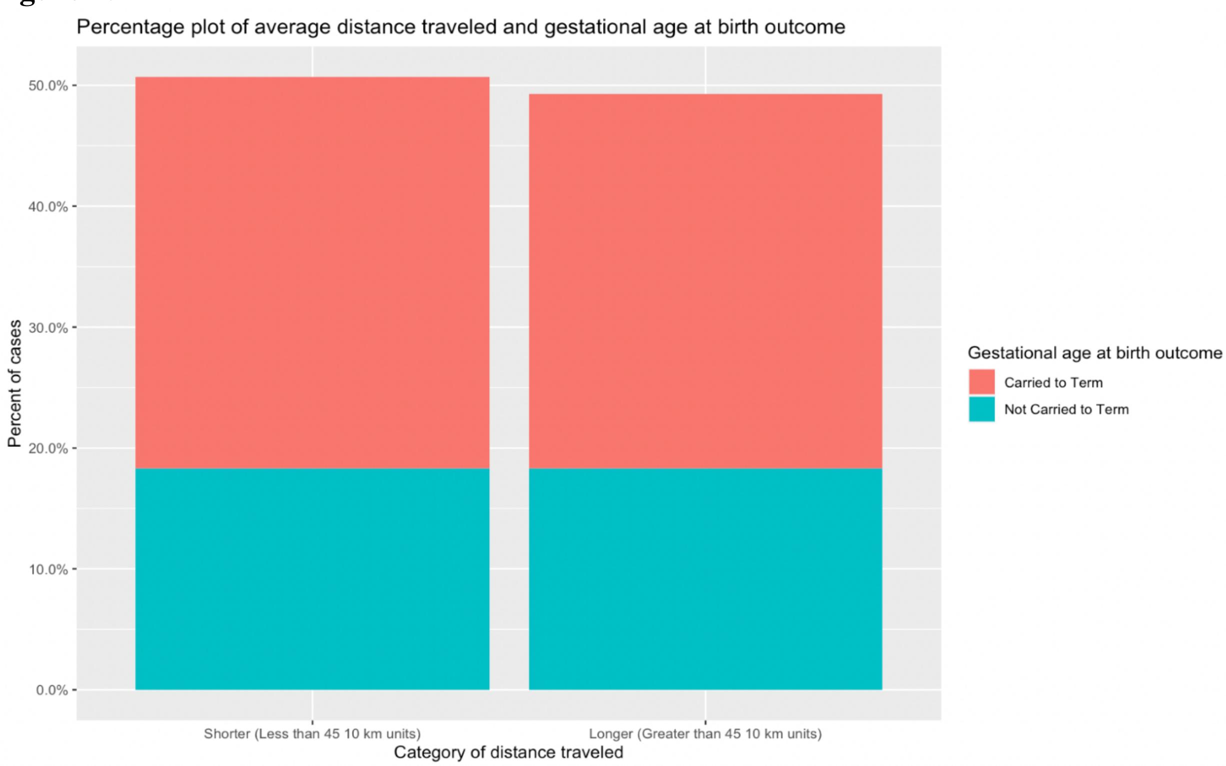


Figure 1 shows how the vaginal microbiome composition types are distributed across the two categories of average distance traveled

Figure 2.

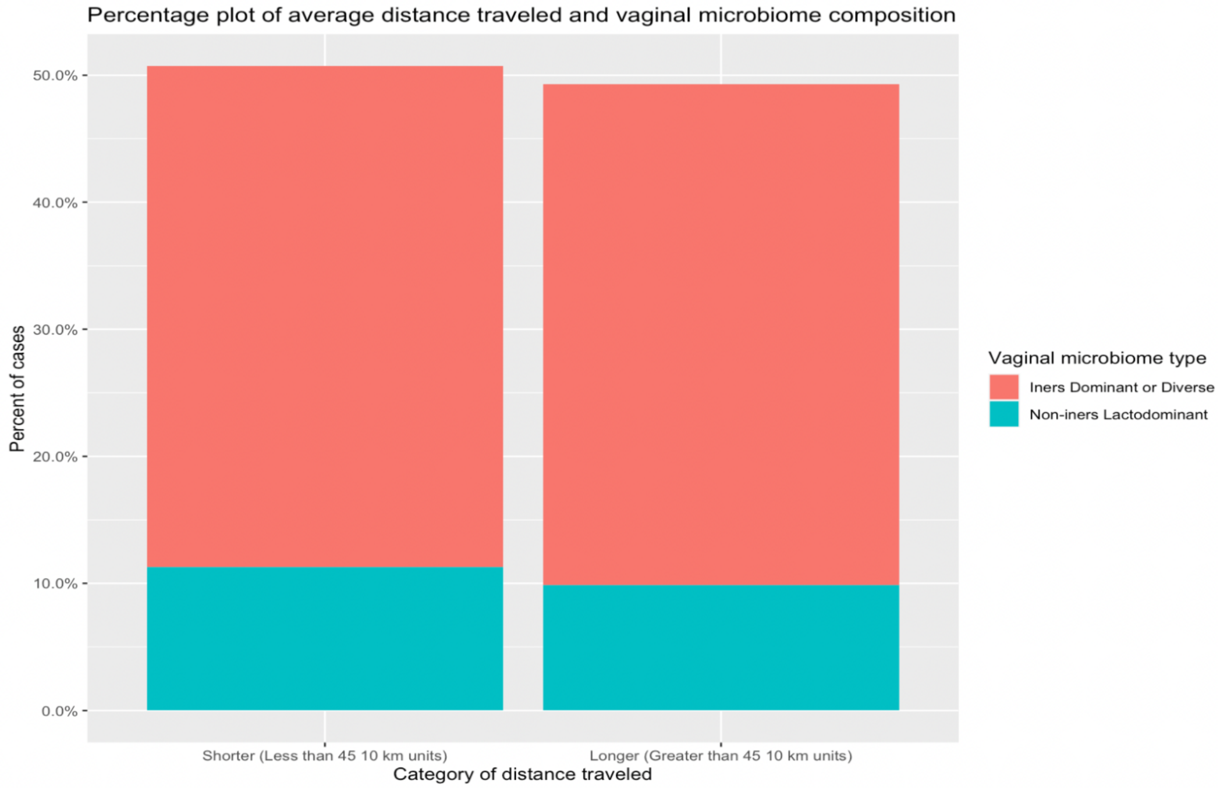


Figure 2 shows the percentage of how the vaginal microbiome composition types are distributed across the two categories of average distance traveled

The reference group for Poisson regression analyses was 'Shorter (Less than 45 10 km units)'. The calculated prevalence ratio for the unadjusted model of the relationship between average distance traveled outside the residence and gestational age at birth outcome was 1.03 (0.558, 1.90). The calculated prevalence ratio for the unadjusted model of the relationship between average distance traveled outside the residence and vaginal microbiome composition was 1.03 (0.809, 1.31).

Additional models were run adjusting for demographic, socioeconomic, and preterm birth risk factors. These models can be seen in Tables 2 and 3. The adjusted models did not greatly change the estimated odds ratios for either outcome of interest.

Table 2. Poisson regression analysis of gestational age at birth outcome and average distance traveled (ref= Shorter (less than 45 10 m units))

Model	PR	2.5%	97.5%
Gestational age at birth outcome ~ Average distance traveled	1.03	0.59	1.90
Gestational age at birth outcome ~ Average distance traveled + Age + Educational Level + Cohabitation Status	1.02	0.55	1.89
Gestational age at birth outcome ~ Average distance traveled + Age + Educational Level + Cohabitation Status + Insurance Coverage Level + Household Income Level	1.13	0.62	2.07
Gestational age at birth outcome ~ Average distance traveled + Age + Educational Level + Cohabitation Status + Insurance Coverage Level + Household Income Level + First Prenatal BMI Level + Parity	1.12	0.62	2.01

Table 2 shows the estimated prevalence ratio and corresponding confidence intervals from a Poisson regression analysis of various models exploring the relationship between gestational age at birth outcome and average distance traveled outside the residence during pregnancy

Table 3. Poisson regression analysis of vaginal microbiome composition and average distance traveled (ref= Shorter (less than 45 10 m units))

Model	PR	2.5%	97.5%
Vaginal microbiome composition ~ Average distance traveled	1.03	0.81	1.31
Vaginal microbiome composition ~ Average distance traveled + Age + Educational Level + Cohabitation Status	0.88	0.65	1.21
Vaginal microbiome composition ~ Average distance traveled + Age + Educational Level + Cohabitation Status + Insurance Coverage Level + Household Income Level	0.96	0.77	1.21
Vaginal microbiome composition ~ Average distance traveled + Age + Educational Level + Cohabitation Status + Insurance Coverage Level + Household Income Level + First Prenatal BMI + Parity	0.99	0.79	1.25

Table 3 shows the estimated prevalence ratio and corresponding confidence intervals from a Poisson regression analyses of various models exploring the relationship of vaginal microbiome composition and average distance traveled outside the residence during pregnancy

4. Discussion

Key Findings

We hypothesized that the average distance traveled outside the residence by pregnant African American women living within Metropolitan Atlanta was associated with preterm birth and microbiome composition. Our hypotheses were not confirmed. Our outcomes of interest were preterm births and non-iners Lactodominant microbiome composition. Of the 71 women in the study, 26 women (37%) did not carry their baby to full term and 15 women (21%) had non-iners Lactodominant vaginal microbiome composition. The prevalence ratio was 1.03 (0.558,1.90) for the unadjusted model of average distance traveled outside the residence and gestational age at birth outcome. The prevalence ratio was 1.03 (0.809, 1.31) for the unadjusted model of average distance traveled outside the residence and vaginal microbiome composition. These estimates are not statistically significant and suggest no association for gestational age at birth outcome or vaginal microbiome composition. Models adjusting for demographic variables, demographic and socioeconomic variables, and for demographic, socioeconomic, and preterm birth risk factors were run as well. These models returned similar estimates to the unadjusted models, which can be seen in Tables 2 and 3.

Strengths

This study has several strengths. Women were followed closely and answered comprehensive questionnaires about their health status, reproductive history, socioeconomic status, and demographic information. Vaginal microbiome samples were taken and birth outcomes were abstracted from medical charts. Coordinates of locations visited were obtained from questionnaires and used to calculate distance traveled. Poisson regression analyses were run on unadjusted models, models adjusted for demographic factors, models adjusted for demographic and socioeconomic factors, and models adjusted for demographic, socioeconomic, and preterm birth risk factors. These analyses were run for both outcomes.

Limitations

There were limitations to this study. Since the study is ongoing, the number of women with available data was small. This could result in inaccurate estimates. Efforts were made to reduce selection bias by selecting hospitals that treated a diverse group of patients. Women in the Sesame Street study were randomly selected from the Emory University African American Microbiome in Pregnancy Cohort Study. Activity space data and demographic, socioeconomic, and preterm birth risk factors were self-reported, giving opportunity for measurement error and imprecision. Distance traveled was calculated using a google maps algorithm in R, but assumed women drove to their destinations. This provides opportunity for measurement error or imprecision if women used other modes of transportation.

Interpretation

There is no evidence to suggest a direct relationship between average distance traveled outside the residence and birth status outcome or vaginal microbiome composition. The prevalence ratio of 1.03 (0.558, 1.90) for the unadjusted model of the relationship between average distance traveled outside the residence and gestational age at birth outcome means that the likelihood of not carrying a baby to term having traveled longer is 1.03 times the likelihood of this occurring having traveled shorter. The calculated prevalence ratio of 1.03 (0.809, 1.31) for the unadjusted model of the relationship between average distance traveled outside the residence and vaginal microbiome composition means that the likelihood of having a non-iners Lactodominant composition having traveled longer is 1.03 times the odds of this occurring having traveled shorter. Both confidence intervals for these estimates contain 1, suggesting these results are not statistically significant. These results suggest no causative relationship with either outcome of interest.

Our original hypothesis was that women who traveled further on average to important places (work, school, and doctor's offices) would have higher incidence of preterm birth and Iners dominant or diverse microbiome composition. Stress is a known risk factor of both preterm birth and vaginal microbiome changes (Kramer et al., 2011; Wadhwa et al., 2001) and we believed that having to travel further would increase stress and, consequently, likelihood of preterm birth and iners dominant or diverse microbiome composition. However, we failed to account for the poverty paradox (Sumner, 2016). Women who traveled less on average might not have had the resources to travel to important locations. This could also increase stress, which could consequently increase odds of preterm birth and Iners dominant or diverse microbiome composition. These two competing theories could have worked against each other and affected the regression analyses and calculated risk ratios.

It is also important to note that vaginal microbiome composition varies by ethnic group. Previous studies have found women of African descent to have more diverse microbiomes than other races or ethnicities (MacIntyre et al., 2015; Ravel et al., 2010). This could partially explain why there was a high percentage of Iners dominant or diverse microbiome compositions. Historically, Iners dominant or diverse microbiome compositions are not considered health or ideal for a complication free pregnancy and delivery. However, if this type of microbiome composition is more normal for women of African descent, it could partially explain why there were not as many preterm births in this sample.

Activity space analysis is a valuable tool that is underutilized in public health. The relatively small sample size could have contributed, in part, to the conclusion that there was no association between average distance traveled outside the residence and gestational age at birth outcome or vaginal microbiome composition. A significant amount of time is spent outside the residence and exploring this environment could be useful. Activity space analyses could be conducted on this topic in the future to look at relationships between location-related variables like crime, pollution, water quality, neighborhood income, and access to reliable transportation. Findings from these studies could inform public policy decisions or programs and interventions designed to improve health and prevent adverse health outcomes. A mediation analysis where vaginal microbiome composition is the mediator between average distance traveled outside the residence and birth status outcome would be the suggested next step to examine a potential relationship between these three variables as vaginal microbiome composition could also have an effect on preterm birth.

Generalizability

This sample was small and consisted only of pregnant, African American women living in Metropolitan Atlanta, so the findings should not be generalized to other races or ethnicities. However, this analysis could be conducted on other populations for whom activity space, vaginal microbiome composition, and birth status outcome data are available. Analyses were conducted in R and can be replicated using our code.

Public Health Relevance

Preterm births are still a pressing issue facing women around the world and in the United States, despite great advances in medicine. Preterm births accounted for 10% of live births and 75% of perinatal deaths in the United States in 2008 (Goldenberg et al., 2008; Purisch & Gyamfi-Bannerman, 2017). Preterm births disproportionately affect African American women (Schaaf et al., 2012). This study explored possible relationships between average distance traveled outside the residence and both birth status outcome and vaginal microbiome composition in African American women living in Metropolitan Atlanta. Stress is a known risk factor of preterm birth and changes in vaginal microbiome composition, but data from this study suggests that distance traveled is not a likely direct contributor to stress. This helps direct future studies to explore other causes of stress and other aspects of activity space analyses.

Conclusion

The United States has made many advances in health and medicine over time yet still suffers from one of the highest preterm birth rates among developed countries. Both mother and child face higher risk of adverse health outcomes following preterm births. It is important to understand the factors that lead to preterm births in order to know which women may be at risk and be able to effectively prevent them from having preterm births. Identifying risk factors will allow for better preventative services, interventions, and maternal and neonatal care. This information could inform public health officials and healthcare providers where to implement these interventions and how best to structure them in different areas and populations. There has not been extensive research into the effect of the activity space on the rate of preterm births nor on a possible relationship with vaginal microbiome composition. People spend a significant amount of time outside of their place of residence and it is important to consider how activity outside of the home affects health and health outcomes. Vaginal microbiome composition has been investigated in several studies, but little research has been done attempting to link specific stressors or factors to changes in composition throughout the course of pregnancy. This information would be valuable in screening pregnant women for preterm birth risk and preventative measures. Preventing preterm births will improve health outcomes for both the mother and the child.

Funding

This study was funded by a grant from the National Institutes of Health, National Institute of Nursing Research (R01NR014800).

5. References

1. Purisch, S. E., & Gyamfi-Bannerman, C. (2017). Epidemiology of preterm birth. *Seminars in Perinatology*, *41*(7), 387-391. https://doi.org/https://doi.org/10.1053/j.semperi.2017.07.009

2. Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Epidemiology and causes of preterm birth. *The Lancet*, *371*(9606), 75-84. https://doi.org/https://doi.org/10.1016/S0140-6736(08)60074-4

3. Ely, D. M., & Driscoll, A. K. (2020). Infant Mortality in the United States, 2018: Data From the Period Linked Birth/Infant Death File. *National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System*, *69*(7), 1-18. http://europepmc.org/abstract/MED/32730740

4. Schaaf, J. M., Liem, S. M., Mol, B. W., Abu-Hanna, A., & Ravelli, A. C. (2013). Ethnic and racial disparities in the risk of preterm birth: a systematic review and meta-analysis. *Am J Perinatol*, *30*(6), 433-450. https://doi.org/10.1055/s-0032-1326988

5. Wadhwa, P. D., Culhane, J. F., Rauh, V., Barve, S. S., Hogan, V., Sandman, C. A., Hobel, C. J., Chicz-DeMet, A., Dunkel-Schetter, C., Garite, T. J., & Glynn, L. (2001). Stress, infection and preterm birth: a biobehavioural perspective. *Paediatr Perinat Epidemiol*, *15 Suppl 2*, 17-29. https://doi.org/10.1046/j.1365-3016.2001.00005.x

6. Kramer, M. R., Hogue, C. J., Dunlop, A. L., & Menon, R. (2011). Preconceptional stress and racial disparities in preterm birth: an overview. *Acta Obstet Gynecol Scand*, *90*(12), 1307-1316. https://doi.org/10.1111/j.1600-0412.2011.01136.x

7. Kramer, M. R., & Hogue, C. R. (2009). What Causes Racial Disparities in Very Preterm Birth? A Biosocial Perspective. *Epidemiologic Reviews*, *31*(1), 84-98. https://doi.org/10.1093/ajerev/mxp003

8. Huang, B., Fettweis, J. M., Brooks, J. P., Jefferson, K. K., & Buck, G. A. (2014). The Changing Landscape of the Vaginal Microbiome. *Clinics in Laboratory Medicine*, *34*(4), 747-761. https://doi.org/10.1016/j.cll.2014.08.006

9. Fettweis, J. M., Serrano, M. G., Brooks, J. P., Edwards, D. J., Girerd, P. H., Parikh, H. I., Huang, B., Arodz, T. J., Edupuganti, L., Glascock, A. L., Xu, J., Jimenez, N. R., Vivadelli, S. C., Fong, S. S., Sheth, N. U., Jean, S., Lee, V., Bokhari, Y. A., Lara, A. M., . . . Buck, G. A. (2019). The vaginal microbiome and preterm birth. *Nature Medicine*, *25*(6), 1012-1021. https://doi.org/10.1038/s41591-019-0450-2

10. Sherman, J. E., Spencer, J., Preisser, J. S., Gesler, W. M., & Arcury, T. A. (2005). A suite of methods for representing activity space in a healthcare accessibility study.

International Journal of Health Geographics, *4*(1), 24. https://doi.org/10.1186/1476-072X-4-24

11. Zenk, S. N., Schulz, A. J., Matthews, S. A., Odoms-Young, A., Wilbur, J., Wegrzyn, L., Gibbs, K., Braunschweig, C., & Stokes, C. (2011). Activity space environment and dietary and physical activity behaviors: A pilot study. *Health & Place*, *17*(5), 1150-1161. https://doi.org/https://doi.org/10.1016/j.healthplace.2011.05.001

12. Dunlop AL, Satten GA, Hu YJ, et al. Vaginal Microbiome Composition in Early Pregnancy and Risk of Spontaneous Preterm and Early Term Birth Among African American Women. Front Cell Infect Microbiol. 2021;11:641005. doi:10.3389/fcimb.2021.641005

13. MacIntyre, D. A., Chandiramani, M., Lee, Y. S., Kindinger, L., Smith, A., Angelopoulos, N., Lehne, B., Arulkumaran, S., Brown, R., Teoh, T. G., Holmes, E., Nicoholson, J. K., Marchesi, J. R., & Bennett, P. R. (2015). The vaginal microbiome during pregnancy and the postpartum period in a European population. Scientific Reports, 5(1). https://doi.org/10.1038/srep08988

14. Ravel, J., Gajer, P., Abdo, Z., Schneider, G. M., Koenig, S. S., McCulle, S. L., Karlebach, S., Gorle, R., Russell, J., Tacket, C. O., Brotman, R. M., Davis, C. C., Ault, K., Peralta, L., & Forney, L. J. (2010). Vaginal microbiome of reproductive-age women. Proceedings of the National Academy of Sciences, 108(supplement_1), 4680–4687. https://doi.org/10.1073/pnas.1002611107

15. Sumner, A. (2016). The poverty paradox. *Global Poverty*, 90–129. https://doi.org/10.1093/acprof:oso/9780198703525.003.0005

6. Tables

Table 1. Summary of gestational age at birth outcomes, vaginal microbiome composition, and demographic, socioeconomic, and preterm birth risk factors by average distance traveled outside the residence

	Shorter (less than 45 10 km units) (N=36)	**Longer (greater than 45 10 km units) (N=35)**	**Overall (N=71)**
Gestational Age at Birth Outcome			
Carried to Term	23 (63.9%)	22 (62.9%)	45 (63.4%)
Not Carried to Term	13 (36.1%)	13 (37.1%)	26 (36.6%)
Vaginal Microbiome Composition			
Iners Dominant or Diverse	28.00 (77.80%)	28.00 (80.00%)	56 (78.90%)
Non-iners Lactodominant	8.00 (22.20%)	7 (20.00%)	15 (21.10%)
Age	26.10 (4.26)	25.10 (5.02)	25.6 (4.65)
Education Level	2.56 (1.00)	2.34 (0.97)	2.45 (0.98)
Cohabitation Status	0.53 (0.51)	0.49 (0.51)	0.51 (0.50)
Insurance Coverage Level	1.94 (0.72)	1.89 (0.80)	1.92 (0.75)
Household Income Level	-0.22 (0.22)	-0.16 (0.24)	-0.19 (0.226)
Parity	0.67 (0.48)	0.60 (0.50)	0.63 (0.49)
First Prental BMI Level	2.81 (1.01)	2.91 (0.95)	2.86 (0.98)

Table 1 shows how average gestational age at birth outcomes, vaginal microbiome types, demographic variables, socioeconomic variables, and preterm birth risk factors are distributed across categories of average distance traveled outside the residence by women during their pregnancy (in 10 km units)

Values are percentages for gestational age at birth outcome and vaginal microbiome composition and mean (standard deviation) for all other variables

Table 2. Poisson regression analysis of gestational age at birth outcome and average distance traveled (ref= Shorter (less than 45 10 m units))

Model	PR	2.5%	97.5%
Gestational age at birth outcome ~ Average distance traveled	1.03	0.59	1.90
Gestational age at birth outcome ~ Average distance traveled + Age + Educational Level + Cohabitation Status	1.02	0.55	1.89
Gestational age at birth outcome ~ Average distance traveled + Age + Educational Level + Cohabitation Status + Insurance Coverage Level + Household Income Level	1.13	0.62	2.07
Gestational age at birth outcome ~ Average distance traveled + Age + Educational Level + Cohabitation Status + Insurance Coverage Level + Household Income Level + First Prenatal BMI Level + Parity	1.12	0.62	2.01

Table 2 shows the estimated prevalence ratio and corresponding confidence intervals from a Poisson regression analysis of various models exploring the relationship between gestational age at birth outcome and average distance traveled outside the residence during pregnancy

Table 3. Poisson regression analysis of vaginal microbiome composition and average distance traveled (ref= Shorter (less than 45 10 m units))

Model	PR	2.5%	97.5%
Vaginal microbiome composition ~ Average distance traveled	1.03	0.81	1.31
Vaginal microbiome composition ~ Average distance traveled + Age + Educational Level + Cohabitation Status	0.88	0.65	1.21
Vaginal microbiome composition ~ Average distance traveled + Age + Educational Level + Cohabitation Status + Insurance Coverage Level + Household Income Level	0.96	0.77	1.21
Vaginal microbiome composition ~ Average distance traveled + Age + Educational Level + Cohabitation Status + Insurance Coverage Level + Household Income Level + First Prenatal BMI + Parity	0.99	0.79	1.25

Table 3 shows the estimated prevalence ratio and corresponding confidence intervals from a Poisson regression analyses of various models exploring the relationship of vaginal microbiome composition and average distance traveled outside the residence during pregnancy