Identifying risk factors associated with preterm birth in African American women

by

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Abstract

Preterm birth (PTB) is a leading cause of infant mortality and long-term morbidity. Preterm infants are more likely to develop respiratory problems, have neurological and cognitive conditions, and develop long-term health issues compared to full-term infants. PTB disproportionately affects African American women in the United States. The risks for PTB have been primarily identified either among women of European ancestry or from a comparison between women of European ancestry and women of African ancestry. The purpose of this study is to identify novel genetic and non-genetic risk factors associated with risk of preterm birth in African American women.

We analyzed data from 2,000 participants of the All of Us Research Program recruited between 2018 to the present. To identify non-genetic risk factors for PTB, we examined data from surveys, lab measurements, and electronic health records from participants that self-identify as African American and over the age of 18 years. In addition, a systematic literature review of genetic risk factors for PTB was conducted to identify potential genetic risks. We found that marital status, health insurance, and clinical labs measuring blood pressure, blood cells, and kidney function were significantly associated with risk of PTB in cases compared to controls. In the literature review, we found that there are population-specific genetic risk factors more commonly associated with African American women and risk of PTB, e.g., *IL6R, MMP9, COL24A1*.

The public health significance is that African America women have a disproportionately higher risk of PTBs compared to European American women by identifying risk factors associated with PTB in African American women, we can create and implement strategies to reduce those risks thereby reducing the overall prevalence of PTB among African American women.

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1.0 Introduction

Preterm birth (PTB), defined as delivery before 37 completed gestational weeks,[5] is estimated to affect 10% of the population worldwide.[1-3] It is one of the leading causes of infant mortality and long-term morbidity in children 5 years old and younger.[4-7] Although PTB typically has a higher incidence in low- and middle-income countries, a recent study noticed a rise in PTB in well-developed and high-income countries, such as the United States (US).[1,4] In the US, the incidence of preterm birth has increased, and the current national incidence rate is approximately 12%.[1-4]

The cost associated with PTB, such as hospital stays and post-hospital care, is approximately $26 billion, annually.[4] The consequences due to PTB have been well-established in infants and contributes to approximately 1 million infants deaths annually.[4] Among the complications that preterm infants suffer from include difficulty feeding, high risk of bacterial infections, impaired hearing, impaired vision, and various neurodevelopmental disorders.[1,4] In addition, pregnant women delivering prematurely suffer from complications including hemorrhage or increased risk of cardiovascular diseases.[8,9]

There is a significant disparity in the incidence of PTBs and mortality from PTBs in the US. PTB occurs at an increased rate in African American women (14.1%) compared to European American women (9.1%).[10] Even more alarming, African American women are also more likely to die from preterm labor complications than European American women.[11] In 2019, the estimated rate of maternal mortality due to pregnancy complications is 1,800 maternal deaths, or a mortality rate of 55.3 per 100,000 live births.[46] Most research studies aimed at identifying risk factors and causes of PTB have been primarily conducted in populations of European ancestry. Even when

studies have included African American women, it has been done in the context of identifying PTB risk factors by comparing African American women to European American women. The overall goal of this study is to lessen the health disparity gap found in African American women and risk of PTBs by conducting population-specific research that aims to identify risk factors for PTB that will lead to therapeutics and interventions.

1.1 Specific aims

PTBs have long-term consequences affecting both the mother and infant's health. African American women have disproportionately higher rates of PTBs compared to European American women. Our goal is to contribute to the knowledge of risk factors for PTB in African American women in order to provide therapeutic targets, implement prevention strategies or policies, and discover novel biological mechanisms underlying the condition. We did this through the following aims:

1. To identify novel non-genetic risk factors associated with preterm births among African American women.
2. To conduct a systematic literature review of genetic risk factors for PTB in African American women.

2.0 Preterm birth (PTB)

PTB is defined as parturition before 37-gestational weeks.[5-7] It is well-established that each year PTB affects 15 million infants and accounts for 50-70% of infant deaths worldwide, making it one of the leading causes of long-term infant morbidity and mortality.[6,7,22,23]

PTB is sub-categorized into different groups depending on the stage of pregnancy—extremely preterm, born before 28 weeks (0.73%); very preterm, born between 28 and 32 weeks (1.2%); moderate preterm, born between 32 and 34 weeks of pregnancy (1.52%); and late preterm, born between 34 and 36 completed weeks of pregnancy (8.28%).[6,22,58] In contrast, full term birth is delivery between 37 to 41 gestational weeks.[23] Earlier delivery leads to more detrimental, long-term health effects for the preterm baby.

PTB is a multifactorial condition with different classifications.[7] A pregnant person can experience either a spontaneous PTB or a provider initiated PTB, where the physician induces labor due to maternal medical condition or fetal distress.[7] The focus of our study is spontaneous PTB. Furthermore, PTB is categorized into 3 subgroups: spontaneous PTB, indicated PTB, and preterm premature rupture of membranes (PPROM).[2-4] Spontaneous PTB is the most common type and accounts for approximately 45% of all PTBs. Indicated PTB and PPROM account for the remaining types of PTB at approximately 30% and 25%, respectively.[2,3] PPROM is frequently linked with spontaneous PTB and typically occurs due to intrauterine infections.[2,32] Pregnant women whose membrane ruptures are more likely to begin labor and premature ruptures are likely to have a PTB.[32] While the specific causes of PTB are unknown, current research postulates that PTB can occur through multiple mechanisms including inflammation or uterine hemhorrage.[2,3] Studies have also shown that PTB can be a heritable condition.[23,25] For example, women who were

premature are more likely to deliver a premature baby themselves, and women who gave birth to a premature baby are at an increased risk of delivering prematurely in their next pregnancy.[23,25]

2.1.1 Consequences and treatment of PTB

In addition to being a leading cause of death in children under the age of 5 years, many adverse medical conditions in infants due to PTB have been well-established. Earlier delivery (e.g., extreme PTB) increases the risk of mortality and morbidity in the infant.[6] Preterm infants are more likely to be admitted into the neonatal intensive care unit or die from complications.[6,8] The earlier a premature baby is born, the more severe the consequences and number of long-term health conditions that the baby will have. Preterm infants are more likely to return home on oxygen.[6] There is also an incidence rate of 4-7% for necrotizing enterocolitis in preterm infants.[6] Necrotizing enterocolitis is a disease that causes inflammation in the gut and can lead to high rates of mortality and is associated with long-term morbidity in preterm infants.[48] The causes of necrotizing enterocolitis are unknown but it is associated with bacterial colonization and inflammation of the gut.[48] Preterm infants with necrotizing enterocolitis display neurodevelopmental delay, abdominal distension, and bloody stool.[48,49]

Preterm children are also more likely to develop respiratory issues, such as bronchopulmonary dysplasia, respiratory distress syndrome, underdeveloped lungs, and asthma.[6,722] Hospital read-admission due to infections are more common in preterm infants.[22] Preterm infants are also more likely to develop retinopathy, possibly leading to blindness; neonatal jaundice; hypoxic-ischemic encephalopathy; various neurodevelopmental conditions; or cognitive impairment and are more likely to suffer from cerebral palsy or epilepsy.[28,6] Current research

includes understanding the association between PTB and neurodevelopmental disorders such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD).[28]

Pregnant women who deliver prematurely are also more likely to suffer from one or more complications compared to women who deliver at full term. They can suffer from antepartum hemorrhage or placental abruption. Retained placenta is also more common in women who delivered prematurely, this is a condition where the placenta remains in the uterus and needs to be removed.[8,11] They may need to have their cervix repaired, and it's possible the women need to be admitted into the intensive care unit due to these complications.[8]

While the medical conditions that premature infants and mothers face is daunting, one also needs to take into account the high medical costs for treatment and future medical expenditures as premature babies have an increased chance of returning to the hospital within a couple of weeks or months compared to full-term babies.[5,6] For many pregnancies in the US, the costs are paid for by Medicaid and these costs tends to be higher than commercial insurance.[57] The hospitalization and medical costs for infants born extremely and very preterm is approximately $11 billion.[57]

There is currently no treatment for PTB. While there used to be FDA-approved medication for slowing down the progression of PTB, it was taken off the market due to it causing severe maternal side effects.[5] There are, however, methods to prevent PTB in pregnant persons. For example, studies have shown that increasing intake of folic acid decreases the risk of PTB.[22,25] Accessing appropriate prenatal care, understanding the risk factors, and warning signs associated with PTB, and eating healthy are all appropriate measures in preventing PTB.[22] Other prevention measures include checking for bacterial vaginosis, measuring cervix length, and getting treatment for those medical conditions reduces the risk.[22]

2.1.2 Pathophysiology of PTB

The specific mechanisms leading to PTB are not known.[2,3] PTB can be caused by several pathologies, and it appears to be affected by many factors, such as age, disease status, etc.[26] Some consider PTB to be a syndrome caused by various risk factors such as infection, inflammation, uterine over-distension, hemorrhage, and other processes mediated by the immune system.[26] One potential mechanism through to initiate PTB is activation of the immune system because many of the known risk factors involve release of cytokines and chemokines.[2]

The immune system is activated by Toll-like receptors, which recognizes specific antigens, and it recruits chemokines and cytokines to trigger neutrophil activity, increases prostaglandin production and release, and expression of matrix metalloproteinases. The prostaglandin stimulates the uterus to contract and the metalloproteinases degrades the fetal membrane's extracellular matrix. In the maternal membrane, the extracellular matrix in the cervix is remodeled and broken down thereby causing labor and membrane rupture.[2,3]

Another potential initiator to preterm labor is maternal progesterone and oxytocin concentration.[3,4] In the myometrium, progesterone keeps the cells in a quiescent state by suppressing procontractile genes, such as Connexin-43.[4] It also produces an anti-inflammatory effect by reducing the production of cytokines and chemokines.[4] Progesterone also modulates the release of prostaglandins controlling level of uterine contraction and extending the fetal membrane thereby reducing inflammation-mediated membrane rupture.[3,4] Oxytocin is involved in the frequency and intensity of uterine contraction so increased oxytocin increases the likelihood of preterm labor.[3]

2.1.3 Risk factors associated with PTB

Due to the unknown etiology surrounding PTB, many scientists are looking to identify the risk factors correlated with PTB. There are several well-established risk factors correlated with PTB such as uteroplacental ischemia, a previous PTB, shortened cervical length, pre-eclampsia, smoking, and severe hyperdistension.[2,3,26] Uterine and gastrointestinal infections are also common precursors to PTB.[2]

2.1.3.1 Environmental risk factors

There are many environmental risk factors associated with PTB due to the fact that PTB appears to be multifactorial and can happen through many different pathways.[2,3,26] Pregnant women with a medical condition such as severe hypertension, pre-eclampsia, gestational diabetes, uterine overdistention, or eclampsia are more likely to deliver prematurely; this is known as indicated PTB.[27,28] Other risk factors known to induce PTB include smoking, vaginal or gastro-intestinal infections, inflammation, alcohol and illegal substance use, and urinary tract infections.[2,3] Some risk factors are associated with an increased risk of PTB such as maternal age, delivering prematurely in a previous pregnancy, multiple pregnancy, poor nutrition, air pollution, stress, and neighborhood safety.[29]

It is estimated that 25- 40% of PTBs are due to intra-uterine infections or infections in the gastro-intestinal tract in the pregnant women. Since many of these infections are microbial in nature, this triggers the immune system to recruit cytokines and chemokines and initiate labor. It can also trigger a response in the placenta where the fetus releases corticotropin and cortisol. Infections can occur in the amnion, placenta, amniotic fluid, umbilical cord, or in the fetus. The most well-known pathogens involved in PTB include *Ureaplasma spp.* and *Mycoplasma* because

it is isolated from the placenta or amniotic fluid. Viruses, such as human papilloma virus (HPV), herpes virus, and influenza virus, can also lead to PTB via placenta dysfunction.[2]

The vaginal microbiome has been associated with PPROM and risk of PTB. Increased diversity of the vaginal microbiome is associated with increased infection, such as bacterial vaginosis.[30] However, a vaginal microbiome made up of *Lactobacillus spp*. is associated with a healthy reproductive tract and decreased risk of PTB.[59] This decrease in risk is seen in pregnant women of European and African descent.[30] However, those of African descent are less likely to only have *Lactobacillus spp.* and typically have a more diverse vaginal microbiome.[60] The diverse vaginal microbiome triggers proinflammatory cytokines and induces preterm labor.[30]

More recently, exposures to toxicants—chemical and non-chemical—have been found to be associated with increased risk of PTB. Through a systematic review, Bekkar et al. found an association between air quality, heat and PTB. There is a positive correlation between PTB and increased exposure to ozone and particulate matter 2.5 (PM2.5) but it was dependent on timing of exposure.[31,50,51] In terms of air pollution, PM2.5 are particles that have a diameter of <2.5um.[61] Exposure to PM2.5 during the early stages pregnancy increased the odds PTB depending on the month of exposure and temperature.[50] When adjusting for temperature, one study found that PM2.5 exposure during month 4 increased the risk of PTB, but unadjusted analysis found an increased risk in the third month.[50] This difference could be due to how air quality was measured. A study in China found that an increase of PM2.5 concentration (10ug/m^3 or higher) during each trimester increased the risks of delivery prematurely.[52] Studies has also found an increased risk of PTB in pregnant women with asthma.[31,51] Extreme heat is associated with an increased risk of PTB, but extreme heat can cause other harmful conditions.[31,53,54] Increases of 5-6℃ were associated with elevated risk of PTB.[53,54]

Another environmental factor is exposure to phthalates. Phthalates are known as endocrine disrupting chemicals and tend to disrupt thyroid hormone levels, increase oxidative stress and inflammation. [32] It is also linked to endometriosis and breast cancer. Pregnant women are frequently exposed to phthalates through personal care products. [32] Exposure to phthalates at any time during pregnancy increases the odds of delivering prematurely. [32] Exposure in the third trimester greatly increases the odds of PTB. The possible trigger for PTB may be through hormone disruption or inflammation cascade.[32]

Social determinants of health, such as neighborhood deprivation or socioeconomic status, have been associated with increased risk of PTB.[29] Neighborhood deprivation was categorized based on the socioeconomic status of each neighborhood and into different quantiles: 1) mean income; 2) percentage of household with low income; 3) percentage with a paid job; 4) percentage of household with low education.[29] Possible pathways that neighborhood deprivation can increase the risk of PTB include poor prenatal care, more risks at the personal-level (e.g., domestic violence or medical condition), or exposure to environmental stressors, such as crime or air pollution.[29]

2.1.3.2 Genetic risk factors

While the underlying genetics of PTB is not well-understood, studies have shown that the genetics of PTB represent a complex interplay between maternal, fetal, and environmental factors. Current studies are showing PTB to be heritable and that genetics accounts for 17-36% of risk in PTB.[55,56] Mothers with a history of PTB are more likely to deliver premature infants at earlier gestation weeks than the previous pregnancy.[3,55] Women born premature themselves are also more likely to have PTB (20%).[55,56] There is an 80% increased risk for sisters of premature infants deliver PTB as adults.[55] However, the genetics between the pregnant women and the fetus plays a role in PTB.[33] Twin studies have shown that maternal genetics are a stronger contributor to early labor

and delivery compared to the fetus's genetics, 25% and 13% respectively.[56] In a study determining the genetic susceptibility between smoking and adverse birth outcomes (e.g., preterm or low-birth weight) researchers found two genetic polymorphisms in maternal metabolic genes, *CYP1A1* and *GSTT1*, leading to an increased risk of PTB in the context of smoking.[12]

Candidate gene studies have identified genes in the immune system, inflammation, tissue remodeling, and metabolic pathways as potential markers of PTB.[55] Various single nucleotide polymorphisms (SNP) encoding anti-inflammatory cytokines, such as interleukin 10 (*IL10*) and interleukin 13 (*IL13*), have been associated with an increased risk of PTB, possibly through activation of the immune system or through cell migration and proliferation.[55] SNPs involved in tissue remodeling genes are associated with PTB by disrupting the normal function of the tissues and proteins in the uterus potentially activating preterm labor.[55] However, many of these studies consisted of individuals of European ancestry and studies that included individuals of African ancestry were underpowered.[56]

In a meta-analysis examining maternal loci and PTB, researchers found variations in *WNT4, EBF1, AGTR2, KCNAB1* can affect the timing of pregnancy in the pregnant women.[33] Two genes found to be associated with length of gestation and spontaneous PTB were, *EBF1* and *EESFEC*.[33,34] Additional loci associated with length of gestation were found in *DNAH2, WNT4, ZBTB38, HAND2, TET3*, and *RAP2C*.[33] These results were replicated findings except for *DNAH2*.[33] Researchers also discovered novel loci—WNT3A, *ADCY5, GNAQ, KCNN3, GC, COL27A1,* and *KCNAB1*—that may play a role in regulating labor in reproductive tissue.[33] Higher expressions of *ZBTB38* lead to longer length of gestation and variations in *KCNAB1* were associated with length of gestation in reproductive tissue.[33] Variations in *HAND2* (expressed in uterine tissue) may have a role in the release of progesterone and in the immune system.[33] *COL27A1* is associated with slow

growth, abnormal placental development, and abnormal placental blood vessel development.[33] It is expressed in the endometrium, and it may have a protective role in preventing oxidative stress. Researchers postulated that *WNT3A* may play a role in the regulation between maternal and fetal tissues.[33] More research needs to happen to understand how these genes are associated with PTB and the biological mechanism of action.

Another study looking at whole genome sequencing, RNA-sequencing, and methylation found alleles in *RAB21* and *RBPJ* to be significantly associated with PTB.[33] RAB31 is involved in the RAS signaling pathway, and RBPJ is involved in the Notch pathway.[33,34] Their research also found *EBF1* and *EEFSEC* to be associated with PTB.[33] These genes are more common in individuals of European descent. Many of the genes found to have an association with PTB are involved in the immune response, inflammation, coagulation, and connective tissue remodeling.[34]

Some studies have examined gene-environment interactions associated with risk of PTB. Many environmental factors, such as social, cultural, and other external exposures, can interact with maternal and fetal genes. Researchers looked at variations in specific molecules involved in immune response, such as IL6, IL1B.[35] When controlling for smoking, IL1B and IL6 are significantly associated with risk of PTB.[35] When controlling for PPROM, genetic variation within *TLR4* is significantly associated with severe PTB.[35] Further research needs to be done to understand how maternal and fetal genetic variations or epigenetic changes are associated with risk of PTB.[35]

2.1.4 Preterm birth in African American women

Unfortunately, pregnant African American women consistently have higher rates of PTB compared to other populations, even after accounting for known risk factors such as socioeconomic status and education level.[10,36] The rates of PTB in pregnant African American

women also differs based on geographical location of delivery and whether delivery occurred in the US or outside of the US.[37] Pregnant African American women who delivered outside of the US had lower rates of PTB compared to women who gave birth in the US.[10,36] One study found higher rates of PTB in African American women in the District of Columbia, Michigan, Illinois, Wisconsin, and Louisiana (rates ranged from 67-59%).[36] On the other hand, lower rates of PTB occurred in Minnesota, Oregon, Washington, Nevada, and Kentucky (5-29%).[36] However, all states showed some disparity towards higher rates of PTB in African American women.[36] Possible reasons for this includes structural racism and racial discrimination, especially between health care providers and African American patients.[36]

There are many environmental, social health determinants, and clinical risk factors associated with high rates of PTB in pregnant African American women. Many studies are looking at various acute and chronic stressors associated with increased risk of PTB as well as age of the pregnant woman. One study found that there was no association with PTB in African American women less than 18 years old compared to non-African American women.[36] On the other hand, researchers found that African American women aged 35 years or old tended to have higher rates of PTB compared to other women.[36] Perceived risk factors from African American women include a lack of social and financial support, outside pressures and judgement, no emotional support, racial discrimination, lack of prenatal care, dangerous neighborhoods, drug use, increased violence and crime, mental illness, and chronic medical conditions such as gestation hypertension or ecclampsia.[10,37] Other potential risk factors more commonly associated in African American women and PTB include different types of stressor exposures and inflammation markers.[11] One study found that African American women with increased plasma levels of IL-6 during their third

trimester were more likely to have delivered prematurely compared to European American women.[11]

Preterm birth can occur through various pathways and is affected by an intricate combination of environmental, clinical, and genetic risk factors. In order to understand the biological mechanism leading to PTB, one must conduct population-specific research.

2.2 Public health significance

Preterm birth occurs in approximately 12% of the population the US and predominantly affects those who self-identify as African American (14.5%).[1,10] Premature infants have high rates of infant mortality and long-term health problems.[1-4] Although more research is emerging on understanding the risk factors and biological mechanisms associated with PTB, pregnant women who self-identify as African American still have higher rates of PTB compared to other populations.[36,37] Specifically more research needs to be done to understand the population-specific risk factors associated with PTB in the African American population. These non-genetic risk factors include environmental, social determinants of health, and maternal medical conditions.

3.0 Materials and methods

3.1 All of Us Research Program

This study was conducted using data from the All of Us Research Program, a biomedical data resource that allows researchers to conduct studies into various health conditions using multiple datasets, such as demographics, genomic data, or survey data. The goal of the research program is to make research and its results accessible to participants and to develop new methods to generate and access data that will be available to approved researchers. The All of Us Research Program plans to enroll at least a million participants across the United States. The University of Pittsburgh has a Data Use and Registration Agreement with the All of Us Research program. Due to the use of secondary, de-identified data, an Institutional Review Board (IRB) was not necessary to conduct this research (Appendix A.1). Nonetheless, researchers in this study received training on the ethics of human research and analysis on All of Us data as well as CITI training on responsible conduct of research; privacy and information security; and PHS regulated course. In addition, results reported in this study are in compliance with All of Us Data and Statistics Dissemination Policy disallowing disclosure of group counts under 20.[38]

There are three tiers in which the public or researchers can access data. The public tier contains aggregated data that is de-identified and available for everyone. The registered tier contains individual-level data from the electronic health records (EHRs), demographics, surveys, labs and physical measurements, and wearables (e.g., Fitbit), which have been altered to protect participant privacy. The controlled tier includes genomic data as well as the available data from the registered tier. For this study, we utilized controlled tier data from participants enrolled

between May 2018 to March 2024 that self-identified as African American women over the age of 18 years.[43]

The All of Us Researcher Workbench is a cloud-based platform where approved researchers can access and analyze All of Us data. Through the workbench, researchers can build cohorts, create concept sets containing data one is interested in, and collect all statistical analysis. The workbench also contains the Jupyter notebook allowing the researcher to analyze their data using R or Python or through their new R Studio platform.[40]

3.2 Identification of cases

Cases were defined as women who had a PTB(s). Preterm birth has been defined as delivery before 37 gestational weeks, specifically 17 weeks of gestation to 36 weeks of gestation and in accordance to previous studies.[41,42] The cases were chosen if individuals were classified as African American (according to self-reported demographic survey) AND if any of the following ICD-10 codes were present: O60.1 (preterm labor with preterm delivery) OR O42.01 (preterm premature rupture of the membrane, onset of labor within 24 hours, trimester specified or unspecified) OR O42.11 (preterm premature rupture of the membrane, onset of labor more than 24 hours, trimester specified or unspecified) O42.91 (preterm premature rupture of the membrane, onset of labor unspecified, trimester specified or unspecified) OR Z3A17 OR Z3A18 OR Z3A19 (weeks of gestation of pregnancy, weeks 17 to 19) OR Z3A.2 (weeks of gestation of pregnancy, weeks 20 to 29) OR Z3A.3 OR Z3A.31 OR Z3A.32 OR Z3A.33 OR Z3A.34 OR Z3A.35 OR Z3A.36 (weeks of gestation of pregnancy, weeks 30 to 36).

Individuals with ICD-10 codes: Z3A.37 OR Z3A.37 OR A.39 (weeks of gestation, weeks 37 to 39) OR Z3A.4 (weeks of gestation, weeks 40 and greater) were excluded. Also, individuals with sickle cell disease (SCD), or sickle cell trait, were excluded from the study population due to the known complications SCD can cause in pregnant women, such as miscarriage, PTB, in uterine growth restriction, in utero fetal death, and various other crises.[44] The excluded individuals with sickle cell disorder was selected based on whether their EHR had the ICD10 code: D57.

3.3 Identification of controls

Controls are African American women that did not have a PTB and contained any of the following ICD-10 codes: 3A.37 OR Z3A.38 OR A.39 (weeks of gestation, weeks 37 to 39) OR Z3A.4 (weeks of gestation, weeks 40 and greater).

Also, individuals with sickle cell disease (SCD), or sickle cell trait, were excluded from the study population due to the known complications SCD can cause in pregnant women, such as miscarriages, PTB, in uterine growth restriction, in utero fetal death, and various other crises.[44]

3.4 Study population

The cohort consisted of 529 PTB cases and 1,409 controls (Figure 1). All study participants were selected from the All of Us Research Program. Individuals were sampled from a cohort of African American women. A case-control study design was used to assess the risks associated with PTB. This study design allowed us to analyze the risks of various exposures and discover novel

risk factors in individuals who had a preterm, or premature, delivery compared to individuals who delivered at full term.

3.4.1 Data collection

The All of Us data repository contains data from participant's EHRs, including their clinical labs and measurements. We also gathered self-reported information on marital status, income, education level, smoking status, alcohol status, substance use, health insurance status and type, and age at consent.

The clinical lab measurements were selected based on whether 50% or more participants had clinical lab results (n = 65 [Table 1 Appendix A.2]). The clinical lab measurements were queried after going to 'Labs & Measurement' section in All of Us Data Browser then top 43 labs and measurements were selected for analysis. Labs and measurements collecting information on antibody count was also queried due to the immune system having a partial role in PTB. The clinical labs with no measurements were excluded and removed thereby reducing the clinical lab measurements by 26 variables (Table 2 in Appendix A.2). The final list of clinical lab measurements resulted in 39 variables (Table 3 in Appendix A.2). These variables were chosen to help elucidate other biological mechanisms that increases the risk of PTB.

3.5 Systematic literature review

We performed a systematic search using the PubMed database to identify studies looking into the association between genetics and risk of preterm birth in African American women.

PubMed search terms included ‘preterm birth or delivery,’ ‘African American, ‘risk factor,’ and ‘genetics or genome-wide.’

Eligibility criteria included studies looking at maternal (or fetal) genetics and risk of PTB and studies looking at PTB in African American women or stratified race in which a comparison with the African American population was analyzed. Studies that did not look at maternal or fetal genetics and its association with risk of PTB, studies looking into outcomes other than PTB, review articles, and epigenetic studies were excluded from the literature review.

The search resulted in 106 articles and of those articles only 35 articles mentioned PTB as an outcome. Inclusion and exclusion criteria reduced those result to 11 articles on risk of PTB in African American women (Appendix A.6). The extracted data includes information on the authors, title, publication date, methods, and significant results. The data extracted from these studies was used to identify potential gene candidates associated with risk of PTB in the African American population.

3.6 Statistical analysis

The analysis was completed on a R Studio platform on the All of Us Research Workbench. Missing and/or incomplete data was removed and accounted for. Descriptive statistics was collected for the lifestyle factors and analyzed using Fisher’s exact test. For each factor, individuals that skipped or preferred not to answer were excluded in the analysis. The descriptive analysis on ‘age at consent’ allowed us to determine the age ranges of the study population in the All of Us Research Program. Prevalence rate was calculated by dividing the preterm cases by the total female

population in the All of Us data repository. The female population was counted based on whether the participants answered the self-reported 'sex at birth' demographics survey.

Continuous variables from the clinical lab measurements were summarized by average mean ($\pm$SD). To determine the significance of the model and whether a Welch t-test was necessary, an F-test was performed. If the values from the F-test was below 0.05 then a Welch t-test was deemed to be unnecessary. F-test analysis showed the variables to be greater than 0.05 (Appendix A.4), so a Welch t-test was used to analyze the clinical lab measurement variables. The clinical lab measurements were analyzed using an unadjusted Welch t-test. Variables were considered significant when the p-value <0.05.

4.0 Results

The prevalence rate of PTB among All of Us participants in different racial groups is provided in Table 1. Participants who chose 'More than one race' or did not specify a race were not included. In addition, racial/ethnic groups containing less than 20 participants were not included in the analysis (i.e. Middle Eastern and Native Hawaiian/Other Pacific Islander). We found that African American women have higher rates of PTB compared to the White women (1.20% and 0.87%, respectively; Figure 2). These rates are much lower compared to the national rates and may be due to several factors including non-response bias from participants.

Age of consent was also selected to determine the age ranges of the participants (Table 2). Due to the low sample population in most of the racial groups, ages were grouped together as '18-44 years' or '>45 years.' The age of consent was primarily composed of ages ranging between 18-44 years old (Figure 3 and Table 3).

4.1 Association between lifestyle factors and PTB

To determine the environmental risk factors in African American women, we looked at the annual income, smoking frequency, health insurance status, educational level, alcohol intake, marital status, and recreational drug use between cases and controls. Our analysis showed that marital status and health insurance status is associated with risk of PTB (P = 0.01 [Table 3]; P = 0.03 [Table 4]; respectively). Cases were more likely to have never been married compared to controls. In addition, cases were less likely to have had health insurance coverage. Annual income,

smoking frequency, educational level, alcohol intake, and recreational drug use were not significantly associated with risk of PTB (P = 0.24; P = 0.56; P = 0.63; P = 0.75; P = 0.072; respectively) between cases and controls (Appendix A.3).

4.2 Association between clinical lab measurements and PTB

We analyzed 39 clinical lab measurement variables (Appendix A.2). We identified 11 clinical lab variables to be statistically significantly associated with risk of PTB in African American women (Table 5). Blood pressure was found to be statistically significant to risk of PTB in our cohort, replicating previous findings (Table 5).[27,28] Cases had higher systolic blood pressure compared to controls (122.36 and 119.53, respectively; P = 3.11E-05; 95% CI, -4.15 to -1.50 [Table 5]). Diastolic blood pressure was also higher in cases than controls (75.55 and 74.00, respectively; P = 1.94E-03; 95% CI, -2.53 to -0.57 [Table 5]). Similar to current studies on heat and PTB, we found that body temperature was higher in cases compared to controls (48.05 and 44.17, respectively; P = 0.01; 95% CI, -6.47 to -1.01); it was significantly associated with PTB.[53,54]

Cases had higher levels of urea nitrogen in plasma than controls (10.17 and 8.90, respectively; P = 3.44E-06; 95% CI, -1.80 to -0.74) and was found to be associated with increased risk of PTB in this population. Cases versus controls also had higher concentration of basophils in blood (2.52 and 1.09, respectively; P = 4.97E-05; 95% CI, -2.42 to -0.43), creatinine in plasma (0.80 and0.69, respectively; P = 2.28E-03; 95% CI, -0.17 to -0.04), and MCHC (32.86 and 32.67, respectively; P = 3.45E-03; 95% CI, -0.31 to -0.06). These clinical lab measurements were found to be statistically significant in risk of PTB. In a comparison between cases and controls, alkaline phosphatase (82.87 and 88.90, respectively; P = 0.01; 95% CI, 1.66 to 10.39), lymphocytes (123.04

and 68.04, respectively; P = 0.03; 95% CI, -105.73 to -4.27), monocytes (36.93 and 17.51, respectively; P = 0.01; 95% CI, -34.90 to -3.95), and potassium in plasma (3.94 and 3.89, respectively; P = 0.01; 95% CI, -0.09 to -0.01) were statistically significant risk factors associated with PTB in cases rather than controls. The other 28 clinical lab variables were not statistically significant in the risk of PTB between cases and controls among our study population (Appendix A.5).

4.3 Genetics associated with risk of PTB in African American women

We identified 11 articles researching how maternal, or fetal, genetics are associated with risk of PTB in the African American population. Of those, 5 articles compared the genetics between White, or European American, women and African American women, and there were 6 articles looking at the genetic risk factors of PTB in African American women. Some studies looked only at maternal genetics while others looked at both maternal and fetal genetics. For the purpose of this literature review, we focused on the statistically significant results in African American subjects.

Four studies identified polymorphisms involved in *IL6R, IL6RAP, TNFRSF1B, TNFR2* to be associated with an increased risk of PTB in African American mothers.[72,74-76] In infants, the genes associated with increased risk of PTB include *IL1RAP, IL6R, TNFRSF1B, SERPINH1* which were identified in two studies.[75,76]

One study identified a *PTPRD* polymorphism that is associated with a 2-fold higher risk of PTB; in particular, the variant rs35331017-II has a higher risk compared to the variant rs35331017-ID/DD.[71] Another study trying to understand the gene-environment interaction

between obesity and risk of PTB in African American women found that the *COL24A1* variant (rs11161721-CC) in obese and normal weight women has a 2-fold increased risk of spontaneous PTB.[70] On the other hand, *COL24A1* variant (rs11161721-AA) in obese women confers a protective phenotype and decreases the risk of spontaneous PTB by more than 50%[70] Others genes specific to risk of PTB in African American mothers include *IL12A, CSF3, PRKCA, FLT1, MMP2, TIMP2, IL16, MMP1, LIFR-AS1, TNF* and *LTA*. [66,68,69]

5.0 Discussion

In the US, the incidence of preterm birth has increased to approximately 12% making it a significant public health burden. Most research studies aimed at identifying risk factors and causes of PTB have been primarily conducted in populations of European ancestry. Our study was conducted exclusively in African American women and replicated known risk factors and identified novel risk factors associated with increased risk of PTB in African American women. The prevalence rate of PTB in African American women in our study (1.2%) is less than the national rate in the US (14%). This could be due to the sample population in the All of Us Research Program and our selection criteria which included exclusion of participants with sickle cell disease. In addition, there were participants that were not included because of missing information. Nonetheless, when comparing it to the prevalence rate of the White women participants from the All of Us data, African American women were still more likely to have had a PTB.

We found that marital status and health insurance were associated with an increased risk of PTB in cases compared to controls. Cases were more likely to have never been married compared to controls (56.49% and 54.92%, respectively; P = 0.01 [Table 3]). There are no studies looking into how marital status affects birth outcome in African American women specifically. However, studies conducted in the UK and Canada, have found that single mothers are more at risk of adverse birth outcomes, such as PTB, compared to married mothers.[62-64] Due to the changing perception on marriage couples today are having child(ren) without getting married but are still in a relationship. Researchers have found not found any differences between married mothers and cohabiting mothers.[65] Researchers believe this is due to the support from their partner, stable economics, and health benefits from their partner.[65] It is possible that being single, or

without a permanent partner, decreases the social support one needs to manage their pregnancy or to get the help they need.[29] Giurgescu et al. found that African American women believe that a lack of social support and interpersonal conflicts increases the likelihood of delivering prematurely.[37] Another study looking at the effect singlehood has on birth outcome found that single mothers have poor diets, such as having lower fruit, fiber and vegetable intake but higher sugar intake.[63] Also, unemployment can have an adverse effect on birth outcome in single mothers.[64] Our finding shows marital status plays a role in the risk of preterm birth, but further research needs to be done to understand how.

Cases were less likely to have health insurance coverage compared to controls (91.05% and 93.65%, respectively; P = 0.03 [Table 4]). The disparities in healthcare access are well-established in the United States.[11] If an individual does not have health insurance, it is more difficult for them to get the necessary treatments or medications for their condition. A lack of health insurance may impact a pregnant woman's ability to get prenatal care. Tanz et al., found that receiving and going to prenatal care appointments to be protective factors in decreasing risk of PTB.[10] Our finding shows that the environment during pregnancy and interpersonal relationships may play a significant role of PTB risk in African American women.[37]

Another statistically significant finding associated with PTB was blood pressure; cases had higher levels of systolic and diastolic blood pressure compared to controls (Table 5). In addition, we identified novel clinical risk factors for PTB in African American women. We found statistically higher basophil, lymphocyte, and monocyte levels among cases than controls (Table 5). Vaginal or gastro-intestinal infections and inflammation are known to increase the likelihood of PTB in pregnant women.[2,3] The leading hypothesis is that activation of the immune system initiates preterm labor. These results suggest that immune cells are important risk factors in PTB

risk in African American women. Cases also had higher levels of creatinine, MCHC, urea nitrogen levels compared to controls (Table 5). These clinical lab measurements are associated with kidney function. However, more work needs to be done to determine if risk of kidney disease is a confounding factor. Nonetheless, this finding presents a new research pathway to investigate if kidney function is related to PTB risk and if so, how.

Our study did not find a statistical significance between smoking, income, education level, alcohol intake, or recreational drug use, and risk of PTB (Appendix A.3). These factors have been previously associated with risk of PTB.[29,35,36] However, those studies were primarily composed of European American women. This highlights the need to conduct more research to understand how these risk factors affect African American women and PTB.

Many of the studies of the literature review investigating the association between genetic risk factors and risk of PTB identified many genes involved in the immune system, such as *IL6, IL6R, IL16, IL12A, TNF*, etc.[68,75,76] This makes sense because many incidences of spontaneous PTB is associated with inflammation and infection in the mother.[2,75] Many cytokine are associated with various signaling pathways, such as MAPK signaling or JAK-STAT signaling, and are involved in cell proliferation, differentiation, or cell growth.[76] In the case of IL16, higher concentrations of this cytokine in the amniotic fluid can lead to increased rates of PTB although the mechanism of action is not known.[68] Matrix metallopeptidase (MMP) genes and *SERPINH1* appear to increase risk of PTB by destabilizing the collagen and tensile strength of the amnion.[68,76] It appears that many of the genes associated with risk of PTB are also associated with initiation of PTB or cell growth which could have adverse effects on infant growth thereby initiating premature labor.

Genetic risk factors identified in one population may not be informative in other populations. Therefore, more genetic research in African Americans is needed to identify population-specific genetic risk factors that will help elucidate the biological pathways causing PTB and possibly developing therapeutics to prevent the high rate of PTB in African Americans.

A limitation in our study is the collected information is self-reported, leading to recall bias, and due to the ongoing nature of recruiting participants, the survey answers may not be current for the participant. There were other known risk factors, such as pre-eclampsia and age, that we could not adjust for due to the inability to exclude the provider initiated PTB from spontaneous PTB. Another limitation includes not obtaining the age of the participant when they were pregnant; instead, we used age at consent. Also, the mean clinical lab results were taken at different timepoints in the participants medical journey and not just when they were pregnant. Nonetheless, by utilizing the All of Us Research Program, we were able tailor our cohort specifically to African American women to identify population-specific risk factors for PTB.

5.1 Conclusions

In summary, our study has identified novel, non-genetic risk factors for PTB in African American women. Our results suggest that the immune system, inflammation, and kidney function may play significant roles in the risk for PTB in African American women. These results demonstrate the need for more research into population-specific risk factors for PTB in African American women. They have the highest rates of PTB (14%) and environmental and clinical risk factors do not fully explain why African American women are disproportionately affected. The identification of these population-specific genetic and non-genetic risk factors will help us

elucidate the underlying causes of PTB and develop prevention strategies for African American women.

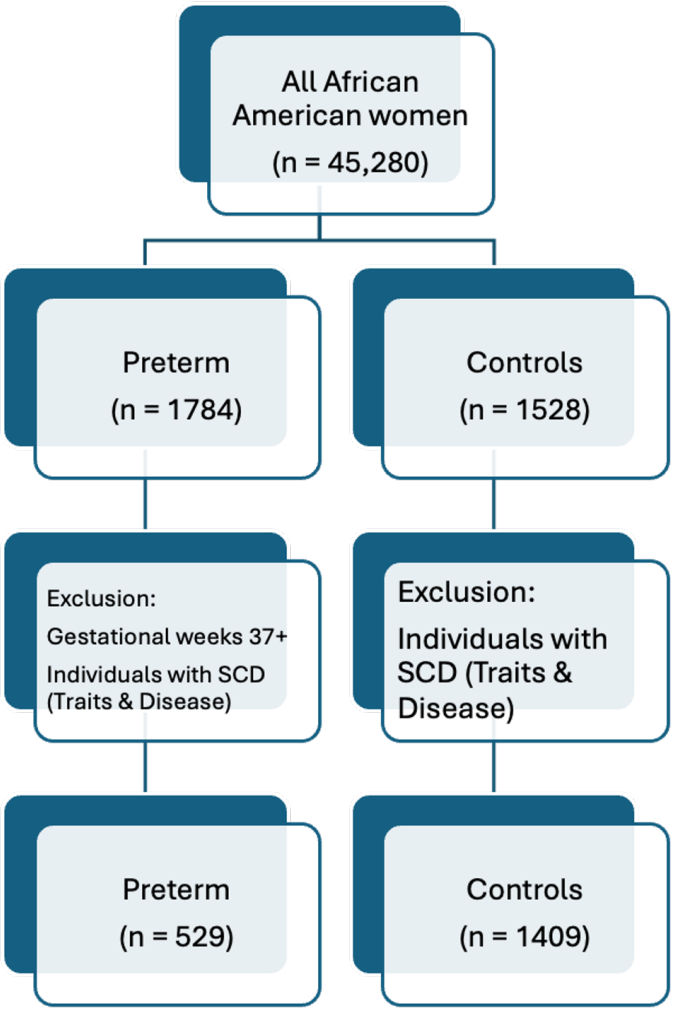

Figure 1 Flow chart of study participants from the All of Us Research Program.

Table 1 Distribution of PTB prevalence rate among racial groups.

Race	Preterm Cases (Percent)
African American	533 (1.20%)
White	1210 (0.87%)
Asian	98 (1.15%)

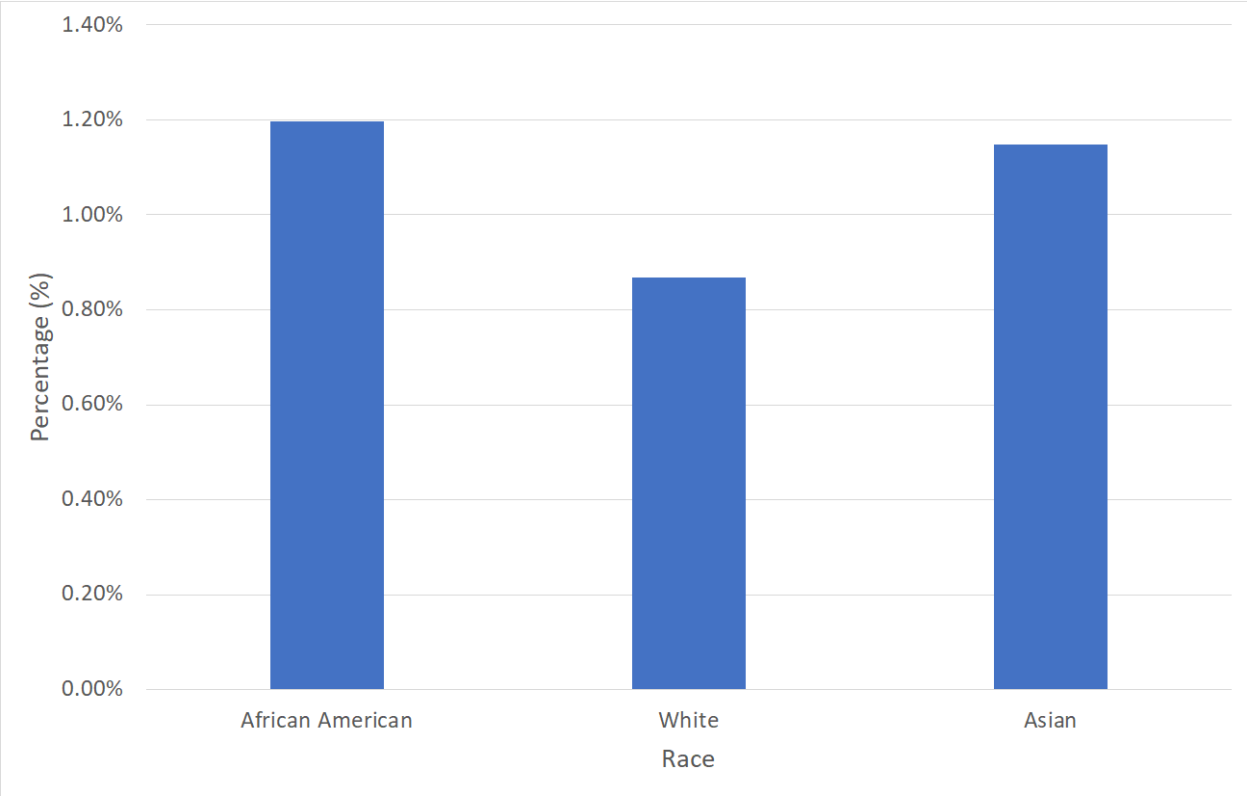

Figure 2 Distribution of PTB prevalence rate among racial groups.

Table 2 Distribution of 'Age at Consent' among cases.

Race	Age at Consent	
	18 - 44 years	> 45 years
African American	504 (3%)	25 (0.09%)
White	1132 (2.5%)	77 (0.09%)
Asian	85 (1.6%)	<20 (<0.5%)

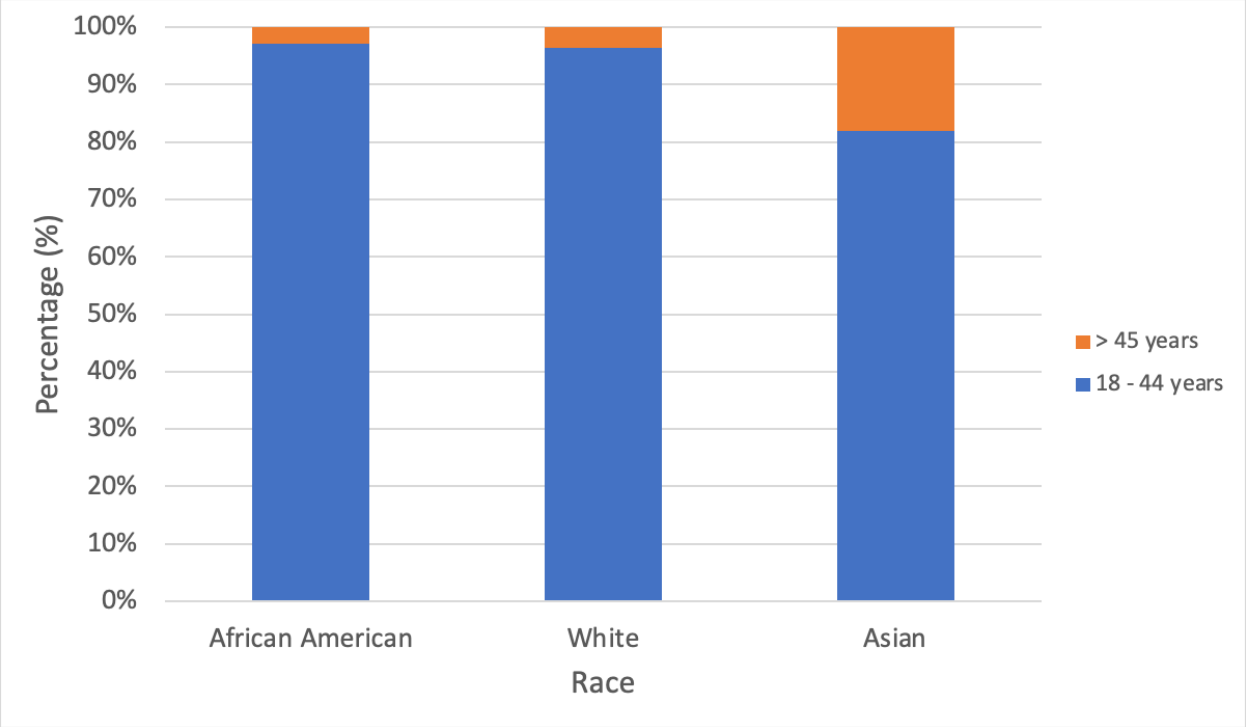

Figure 3 Distribution of 'Age of Consent' for cases.

Table 3 Association between marital status and risk of PTB in African American women.

Current Marital Status	Cases	Controls	P-value
Never Married	283 (56.49%)	726 (54.92%)	0.01
Married / Living with a Partner	172 (34.33%)	514 (38.88%)	
Divorced / Separated / Widowed	46 (9.18%)	82 (6.20%)	

Table 4 Prevalence of health insurance coverage and risk of PTB in African American women.

Health Insurance	Cases	Controls	P-value
Yes	468 (91.05%)	1284 (93.65%)	0.03
No	46 (8.95%)	87 (6.35%)	

Table 5 Clinical characteristics associated with risk of PTB in African American women.

Variable	Cases (n = 529)	Controls (n = 1409)	P-Value	95% CI	
	Mean			lower	Upper
Alkaline phosphatase [Enzymatic activity/volume] in Serum or Plasma	82.87	88.90	0.01	1.66	10.39
Basophils [#/volume] in Blood by Automated count	2.52	1.09	4.97E-03	-2.42	-0.43
Body temperature	48.05	44.17	0.01	-6.74	-1.01
Creatinine [Mass/volume] in Serum or Plasma	0.80	0.69	2.28E-03	-0.17	-0.04
Diastolic blood pressure	75.55	74.00	1.94E-03	-2.53	-0.57
Lymphocytes [#/volume] in Blood by Automated count	123.04	68.04	0.03	-105.73	-4.27
MCHC [Mass/volume] by Automated count	32.86	32.67	3.45E-03	-0.31	-0.06
Monocytes [#/volume] in Blood by Automated count	36.93	17.51	0.01	-34.90	-3.95
Potassium [Moles/volume] in Serum or Plasma	3.94	3.89	0.01	-0.09	-0.01
Systolic blood pressure	122.36	119.53	3.11E-05	-4.15	-1.50
Urea nitrogen [Mass/volume] in Serum or Plasma	10.17	8.90	3.44E-06	-1.80	-0.74

Appendix A Supplemental Content

Appendix A.1 IRB documentation

Due to the use of secondary data, an IRB was not necessary. An email from IRB support is attached to this document (Email - IRB documentation).

Appendix A.2 Clinical characteristics

Supplementary Table 1 Initial list of clinical characteristics.

Variables
3-epi-25-Hydroxyvitamin D2 [Mass/volume] in Serum or Plasma
Alanine aminotransferase [Enzymatic activity/volume] in Serum or Plasma
Albumin [Mass/volume] in Serum or Plasma
Alkaline phosphatase [Enzymatic activity/volume] in Serum or Plasma
Ascorbate [Mass/volume] in Urine by Test strip
Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma
Basophils [#/volume] in Blood by Automated count
Bile acid [Moles/volume] in Serum --fasting
Bilirubin [Presence] in Urine by Confirmatory method
Bilirubin.total [Mass/volume] in Serum or Plasma
Bilirubin.total [Mass/volume] in Urine
Bilirubin.total [Mass/volume] in Urine by Automated test strip
Bilirubin.total [Mass/volume] in Urine by Test strip
Bilirubin.total [Moles/volume] in Urine
Bilirubin.total [Moles/volume] in Urine by Test strip
Blood pressure panel
Body height
Body mass index (BMI) [Ratio]
Body temperature
Body weight
Calcium [Mass/volume] in Serum or Plasma
Carbon dioxide, total [Moles/volume] in Serum or Plasma
Choriogonadotropin [Units/volume] in Urine
Choriogonadotropin.beta subunit (pregnancy test) [Presence] in Serum or Plasma
Choriogonadotropin.beta subunit (pregnancy test) [Presence] in Urine
Choriogonadotropin.beta subunit [Moles/volume] in Serum or Plasma
Choriogonadotropin.intact [Units/volume] in Serum or Plasma
Creatinine [Mass/volume] in Serum or Plasma
Diastolic blood pressure
Eosinophils [#/volume] in Blood by Automated count
Eosinophils/100 leukocytes in Blood by Automated count
Erythrocyte distribution width [Ratio] by Automated count
Erythrocytes [#/volume] in Blood by Automated count
Fibrosis stage
Glucose [Mass/volume] in Serum or Plasma
Heart rate

Hematocrit [Volume Fraction] of Blood by Automated count
Hemoglobin [Mass/volume] in Blood
Intrinsic factor blocking Ab [Presence] in Serum
Leukocytes [#/volume] in Blood by Automated count
Liver fibrosis interpretation in Serum Qualitative
Lymphocytes [#/volume] in Blood by Automated count
Lymphocytes/100 leukocytes in Blood by Automated count
MCH [Entitic mass] by Automated count
MCHC [Mass/volume] by Automated count
MCV [Entitic volume] by Automated count
Metanephrine Free [Moles/volume] in Serum or Plasma
Monocytes [#/volume] in Blood by Automated count
Monocytes/100 leukocytes in Blood by Automated count
Necroinflammatory activity grade
Necroinflammatory activity interpretation in Serum Qualitative
Necroinflammatory activity score
Neutrophils [#/volume] in Blood by Automated count
Nitrite [Mass/volume] in Blood
Nitrite [Mass/volume] in Urine
Nitrite [Presence] in Urine
Platelet mean volume [Entitic volume] in Blood by Automated count
Platelets [#/volume] in Blood by Automated count
Potassium [Moles/volume] in Serum or Plasma
Protein [Mass/volume] in Serum or Plasma
Respiratory rate
Smudge cells [Presence] in Blood by Light microscopy
Sodium [Moles/volume] in Serum or Plasma
Systolic blood pressure
Urea nitrogen [Mass/volume] in Serum or Plasma

Supplementary Table 2 Excluded clinical characteristics.

Variable
3-epi-25-Hydroxyvitamin D2 [Mass/volume] in Serum or Plasma
Ascorbate [Mass/volume] in Urine by Test strip
Bile acid [Moles/volume] in Serum --fasting
Bilirubin [Presence] in Urine by Confirmatory method
Bilirubin.total [Mass/volume] in Urine
Bilirubin.total [Mass/volume] in Urine by Automated test strip
Bilirubin.total [Mass/volume] in Urine by Test strip
Bilirubin.total [Moles/volume] in Urine
Bilirubin.total [Moles/volume] in Urine by Test strip
Blood pressure panel
Choriogonadotropin [Units/volume] in Urine
Choriogonadotropin.beta subunit (pregnancy test) [Presence] in Serum or Plasma
Choriogonadotropin.beta subunit (pregnancy test) [Presence] in Urine
Choriogonadotropin.beta subunit [Moles/volume] in Serum or Plasma
Choriogonadotropin.intact [Units/volume] in Serum or Plasma
Fibrosis stage
Intrinsic factor blocking Ab [Presence] in Serum
Liver fibrosis interpretation in Serum Qualitative
Metanephrine Free [Moles/volume] in Serum or Plasma
Necroinflammatory activity grade
Necroinflammatory activity interpretation in Serum Qualitative
Necroinflammatory activity score
Nitrite [Mass/volume] in Blood
Nitrite [Mass/volume] in Urine
Nitrite [Presence] in Urine
Smudge cells [Presence] in Blood by Light microscopy

Supplementary Table 3 Final clinical characteristics.

Variable
Alanine aminotransferase [Enzymatic activity/volume] in Serum or Plasma
Albumin [Mass/volume] in Serum or Plasma
Alkaline phosphatase [Enzymatic activity/volume] in Serum or Plasma
Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma
Basophils [#/volume] in Blood by Automated count
Bilirubin.total [Mass/volume] in Serum or Plasma
Body height
Body mass index (BMI) [Ratio]
Body temperature
Body weight
Calcium [Mass/volume] in Serum or Plasma
Carbon dioxide, total [Moles/volume] in Serum or Plasma
Creatinine [Mass/volume] in Serum or Plasma
Diastolic blood pressure
Eosinophils [#/volume] in Blood by Automated count
Eosinophils/100 leukocytes in Blood by Automated count
Erythrocyte distribution width [Ratio] by Automated count
Erythrocytes [#/volume] in Blood by Automated count
Glucose [Mass/volume] in Serum or Plasma
Heart rate
Hematocrit [Volume Fraction] of Blood by Automated count
Hemoglobin [Mass/volume] in Blood
Leukocytes [#/volume] in Blood by Automated count
Lymphocytes [#/volume] in Blood by Automated count
Lymphocytes/100 leukocytes in Blood by Automated count
MCH [Entitic mass] by Automated count
MCHC [Mass/volume] by Automated count
MCV [Entitic volume] by Automated count
Monocytes [#/volume] in Blood by Automated count
Monocytes/100 leukocytes in Blood by Automated count
Neutrophils [#/volume] in Blood by Automated count
Platelet mean volume [Entitic volume] in Blood by Automated count
Platelets [#/volume] in Blood by Automated count
Potassium [Moles/volume] in Serum or Plasma
Protein [Mass/volume] in Serum or Plasma
Respiratory rate
Sodium [Moles/volume] in Serum or Plasma
Systolic blood pressure
Urea nitrogen [Mass/volume] in Serum or Plasma

Appendix A.3 Results for lifestyle factors and risk of PTB

Table 6 Association between marital status and risk of PTB in African American women.

Current Marital Status	Cases (%)	Controls (%)	P-value
Never Married	283 (56.49%)	726 (54.92%)	0.01
Married / Living with a Partner	172 (34.33%)	514 (38.88%)	
Divorced / Separated / Widowed	46 (9.18%)	82 (6.20%)	

Table 7 Prevalence of health insurance coverage and risk of PTB in African American women.

Health Insurance	Cases (%)	Controls (%)	P-value
Yes	468 (91.05%)	1284 (93.65%)	0.03
No	46 (8.95%)	87 (6.35%)	

Table 8 Association between income and risk of PTB in African American women.

Annual Income	Cases (%)	Controls (%)	P-value
< $10K	186 (46.62%)	438 (41.99%)	0.24
$10 - $25K	79 (18.80%)	208 (19.94%)	
$25K - $35K	53 (13.28%)	137 (13.14%)	
$35K - $50K	33 (8.27%)	98 (9.40%)	
$50K - $100K	30 (7.52%)	111 (10.64%)	
>$100K	18 (4.51%)	51 (4.89%)	

Table 9 Prevalence of smoking and risk of PTB in African American women.

Smoking Frequency	Cases (%)	Controls (%)	P-Value
Nat at all / NA	424 (80.92%)	1178 (84.14%)	0.56
Some days	30 (5.73%)	78 (5.57%)	
Every day	70 (13.36%)	144 (10.29%)	

Table 10 Association between education level and risk of PTB in African American women.

Education Level: Highest Grade	Cases (%)	Controls (%)	P-Value
11th grade or less	65 (12.62%)	146 (10.63%)	0.64
12th grade or GED	195 (37.86%)	555 (40.39%)	
College: 1-3 years	166 (32.23%)	423 (30.79%)	
College Graduate	63 (12.23%)	161 (11.72%)	
Advanced degree	26 (5.05%)	89 (6.48%)	

Table 11 Prevalence of alcohol intake and risk of PTB in African American women.

Alcohol: Drink Frequency Past Year	Cases (%)	Controls (%)	P-Value
Never / NA	197 (38.10%)	547 (39.93%)	0.75
2 – 3 per week	27 (5.22%)	82 (5.99%)	
4+ per week	14 (2.71%)	38 (2.77%)	
2 – 4 per month	89 (12.21%)	221 (16.13%)	
Monthly or less	190 (36.75%)	482 (35.18%)	

Table 12 Association between drug use and risk of PTB in African American women.

Recreational Drug Use	Cases	Controls	P-Value
Marijuana use	190 (46.57%)	536 (46.21%)	0.07
None of these drugs	218 (53.43%)	624 (53.79%)	

Appendix A.4 Clinical characteristics for F-test analysis

Supplementary Table 4

Variable	P-value	95% CI	
		lower	upper
Alanine aminotransferase [Enzymatic activity/volume] in Serum or Plasma	2.67E-18	0.37	0.53
Albumin [Mass/volume] in Serum or Plasma	1.35E-03	0.63	0.89
Alkaline phosphatase [Enzymatic activity/volume] in Serum or Plasma	1.73E-04	0.62	0.86
Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma	5.91E-03	1.06	1.46
Basophils [#/volume] in Blood by Automated count	0.00	2.60	3.74
Bilirubin.total [Mass/volume] in Serum or Plasma	0.00	3.20E+11	4.45E+11
Body height	6.49E-04	1.11	1.46
Body mass index (BMI) [Ratio]	7.89E-05	1.15	1.52
Body temperature	4.68E-03	1.08	1.51
Body weight	3.96E-02	1.01	1.33
Calcium [Mass/volume] in Serum or Plasma	8.48E-05	1.16	1.58
Carbon dioxide, total [Moles/volume] in Serum or Plasma	7.33E-01	0.87	1.22
Creatinine [Mass/volume] in Serum or Plasma	0.00	23.75	32.23
Diastolic blood pressure	5.18E-10	1.34	1.76
Eosinophils [#/volume] in Blood by Automated count	3.15E-23	0.31	0.44
Eosinophils/100 leukocytes in Blood by Automated count	1.70E-20	0.37	0.51
Erythrocyte distribution width [Ratio] by Automated count	6.37E-05	1.18	1.63
Erythrocytes [#/volume] in Blood by Automated count	9.22E-66	0.20	0.27
Glucose [Mass/volume] in Serum or Plasma	0.00	3.98E+06	5.42E+06
Heart rate	9.17E-01	0.87	1.14
Hematocrit [Volume Fraction] of Blood by Automated count	1.84E-08	1.31	1.76
Hemoglobin [Mass/volume] in Blood	6.60E-01	0.84	1.12
Leukocytes [#/volume] in Blood by Automated count	0.00	8.54E+04	1.14E+05
Lymphocytes [#/volume] in Blood by Automated count	0.00	1.97	2.81
Lymphocytes/100 leukocytes in Blood by Automated count	3.41E-71	0.15	0.21
MCH [Entitic mass] by Automated count	4.43E-01	0.81	1.10
MCHC [Mass/volume] by Automated count	7.93E-01	0.85	1.14
MCV [Entitic volume] by Automated count	5.32E-01	0.83	1.11
Monocytes [#/volume] in Blood by Automated count	0.00	2.46	3.52
Monocytes/100 leukocytes in Blood by Automated count	1.22E-95	0.11	0.15

Neutrophils [#/volume] in Blood by Automated count	0.00	1.97	2.73
Platelet mean volume [Entitic volume] in Blood by Automated count	0.00	2.99E+09	4.11E+09
Platelets [#/volume] in Blood by Automated count	1.58E-01	0.96	1.29
Potassium [Moles/volume] in Serum or Plasma	5.02E-04	1.13	1.54
Protein [Mass/volume] in Serum or Plasma	0.00	1.85	2.56
Respiratory rate	1.10E-01	0.97	1.34
Sodium [Moles/volume] in Serum or Plasma	2.55E-04	1.14	1.55
Systolic blood pressure	1.34E-11	1.41	1.88
Urea nitrogen [Mass/volume] in Serum or Plasma	0.00	3.53	4.80

Appendix A.5 Clinical characteristics for Welch t-test analysis

Supplementary Table 5 Welch t-test for clinical characteristics in African American women.

Variable	Cases (n=529)	Controls (n=1409)	P-value	95% CI	
	Mean			lower	upper
Alanine aminotransferase [Enzymatic activity/volume] in Serum or Plasma	22.03	22.58	0.69	-2.15	3.24
Albumin [Mass/volume] in Serum or Plasma	36.38	36.14	0.59	-1.07	0.61
Alkaline phosphatase [Enzymatic activity/volume] in Serum or Plasma	82.87	88.89	6.84E-03	1.66	10.39
Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma	25.14	23.11	0.12	-4.55	0.50
Basophils [#/volume] in Blood by Automated count	2.52	1.09	4.97E-03	-2.42	-0.43
Bilirubin.total [Mass/volume] in Serum or Plasma	8271.82	0.46	0.32	-2.45E+04	7989.04
Body height	163.44	164.14	0.07	-0.05	1.44
Body mass index (BMI) [Ratio]	33.24	33.23	0.98	-0.99	0.96
Body temperature	48.05	44.17	8.11E-03	-6.74	-1.01
Body weight	88.37	89.62	0.35	-1.37	3.87
Calcium [Mass/volume] in Serum or Plasma	9.03	9.07	0.18	-0.02	0.08
Carbon dioxide, total [Moles/volume] in Serum or Plasma	23.49	23.49	0.96	-0.27	0.26
Creatinine [Mass/volume] in Serum or Plasma	0.80	0.69	2.28E-03	-0.17	-0.04
Diastolic blood pressure	75.55	74.00	1.94E-03	-2.53	-0.57
Eosinophils [#/volume] in Blood by Automated count	7.28	5.31	0.35	-6.10	2.15
Eosinophils/100 leukocytes in Blood by Automated count	1.67	1.57	0.31	-0.27	0.09
Erythrocyte distribution width [Ratio] by Automated count	14.67	14.58	0.39	-0.29	0.11
Erythrocytes [#/volume] in Blood by Automated count	4.62	4.60	0.98	-1.14	1.11
Glucose [Mass/volume] in Serum or Plasma	2525.41	95.01	0.32	-7.19E+03	2326.54
Heart rate	84.28	84.41	0.77	-0.77	1.04
Hematocrit [Volume Fraction] of Blood by Automated count	34.16	34.28	0.55	-0.27	0.52
Hemoglobin [Mass/volume] in Blood	110.66	109.01	0.07	-3.47	0.16

Leukocytes [#/volume] in Blood by Automated count	1996.74	18.17	0.32	-5.86E+03	1904.19
Lymphocytes [#/volume] in Blood by Automated count	123.04	68.04	0.03	-105.73	-4.27
Lymphocytes/100 leukocytes in Blood by Automated count	24.99	25.66	0.39	-0.85	2.20
MCH [Entitic mass] by Automated count	28.24	28.05	0.18	-0.47	0.09
MCHC [Mass/volume] by Automated count	32.85	32.67	3.45E-03	-0.31	-0.06
MCV [Entitic volume] by Automated count	85.51	85.44	0.85	-0.75	0.62
Monocytes [#/volume] in Blood by Automated count	36.93	17.50	0.01	-34.90	-3.95
Monocytes/100 leukocytes in Blood by Automated count	7.19	7.53	0.09	-0.05	0.73
Neutrophils [#/volume] in Blood by Automated count	270.87	158.39	0.06	-228.99	4.03
Platelet mean volume [Entitic volume] in Blood by Automated count	3987.37	9.85	0.32	-1.18E+04	3841.31
Platelets [#/volume] in Blood by Automated count	256.12	250.86	0.13	-12.00	1.47
Potassium [Moles/volume] in Serum or Plasma	3.94	3.89	7.77E-03	-0.09	-0.01
Protein [Mass/volume] in Serum or Plasma	7.04	7.04	0.97	-0.10	0.10
Respiratory rate	17.70	17.61	0.36	-0.28	0.10
Sodium [Moles/volume] in Serum or Plasma	137.47	137.53	0.60	-0.17	0.29
Systolic blood pressure	122.35	119.53	3.11E-05	-4.15	-1.50
Urea nitrogen [Mass/volume] in Serum or Plasma	10.16	8.89	3.44E-06	-1.80	-0.74

Appendix A.6 Systematic literature review

Supplementary Table 6

Article	Study Population	Significant results
Engel et al. (2005)	Comparison between African American and White participants Nested case-control study	Predominantly found statistically significant association between the variants of candidate genes and risk of PTB in White subjects (*TNF [rs2800692]* and *LTA [rs746868]*) In African American subjects, variant in *IL6* is associated with increased risk of PTB (rs1800795)
Erichsen et al. (2006)	Nested case-control study African American and White women (PTB or term) - stratified	Able to identify SNPs associated with risk of PTB and *SLC23A1/2* in White population Not able to identify anything statistically significant in African American population
Frey et al. (2016)	Secondary analysis of randomized trial African American Women	ID's SNP related to 7 genes associated with increased risk of PTB ***PRKCA**, FLT1, MMP2, TIMP2, IL16, MMP1, LIFR-AS1,*
Harmon et al. (2013)	Nested case-control strudy Pregnant study population of European American and African American women	Most genes and their associated SNPs are associated with risk of PTB in European American women 2 genes appear to increase risk of PTB in both ancestries: *IL12A* and *CSF2* 1 SNP in *IL3* (rs31481) - slight increased risk of PTB in both groups 2 genes appear to be protective for both groups: *IL12A* (rs6441282, rs692890)
Hong et al. (2017)	Genome-wide G X E analysis in African American women	Identified maternal *COL24A1* variant associated with risk of PTB and obesity in AA women and obesity (rs11161721) Obese women carrying rs11161721-CC or normal BMI women carrying rs11161721-AA genotype have 2-fold increased risk of PTB Obese women with rs11161721-AA genotype have >50% decreased risk of PTB

Hong et al. (2021)	Genome-wide G X E analysis in African American women from Boston Birth cohort	in PTPRD gene - rs35331017-II genotype (insertion/insertion polymorphism) = ~2=fold increased risk of spontaneous PTB with high stress levels in AA (replicated in other studies) rs35331017-ID/DD genotype = decreased risk of spontaneous PTB with high maternal stress levels (ID/DD = insertion/deletion polymorphism)
Jones et al. (2012)	Stratified comparison between non-Hispanic White and African American women (mother-child pairs)	White subjects, *IL1* and *MMP9* polymorphism associated with increased risk of sPT B African American subjects, *TNFR2* associated with risk of spontaneous PTB. Focused on genes involved in the immune system due to current pathophysiology of PTTB.
Robertson et al. (2017)	African ancestry (GWAS)	No association between high-risk genetic variants of *APOL1* Conflicting with previous study in NEPTUNE and CKD in Children Study who found 4.6-fold increase of PTB in children with high-risk variants of *APOL1*
Velez et al. (2008)	Stratified comparison between non-Hispanic White and African American women (mother and fetal DNA)	Replicated previous studies that IL6 and IL6R are associated with PTB Look at 30 polymorphisms No single SNPs are strongly associated with increased risk of PTB in White mothers and infants in AA mothers rs4553185 for *IL6R* is statistically significant with risk of PTB
Velez et al. (2009)	African American mother-infant pair Case control study	Maternal genes associated with risk of PTB (*IL1RAP, IL6R, TNFRSF1B; ORs 1.69 to 2.04*) Fetal genes associated with risk of PTB (*IL2RB, MMP2, MMP9, PON2*)
Wang et al. (2006)	Case-control study African American mothers and infants	Infants with SERPINH1 - 656 minor T allele have increased risk of PPROM Due to reduced amnion leading to decrease in tensile strength Possibly mediated by the reduction in Hsp47 protein - involved in collagen stabilization of the triple helix

Bibliography

1. Cao G, Liu J, Liu M. Global, Regional, and National Incidence and Mortality of Neonatal Preterm Birth, 1990-2019. *JAMA Pediatr*. 2022;176(8):787-796. doi:10.1001/jamapediatrics.2022.1622

2. Nadeau HC, Subramaniam A, Andrews WW. Infection and preterm birth. *Semin Fetal Neonatal Med*. 2016;21(2):100-105. doi:10.1016/j.siny.2015.12.008

3. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84. doi:10.1016/S0140-6736(08)60074-4

4. Pavlidis I, Stock SJ. Preterm Birth Therapies to Target Inflammation. *J Clin Pharmacol*. 2022;62 Suppl 1(Suppl 1):S79-S93. doi:10.1002/jcph.2107

5. Baxter C, Crary I, Coler B, et al. Addressing a broken drug pipeline for preterm birth: why early preterm birth is an orphan disease. Am J Obstet Gynecol. 2023;229(6):647-655. doi:10.1016/j.ajog.2023.07.042

6. Platt MJ. Outcomes in preterm infants. Public Health. 2014;128(5):399-403. doi:10.1016/j.puhe.2014.03.010

7. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. Best Pract Res Clin Obstet Gynaecol. 2018;52:3-12. doi:10.1016/j.bpobgyn.2018.04.003

8. Morgan AS, Waheed S, Gajree S, Marlow N, David AL. Maternal and infant morbidity following birth before 27 weeks of gestation: a single centre study. Sci Rep. 2021;11(1):288. Published 2021 Jan 11. doi:10.1038/s41598-020-79445-1

9. Tanz LJ, Stuart JJ, Williams PL, et al. Preterm Delivery and Maternal Cardiovascular Disease Risk Factors: The Nurses' Health Study II. J Womens Health (Larchmt). 2019;28(5):677-685. doi:10.1089/jwh.2018.7150

10. McLemore MR, Berkowitz RL, Oltman SP, et al. Risk and Protective Factors for Preterm Birth Among Black Women in Oakland, California. *J Racial Ethn Health Disparities*. 2021;8(5):1273-1280. doi:10.1007/s40615-020-00889-2

11. Gillespie SL, Christian LM, Mackos AR, et al. Lifetime stressor exposure, systemic inflammation during pregnancy, and preterm birth among Black American women. Brain Behav Immun. 2022;101:266-274. doi:10.1016/j.bbi.2022.01.008

12. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. JAMA. 2002;287(2):195-202. doi:10.1001/jama.287.2.195

13. Ayala NK, Lewkowitz AK, Whelan AR, Miller ES. Perinatal Mental Health Disorders: A Review of Lessons Learned from Obstetric Care Settings. Neuropsychiatr Dis Treat. 2023;19:427-432. Published 2023 Feb 23. doi:10.2147/NDT.S292734

14. Dagher RK, Bruckheim HE, Colpe LJ, Edwards E, White DB. Perinatal Depression: Challenges and Opportunities. J Womens Health (Larchmt). 2021;30(2):154-159. doi:10.1089/jwh.2020.8862

15. Byatt N, Biebel K, Friedman L, Debordes-Jackson G, Ziedonis D, Pbert L. Patient's views on depression care in obstetric settings: how do they compare to the views of perinatal health care professionals?. Gen Hosp Psychiatry. 2013;35(6):598-604. doi:10.1016/j.genhosppsych.2013.07.011

16. Nicolaidis C, Timmons V, Thomas MJ, et al. "You don't go tell White people nothing": African American women's perspectives on the influence of violence and race on depression and depression care. Am J Public Health. 2010;100(8):1470-1476. doi:10.2105/AJPH.2009.161950

17. Bauman BL, Ko JY, Cox S, et al. Vital Signs: Postpartum Depressive Symptoms and Provider Discussions About Perinatal Depression - United States, 2018. MMWR Morb Mortal Wkly Rep. 2020;69(19):575-581. Published 2020 May 15. doi:10.15585/mmwr.mm6919a2

18. Chang Q, Ma XY, Xu XR, Su H, Wu QJ, Zhao YH. Antidepressant Use in Depressed Women During Pregnancy and the Risk of Preterm Birth: A Systematic Review and Meta-Analysis of 23 Cohort Studies. Front Pharmacol. 2020;11:659. Published 2020 May 19. doi:10.3389/fphar.2020.00659

19. Huybrechts KF, Straub L, Karlsson P, et al. Association of In Utero Antipsychotic Medication Exposure With Risk of Congenital Malformations in Nordic Countries and the US. JAMA Psychiatry. 2023;80(2):156-166. doi:10.1001/jamapsychiatry.2022.4109

20. Vlenterie R, van Gelder MMHJ, Anderson HR, et al. Associations Between Maternal Depression, Antidepressant Use During Pregnancy, and Adverse Pregnancy Outcomes: An Individual Participant Data Meta-analysis. Obstet Gynecol. 2021;138(4):633-646. doi:10.1097/AOG.0000000000004538

21. All of Us Research Program Overview. (2020, June 22). National Institutes of Health (NIH) — All of Us. https://allofus.nih.gov/about/program-overview

22. Khandre V, Potdar J, Keerti A. Preterm Birth: An Overview. Cureus. 2022;14(12):e33006. Published 2022 Dec 27. doi:10.7759/cureus.33006

23. Kistka ZA, Palomar L, Lee KA, et al. Racial disparity in the frequency of recurrence of preterm birth. Am J Obstet Gynecol. 2007;196(2):131.e1-131.e1316. doi:10.1016/j.ajog.2006.06.093

24. Anderson C, Cacola P. Implications of Preterm Birth for Maternal Mental Health and Infant Development. MCN Am J Matern Child Nurs. 2017;42(2):108-114. doi:10.1097/NMC.0000000000000311

25. Dolan SM. Genetic and environmental contributions to racial disparities in preterm birth. Mt Sinai J Med. 2010;77(2):160-165. doi:10.1002/msj.20169

26. Brink LT, Roberts DJ, Wright CA, et al. Placental pathology in spontaneous and iatrogenic preterm birth: Different entities with unique pathologic features. Placenta. 2022;126:54-63. doi:10.1016/j.placenta.2022.06.004

27. Venkatesh KK, Lynch CD, Powe CE, et al. Risk of Adverse Pregnancy Outcomes Among Pregnant Individuals With Gestational Diabetes by Race and Ethnicity in the United States, 2014-2020. JAMA. 2022;327(14):1356-1367. doi:10.1001/jama.2022.3189

28. Raghavan R, Helfrich BB, Cerda SR, et al. Preterm birth subtypes, placental pathology findings, and risk of neurodevelopmental disabilities during childhood. Placenta. 2019;83:17-25. doi:10.1016/j.placenta.2019.06.374

29. Klumper J, Ravelli ACJ, Roos C, Abu-Hanna A, Oudijk MA. Deprived neighborhoods and spontaneous preterm birth: A national cohort study. Eur J Obstet Gynecol Reprod Biol. 2022;274:88-95. doi:10.1016/j.ejogrb.2022.05.012

30. Fettweis JM, Serrano MG, Brooks JP, et al. The vaginal microbiome and preterm birth. Nat Med. 2019;25(6):1012-1021. doi:10.1038/s41591-019-0450-2

31. Bekkar B, Pacheco S, Basu R, DeNicola N. Association of Air Pollution and Heat Exposure With Preterm Birth, Low Birth Weight, and Stillbirth in the US: A Systematic Review [published correction appears in JAMA Netw Open. 2020 Jul 1;3(7):e2014510]. JAMA Netw Open. 2020;3(6):e208243. Published 2020 Jun 1. doi:10.1001/jamanetworkopen.2020.8243

32. Ferguson KK, McElrath TF, Meeker JD. Environmental phthalate exposure and preterm birth [published correction appears in JAMA Pediatr. 2014 Jul;168(7):684] [published correction appears in JAMA Pediatr. 2019 Mar 1;173(3):295-296]. JAMA Pediatr. 2014;168(1):61-67. doi:10.1001/jamapediatrics.2013.3699

33. Pasanen A, Karjalainen MK; FinnGen, et al. Meta-analysis of genome-wide association studies of gestational duration and spontaneous preterm birth identifies new maternal risk loci. PLoS Genet. 2023;19(10):e1010982. Published 2023 Oct 23. doi:10.1371/journal.pgen.1010982

34. Knijnenburg TA, Vockley JG, Chambwe N, et al. Genomic and molecular characterization of preterm birth. Proc Natl Acad Sci U S A. 2019;116(12):5819-5827. doi:10.1073/pnas.1716314116

35. Pereyra S, Bertoni B, Sapiro R. Interactions between environmental factors and maternal-fetal genetic variations: strategies to elucidate risks of preterm birth. Eur J Obstet Gynecol Reprod Biol. 2016;202:20-25. doi:10.1016/j.ejogrb.2016.04.030

36. Santos P, Joglekar G, Faughnan K, Darden J, Hendrich A. Disproportionate Preterm Delivery Among Black Women: a State-Level Analysis. J Racial Ethn Health Disparities. 2020;7(2):290-297. doi:10.1007/s40615-019-00657-x

37. Giurgescu C, Banks A, Dancy BL, Norr K. African American women's views of factors impacting preterm birth. MCN Am J Matern Child Nurs. 2013;38(4):229-234. doi:10.1097/NMC.0b013e318293bbbb

38. Gillespie SL, Christian LM, Mackos AR, et al. Lifetime stressor exposure, systemic inflammation during pregnancy, and preterm birth among Black American women. Brain Behav Immun. 2022;101:266-274. doi:10.1016/j.bbi.2022.01.008

39. Denny JC, Rutter JL, Goldstein DB, Philippakis A, Smoller JW, Jenkins G, et al. The "All of Us" Research Program. N Engl J Med. 2019;381(7):668–76. doi: 10.1056/NEJMsr1809937

40. All of Us Research program. Data Methods – Genomic Data Curation. Accessed February 22, 2024. https://www.researchallofus.org/data-tools/methods/

41. Nijman TA, van Vliet EO, Benders MJ, et al. Placental histology in spontaneous and indicated preterm birth: A case control study. Placenta. 2016;48:56-62. doi:10.1016/j.placenta.2016.10.006

42. Fogacci MF, Cardoso EOC, Barbirato DDS, de Carvalho DP, Sansone C. No association between periodontitis and preterm low birth weight: a case-control study. Arch Gynecol Obstet. 2018;297(1):71-76. doi:10.1007/s00404-017-4556-9

43. The All of Us Research Program Genomics Investigators. Genomic data in the All of Us Research Program. Nature 627, 340–346 (2024). https://doi.org/10.1038/s41586-023-06957-x

44. Carrara J, Habibi A, Benachi A, Cheminet G. Sickle cell disease and pregnancy. Presse Med. 2023;52(4):104203. doi:10.1016/j.lpm.2023.104203

45. Njoku A, Evans M, Nimo-Sefah L, Bailey J. Listen to the Whispers before They Become Screams: Addressing Black Maternal Morbidity and Mortality in the United States. *Healthcare (Basel)*. 2023;11(3):438. Published 2023 Feb 3. doi:10.3390/healthcare11030438

46. Wang Y, Max W, Yao T, Keeler C, Sung HY. Differential price-responsiveness of smoking behaviors among non-Hispanic African Americans and non-Hispanic whites in the United States. Addiction. 2021;116(10):2859-2869. doi:10.1111/add.15504

47. Smith LK, Draper ES, Manktelow BN, Dorling JS, Field DJ. Socioeconomic inequalities in very preterm birth rates. Arch Dis Child Fetal Neonatal Ed. 2007;92(1):F11-F14. doi:10.1136/adc.2005.090308

48. Kim W, Seo JM. Necrotizing Enterocolitis. N Engl J Med. 2020;383(25):2461. doi:10.1056/NEJMicm2020782

49. Berken JA, Chang J. Neurologic Consequences of Neonatal Necrotizing Enterocolitis. Dev Neurosci. 2022;44(4-5):295-308. doi:10.1159/000525378
50. Alman BL, Stingone JA, Yazdy M, et al. Associations between PM2.5 and risk of preterm birth among liveborn infants. Ann Epidemiol. 2019;39:46-53.e2. doi:10.1016/j.annepidem.2019.09.008

51. Mendola P, Wallace M, Hwang BS, et al. Preterm birth and air pollution: Critical windows of exposure for women with asthma. J Allergy Clin Immunol. 2016;138(2):432-440.e5. doi:10.1016/j.jaci.2015.12.1309

52. Zhang X, Fan C, Ren Z, et al. Maternal PM2.5 exposure triggers preterm birth: a cross-sectional study in Wuhan, China. Glob Health Res Policy. 2020;5:17. Published 2020 May 1. doi:10.1186/s41256-020-00144-5

53. Avalos LA, Chen H, Li DK, Basu R. The impact of high apparent temperature on spontaneous preterm delivery: a case-crossover study. Environ Health. 2017;16(1):5. Published 2017 Feb 1. doi:10.1186/s12940-017-0209-5

54. Basu R, Chen H, Li DK, Avalos LA. The impact of maternal factors on the association between temperature and preterm delivery. Environ Res. 2017;154:109-114. doi:10.1016/j.envres.2016.12.017

55. Mead EC, Wang CA, Phung J, et al. The Role of Genetics in Preterm Birth. Reprod Sci. 2023;30(12):3410-3427. doi:10.1007/s43032-023-01287-9

56. Wadon M, Modi N, Wong HS, Thapar A, O'Donovan MC. Recent advances in the genetics of preterm birth. Ann Hum Genet. 2020;84(3):205-213. doi:10.1111/ahg.12373

57. Barfield WD. Public Health Implications of Very Preterm Birth. Clin Perinatol. 2018;45(3):565-577. doi:10.1016/j.clp.2018.05.007

58. Glass HC, Costarino AT, Stayer SA, Brett CM, Cladis F, Davis PJ. Outcomes for extremely premature infants. Anesth Analg. 2015;120(6):1337-1351. doi:10.1213/ANE.0000000000000705

59. Callahan BJ, DiGiulio DB, Goltsman DSA, et al. Replication and refinement of a vaginal microbial signature of preterm birth in two racially distinct cohorts of US women. Proc Natl Acad Sci U S A. 2017;114(37):9966-9971. doi:10.1073/pnas.1705899114

60. Fettweis JM, Brooks JP, Serrano MG, et al. Differences in vaginal microbiome in African American women versus women of European ancestry. *Microbiology (Reading)*. 2014;160(Pt 10):2272-2282. doi:10.1099/mic.0.081034-0

61. Márquez-Lázaro J, Madera M, Bernabe E. Particulate matter 2.5 exposure during pregnancy and birth outcomes: Evidence from Colombia. *Sci Total Environ*. Published online April 9, 2024. doi:10.1016/j.scitotenv.2024.172369

62. Rodríguez-Fernández A, Ruíz-De la Fuente M, Sanhueza-Riquelme X, Parra-Flores J, Dolores Marrodán M, Maury-Sintjago E. Association between Maternal Factors, Preterm Birth, and Low Birth Weight of Chilean Singletons. Children (Basel). 2022;9(7):967. Published 2022 Jun 28. doi:10.3390/children9070967

63. Farbu J, Haugen M, Meltzer HM, Brantsæter AL. Impact of singlehood during pregnancy on dietary intake and birth outcomes- a study in the Norwegian Mother and Child Cohort Study. BMC Pregnancy Childbirth. 2014;14:396. Published 2014 Dec 5. doi:10.1186/s12884-014-0396-9

64. Raatikainen K, Heiskanen N, Heinonen S. Marriage still protects pregnancy. BJOG. 2005;112(10):1411-1416. doi:10.1111/j.1471-0528.2005.00667.x

65. Merklinger-Gruchala A, Kapiszewska M. The Effect of Prenatal Stress, Proxied by Marital and Paternity Status, on the Risk of Preterm Birth. Int J Environ Res Public Health. 2019;16(2):273. Published 2019 Jan 18. doi:10.3390/ijerph16020273

66. Engel SA, Erichsen HC, Savitz DA, Thorp J, Chanock SJ, Olshan AF. Risk of spontaneous preterm birth is associated with common proinflammatory cytokine polymorphisms. Epidemiology. 2005;16(4):469-477. doi:10.1097/01.ede.0000164539.09250.31

67. Erichsen HC, Engel SA, Eck PK, et al. Genetic variation in the sodium-dependent vitamin C transporters, SLC23A1, and SLC23A2 and risk for preterm delivery. Am J Epidemiol. 2006;163(3):245-254. doi:10.1093/aje/kwj035

68. Frey HA, Stout MJ, Pearson LN, et al. Genetic variation associated with preterm birth in African-American women. Am J Obstet Gynecol. 2016;215(2):235.e1-235.e2358. doi:10.1016/j.ajog.2016.03.008

69. Harmon QE, Engel SM, Olshan AF, et al. Association of polymorphisms in natural killer cell-related genes with preterm birth. Am J Epidemiol. 2013;178(8):1208-1218. doi:10.1093/aje/kwt108

70. Hong X, Hao K, Ji H, et al. Genome-wide approach identifies a novel gene-maternal pre-pregnancy BMI interaction on preterm birth. Nat Commun. 2017;8:15608. Published 2017 Jun 9. doi:10.1038/ncomms15608

71. Hong X, Surkan PJ, Zhang B, et al. Genome-wide association study identifies a novel maternal gene × stress interaction associated with spontaneous preterm birth. Pediatr Res. 2021;89(6):1549-1556. doi:10.1038/s41390-020-1093-1

72. Jones NM, Holzman C, Tian Y, et al. Innate immune system gene polymorphisms in maternal and child genotype and risk of preterm delivery. J Matern Fetal Neonatal Med. 2012;25(3):240-247. doi:10.3109/14767058.2011.569614

73. Robertson CC, Gillies CE, Putler RKB, et al. An investigation of APOL1 risk genotypes and preterm birth in African American population cohorts. Nephrol Dial Transplant. 2017;32(12):2051-2058. doi:10.1093/ndt/gfw317

74. Velez DR, Fortunato SJ, Williams SM, Menon R. Interleukin-6 (IL-6) and receptor (IL6-R) gene haplotypes associate with amniotic fluid protein concentrations in preterm birth. Hum Mol Genet. 2008;17(11):1619-1630. doi:10.1093/hmg/ddn049

75. Velez DR, Fortunato S, Thorsen P, Lombardi SJ, Williams SM, Menon R. Spontaneous preterm birth in African Americans is associated with infection and inflammatory response gene variants. Am J Obstet Gynecol. 2009;200(2):209.e1-209.27. doi:10.1016/j.ajog.2008.08.051

76. Wang H, Parry S, Macones G, et al. A functional SNP in the promoter of the SERPINH1 gene increases risk of preterm premature rupture of membranes in African Americans [published correction appears in Proc Natl Acad Sci U S A. 2006 Dec 12;103(50):19212]. Proc Natl Acad Sci U S A. 2006;103(36):13463-13467. doi:10.1073/pnas.0603676103