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Epigenomic pathways from racism to preterm birth: secondary analysis of the Nulliparous Pregnancy Outcomes Study: monitoring Mothers-to-be (nuMoM2b) cohort study in the USA to examine how DNA methylation mediates the relationship between multilevel racism and preterm birth in black women: a study protocol

Veronica Barcelona ,[1] Mitali Ray,[2] Yihong Zhao,[3] Goleen Samari,[4] Haotian Wu,[5] Paolo Reho,[5] Rebecca McNeil,[6] Uma M Reddy[7]

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For numbered affiliations see end of article.

Correspondence to
Dr Veronica Barcelona; vb2534@cumc.columbia.edu

ABSTRACT

Introduction Preterm birth is a significant contributor to pregnancy-related morbidity and mortality, particularly affecting black women. Racism is a key driver of perinatal inequities, but mechanisms remain unclear. Epigenomics research offers promise in understanding how environmental exposures, including racism, influence gene expression and adverse pregnancy outcomes. We present our study protocol describing how we will investigate the interactive effects of individual- and structural-level racism on preterm birth within and across black and white women, characterise the blood-based methylome of black pregnant women and identify whether DNA methylation mediates the association between multilevel racism and preterm birth in black women.

Methods and analysis We will conduct a secondary analysis of data from 6843 participants in the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b), a longitudinal, prospective cohort study (2010–2014). Individual-level racism was collected using the Experiences of Discrimination scale. Structural racism measures include racial residential segregation, income and racial polarisation, political participation, judicial treatment, homeownership and employment. These measures will be calculated using geocoded participant addresses and publicly available census data for black and white populations. Epigenome-wide methylation analyses will be conducted on stored DNA for all enrolled black women using the EPIC 2.0 BeadChip. Preterm birth was determined by abstraction from participant electronic health records. We will determine the joint effects of individual and structural racism on preterm birth, characterise DNA methylation profiles associated with preterm birth among black women and explore the mediating role of DNA methylation in the association between multilevel racism and preterm birth.

Ethics and dissemination Study procedures were approved by the Columbia University Institutional Review Board (#AAAU0215). This study aims to fill critical knowledge gaps regarding the role of racism and epigenomics in preterm birth among black women.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to examine associations of racism-related epigenetic changes with established molecular markers related to preterm birth.
⇒ We have an adequately powered sample of black participants that will allow us to apply an epigenome-wide approach, which was previously limited due to the inclusion of black individuals in epigenomic research in pregnancy.
⇒ Our candidate gene approach is based on a rigorous search of genes associated with stress pathways, using multiple data sources.
⇒ The Experiences of Discrimination was collected during the second trimester, while DNA was collected in the first trimester; however, this instrument assesses discrimination across the life course, thus accounting for some issues with timing.
⇒ The large majority of participants were US born, limiting our ability to examine differences by country of birth among black women.

INTRODUCTION

Preterm birth (PTB; birth occurring <37 weeks of gestation) is a primary contributor to

pregnancy-related mortality and morbidity, with long-term sequelae for both the birthing parent and the infant.[1–3] The aetiology of PTB is likely multifactorial and is not well understood.[4] Despite the establishment of several risk factors for PTB, prevention and treatment options also remain limited. These include low socioeconomic status, infection, prior PTB, multiple gestation, high blood pressure in pregnancy, tobacco, alcohol and substance use, late or inadequate prenatal care and stress.[5] Black women have higher rates of PTB, as well as higher rates of hypertensive disorders in pregnancy and low birth weight.[6] Intervention studies in pregnancy, however, have yielded little improvement in disparities between black and white women, and these disparities persist even for black women who are highly educated, have access to prenatal care and have no comorbidities.[7 8] Racism has been posited as a significant factor underlying perinatal inequities in the USA, including PTB.[9–11] The mechanisms by which racism may be a root cause of these disparities have yet to be elucidated. Epigenomics research (the study of reversible modifications to the DNA sequence that do not alter the sequence) offers a mechanism by which environmental exposures, including stress, are able to influence gene expression. As such, epigenomics represents a field with great promise for understanding the mechanisms and pathways by which racism affects gene expression and adverse pregnancy outcomes (APOs) among black people. APOs represent various disorders in pregnancy that contribute to maternal and fetal morbidity, such as PTB, hypertensive disorders of pregnancy and small for gestational age.[12 13]

Existing research on the epigenomic effects of racism and discrimination is limited.[14] One secondary analysis found that black young adults who had experienced racial discrimination had accelerated epigenetic ageing.[15] Two studies have examined epigenetic changes associated with exposure to racism and discrimination among black and Latina adults in the USA,[16 17] and another among African migrants in Europe.[18] These studies reported differential methylation at stress- and inflammation-related genes, suggesting that DNA methylation (DNAm) may capture a biological signal of these negative exposures in adults.

Large, diverse, prospective studies from early pregnancy to birth are lacking, limiting identification of high-risk individuals for improved prenatal surveillance. Despite the high prevalence of APOs among the black population in the USA, black individuals remain under-represented in studies of epigenomics of pregnancy. There are limited studies on racism and epigenomics in pregnancy, and most are cross-sectional, which limits temporal inference.[19] Few studies have examined DNAm differences among black people by racism exposures, and none have included pregnant individuals.[16] Furthermore, prior researchers have employed candidate-gene approaches, limiting our understanding of the impact of racism on gene expression at the epigenome-wide level, in relation to APOs.[17] Importantly, characterisation of DNAm signatures in early pregnancy has the potential to serve as a molecular marker that may improve risk identification. An improved understanding of root causes of PTB could also inform effective multilevel interventions to narrow the widest racial and ethnic disparity that exists between black and white people.

Although individual-level (personally mediated) racism has been associated with PTB,[11] racism affects childbearing people beyond the individual level, including structural levels as well. Individual-level racism is defined as differential assumptions about people and actions towards them based on race. Structural racism refers to differential access to goods, services and opportunities in society by race.[20] Individual experiences of racial discrimination are associated with greater parenting stress.[21] Structural racism was also associated with greater than three times higher risk of hypertension, a risk factor for PTB, in a sample of black mothers.[22] Social inequality disproportionately affects black women and their families, and studies have documented the association between increased stress and poorer mental[23 24] and physical health outcomes for decades.[25–28] These health inequities are associated with the social construct of race, yielding a concentration of wealth and unequal access to quality education. However, the risk for adverse perinatal outcomes among black people persists even after achievement of high levels of income and education.[7 29] Additional forms of structural racism, such as racial residential segregation, incarceration and higher rates of violence, have been studied in black women, their families and communities.[30–33] These studies reflect social policies which adversely affect neighbourhoods and communities, translating into poor birth outcomes, including PTB. The complex relationship between both individual and structural racism factors remains understudied, especially in the context of pregnancy outcomes.

Individual experiences of everyday racism may interact with structural-level racism to produce poor health.[34] Although some studies have examined structural racism and PTB,[35–37] no study has investigated the interaction of individual and structural racism on birth outcomes, despite the fact that they often occur together. A challenge to this work is that mechanisms underlying the association between racism and PTB are poorly understood. We hypothesise that racism explains the excess PTB observed when comparing black and white individuals and that the epigenomic mechanism of DNAm underlies the pathway from racism to PTB among black individuals.[38]

The theoretical framework for this study is informed by Williams and Mohammed's framework examining racism and health in our society. We aim to narrow these crucial knowledge gaps by leveraging data and samples from one of the largest and most rigorously phenotyped pregnancy cohorts, the *Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b)*. Our overarching goal is to improve perinatal health by examining racism and epigenomic mechanisms underlying PTB. We seek to accomplish this goal through the secondary analysis of the nuMoM2b study with the following aims:

(1) determine the interactive effects of individual- and structural-level racism on PTB within and across black and white women (n=6843); (2) characterise the blood-based methylome of black pregnant individuals (n=1080) by applying a tiered approach: tier 1 analyses will target 60 536 CpGs associated with stress pathways, while tier 2 will apply a discovery-based, epigenome-wide approach (935 000 CpGs) and (3) identify whether DNAm mediates the association between multilevel (individual and structural) racism and PTB in black women (n=1080, with n=162 PTB).

METHODS AND ANALYSIS

Design of the parent study

A full description of the methods of the nuMoM2b study has been previously published.[39] In brief, this was a longitudinal, prospective cohort study of nulliparous women conducted from 2010 to 2014 across eight clinical sites across the USA. Participants were recruited during the first trimester of pregnancy and seen up to four times—once during each of the three trimesters of pregnancy and again during the labour and birth visit (n=10 038). Individuals were eligible for recruitment if they were between 6 and 13 weeks gestation, had a viable singleton gestation and had no prior pregnancy lasting >20 weeks. Verbal or written informed consent was obtained from participants in the parent study. No informed consent was necessary for the study described in the current protocol paper as this is a secondary analysis of already collected data. Race and ethnicity data were collected by self-report. Blood for DNA analysis was collected during the first study visit, and the Experiences of Discrimination (EOD) scale was administered during the second study visit. APOs were defined according to the current clinical criteria and documented by chart abstraction with adjudication. Characteristics of the analytic sample included in the proposed study are presented in table 1.

Phenotyping PTB

PTB was classified as spontaneous or indicated. Spontaneous PTB was defined as delivery of a liveborn or stillborn infant between 20+0 and 36+6 weeks of gestation with spontaneous onset of preterm labour or premature rupture of membranes. Preterm labour was defined in nuMoM2b as: (1) spontaneous uterine contractions that occurred before rupture of amniotic membranes and resulted in delivery or (2) increase in cervical dilation by at least 1 cm or effacement or dilation >2 cm or effacement >80% among those hospitalised for contractions. Indicated PTB was defined as delivery between 20+0 and 36+6 weeks of gestation following induction or caesarean section.[39]

Measures of racism and operationalisation

Racism at the individual level

The EOD scale is a validated metric that measures self-reported individual experiences of racism and discrimination in adults of all races and ethnicities from working-class backgrounds, with high reliability in diverse samples.[40–42] The 9-item scale assesses major discrimination, including frequency of occurrence and the number of situations in which discrimination occurred in various contexts, including school, employment, housing, medical care, service in stores/restaurants, financial settings and judicial settings.

Racism at the structural level

Structural racism systematically excludes racial and ethnic groups that are not white from resources and social mobility to concentrate power.[43–45] While there is no universal accepted instrument to measure structural racism, we have expanded on previous studies[46 47] and calculated six variables at different geographic levels, based on publicly available data. The variables include (1) racial residential segregation (index of dissimilarity), (2) income and racial polarisation (index of concentration at the extremes), (3) political participation, (4) judicial treatment, (5) homeownership and (6) employment. Geocoded addresses of nuMoM2b participants allowed us to apply these measures and indices which represent inequality and disadvantage that span generations.[48] Each individual measure of structural racism was dichotomised by its sample median into high and low structural racism categories for inclusion in models.[46]

Collection of epigenome-wide DNAm data

Whole blood was drawn at each of the nuMoM2b sites according to local protocol.[39] DNA was later extracted, stored at −80°C and normalised before epigenome-wide DNAm data analysis. DNA samples were bisulphite-converted by using EZ-96 DNA methylation kits (Zymo Research), according to the manufacturer's protocol and processed for Illumina Infinium MethylationEPIC v2.0 Beadchips at the University of Minnesota Genomics Center.

DNAm data quality control and accounting for cell type heterogeneity, population stratification and batch effects

The 'minfi' package in R will be used to conduct epigenome-wide quality control of DNAm data. Successful bisulphite conversion will be confirmed using control probes. We will identify and remove poorly performing CpGs that meet any of the following criteria: (1) detection p value of 0.001, (2) known to have common SNPs at the CpG site, (3) annotated to Y chromosomes and (4) cross-reactive probes that map to multiple places in the genome. Outlying DNA samples will be identified using principal components analysis and removed. Functional normalisation will be performed for background correction and dye normalisation using the Noob method.[49] β values will be used as the primary DNAm measure.

As methylation profiles of distinct cell types may lead to biased results due to differences in cell-type heterogeneity across individuals,[50] we will apply a modified version of the gold-standard Houseman method.[51] Relative

Table 1 Black and white participants in the nuMoM2b cohort

	Black (n=1248)	White (n=5595)	Total (n=6843)	P value
Age				<0.001
Mean (SD)	23.27 (5.28)	28.17 (5.19)	27.27 (5.54)	
Category				<0.001
13–17	68 (5.4%)	68 (1.2%)	136 (2.0%)	
18–34	1123 (90.0%)	4941 (88.3%)	6064 (88.6%)	
35–39	45 (3.6%)	496 (8.9%)	541 (7.9%)	
40+	12 (1.0%)	90 (1.6%)	102 (1.5%)	
Ever smoked				0.001
	495 (39.7%)	2499 (44.7%)	2994 (43.8%)	
Smoked during pregnancy				<0.001
	147 (11.8%)	402 (7.2%)	549 (8.0%)	
Education				<0.001
Less than high school	234 (18.8%)	224 (4.0%)	458 (6.7%)	
HS Grad or GED	315 (25.2%)	419 (7.5%)	734 (10.7%)	
Some college	370 (29.6%)	838 (15.0%)	1208 (17.7%)	
Associate/technical degree	121 (9.7%)	561 (10.0%)	682 (10.0%)	
College degree	129 (10.3%)	1934 (34.6%)	2063 (30.1%)	
Degree work beyond college	79 (6.3%)	1619 (28.9%)	1698 (24.8%)	
Income relative to federal poverty level				<0.001
>200%	239 (31.5%)	4002 (78.8%)	4241 (72.7%)	
100–200%	161 (21.2%)	616 (12.1%)	777 (13.3%)	
<100%	358 (47.2%)	458 (9.0%)	816 (14.0%)	
Employed at visit 1				<0.001
	455 (56.0%)	4001 (86.5%)	4456 (81.9%)	
BMI				<0.001
Mean (SD)	29.06 (8.14)	25.84 (5.82)	26.42 (6.42)	
Country of birth				0.529
USA	1183 (95.0%)	5331 (95.4%)	6514 (95.4%)	
Outside of USA	62 (5.0%)	255 (4.6%)	317 (4.6%)	
Among those born outside USA, #of years living in USA				
Mean (SD)	14.31 (8.72)	12.48 (9.54)	12.83 (9.40)	0.169
EOD score				<0.001
0–2	945 (82.9%)	5250 (97.9%)	6195 (95.3%)	
3+	195 (17.1%)	110 (2.1%)	305 (4.7%)	
Birth outcomes				
Preterm birth	153 (12.8%)	434 (8.0%)	587 (8.9%)	<0.001
Small for gestational age	175 (15.2%)	399 (7.5%)	574 (8.9%)	<0.001
Low birth weight (<2500 g)	121 (10.9%)	289 (5.5%)	410 (6.5%)	<0.001
Infant sex				0.793
Male	577 (51.7%)	2683 (51.3%)	3260 (51.4%)	
Female	540 (48.3%)	2543 (48.6%)	3083 (48.6%)	

BMI, b; EOD, Experiences of Discrimination; HS Grad or GED, High school graduate or equivalent; nuMoM2b, Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be.

proportions of immune cell types will be estimated using the 'estimateCellCounts' function from the R package 'Flow-Sorted.Blood.EPIC'.[52]

We will perform SmartSVA analysis[53] on the DNAm data to identify and include significant surrogate variables in analytical models as covariates to correct for potential biases due to population stratification,[54] batch assignments, additional cell-type composition not adjusted for by Houseman's method and unmodelled confounders. The number of significant surrogate variables will be automatically determined based on the random matrix theory.[55]

Selection of candidate CpGs associated with stress gene pathways for targeted epigenome-wide association studies (EWAS)

We performed a systematic search of multiple databases to identify genes (PubMed and GWAS Catalog) and pathways (Kyoto Encyclopedia of Genes and Genomes (KEGG), BioCarta and Gene Ontology (GO) pathway annotations) associated with psychosocial stress (ie, psychosocial stress, cortisol/glucocorticoids, epinephrine/norepinephrine and anxiety). By incorporating multiple sources and excluding duplicates, we identified 403 unique genomic regions of interest and retrieved a total of >60 000 corresponding CpG sites covered by Illumina Infinium MethylationEPIC V.2.0 Beadchips as the candidates for our targeted DNAm analysis. Each category was constructed using multiple alternative keywords, where appropriate, and the sums exclude overlapping regions and sites.

Analytical approaches

This study will employ comprehensive analytical approaches to examine racism and epigenomic mechanisms underlying PTB. The aim of our first study is designed to determine the interactive effects of individual- and structural-level racism on PTB within and across both black and white participants (n=6843). Our second and third aims evaluate the methylome among black participants (n=1080) by performing targeted and discovery-based EWAS studies for PTB status (n=162) and mediation analyses to assess whether DNAm mediates the association between multilevel racism and PTB. For the mediation analysis, we will follow the practice guidelines by VanderWeele[56] to test the potential mediation effects of methylation markers on the relationship between racism and PTB. Briefly, two regressions will be employed. In the outcome model, we regress outcome (ie, PTB status) on the exposure a (ie, racism), the methylation mediator m and a set of covariates C: $E\left(Y|a, m, C\right) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3' C$. In the mediation model, we regress methylation mediator m on the racism and the covariates: $E\left(M|a, C\right) = \beta_0 + \beta_1 a + \beta_2' C$. Functions in R mediation package will be used for the mediation analyses. Sensitivity analyses will be performed to check the robustness of our findings against various confounding effects.

To complete our first study aim, we will use the dichotomised EOD scale score for individual level racism and examine the six measures of structural racism highlighted above. We will study within-racial group differences in PTB and then examine multilevel (the interaction of individual and structural) racism to determine if racism explains the excess PTB observed in black participants compared with white participants. Generalised linear mixed-effects models will be used for this analysis. We expect to show significant differences in PTB rates between low- and high-racism exposure groups. With a full sample size of 6843 and a significance level of 0.005 to account for multiple comparisons, power analyses indicate that our study is adequately powered (with at least 80% power) to detect significant main and interactive effects of racism exposures on PTB with at least low (ie, OR=1.79) to moderate (ie, OR=2.69) effect sizes.

Targeted EWAS

We hypothesise that DNAm of CpGs associated with stress pathways will differ among Black participants by PTB status. We will conduct targeted EWAS with PTB status as the independent variable and DNAm (β values) as the dependent variable. Differentially methylated CpG sites will be identified using the dmpFinder function in the minfi R package.[57] We will use standard thresholds for unadjusted p values for EWAS, where significance is defined as less than 9×10^{-8} and suggestive significance at less than 1×10^{-5}.[58] After evaluating CpGs individually, we will also evaluate differentially mediated regions (DMRs). Associations with DMRs are considered stronger than associations with individual CpGs. These analyses are also more statistically powerful due to the lower multiple testing burden. DMRs will be evaluated at the region and using the bumphunter and blockFinder functions in the minfi R package.

Discovery-based EWAS

We will also perform a discovery-based EWAS to evaluate differentially methylated CpGs and DMRs across the entire methylome by PTB status. The same analytical approach for targeted EWAS will be applied; however, we will evaluate the entire epigenome, rather than specific CpG sites.

Participant age, education, income, employment status, alcohol and drug use, and infant sex will be examined as potential covariates in all statistical models. We will control for participant body mass index (BMI) and smoking, which are known confounders in epigenomic studies.[59 60] We will also examine the potential role of smoking as an intermediate, as racism may influence smoking, which influences DNAm. We will also investigate other covariates such as blood pressure, participant BMI, medication use, infections, social support (Multidimensional Scale of Perceived Social Support),[61] resilience (Connor-Davidson Resilience Scale)[62] and relationship with father of baby (assessed at each trimester), which may be confounders, mediators or moderators. The majority of participants

consented to genetic analyses, and their DNA was genotyped, providing ancestry information for adjustment in models. We will examine other indicators of stress and mental health as covariates and in sensitivity analyses (ie, perceived stress, state-trait anxiety and depression).[63–65]

For epigenetic study aims, our power calculation aimed to ensure adequate statistical power to detect significant group differences on methylation proportions between PTB and full term in the candidate-gene approach. Simulation studies were used to investigate the number of subjects required to detect DNAm differences across 100 CpGs with 80% power for three effect sizes (ie, $\Delta\beta = 0.10, 0.15, 0.20$, representing differences in DNAm between PTB and full birth at 10%, 15% and 20%). The significance level is controlled at false discovery rate of 0.05 level. Our simulation studies showed that with 1295 total samples, we have 70% power to detect at least one CpG out of the 100 differentially methylated CpGs if the targeted group difference in DNAm is 10%. If the targeted group differences are set at 15% and 20%, with 1300 total sample, the study power increased from 70% to 78% and 83%, respectively.

We will replicate findings using unpublished data (n=400), partially described in an initial paper of Emory University African American Vaginal, Oral and Gut Microbiome in Pregnancy Cohort Study.[66] The validation sample is comparable with the nuMoM2b cohort in gestational age, maternal age and timing of psychological assessments to measure discrimination and stress. Genomic data for the replication sample have been processed and are available for replication analyses.

Patient and public involvement

Patients and the public were not involved in the design of the secondary analysis study described here. Participant data from the original parent study are protected, and results cannot be returned to individual participants.

Ethics and dissemination

Study procedures were approved by the Columbia University Institutional Review Board (#AAAU0215). The results of this study will be published, and data will be made available by request once study aims are completed.

This groundbreaking study not only provides essential insights that can potentially help guide future interventions to prevent PTB at both individual and structural levels but also represents a significant leap forward in addressing the intricate interplay of racism factors and epigenomics in pregnancy among US born black people, thereby informing future research directions and health policy development to mitigate perinatal health inequities.

DISCUSSION

This novel multidisciplinary study will provide foundational data directing priority interventions at the individual and structural levels to prevent PTB and will provide necessary data for future research to alter the biological mechanisms underlying this outcome. This will be the largest study to examine multilevel racism factors and epigenomics in pregnancy among black individuals. Previous work in the same study sample found no differences in individual experiences of discrimination and APOs,[67] underscoring the importance of examining structural factors and epigenetic differences that may explain disparities. Findings will address knowledge gaps by (1) contributing epigenomic data towards discovery of mechanisms underlying PTB and other adverse birth outcomes in black individuals and (2) informing health policy development related to racism and perinatal health inequities across diverse geographic locations in the USA.

Author affiliations
[1]School of Nursing, Columbia University, New York, New York, USA
[2]University of Pittsburgh School of Nursing, Pittsburgh, Pennsylvania, USA
[3]Columbia University School of Nursing, New York, New York, USA
[4]Department of Population and Public Health Sciences, University of Southern California Keck School of Medicine, Los Angeles, California, USA
[5]Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, New York, USA
[6]RTI International, Research Triangle Park, North Carolina, USA
[7]Irving Medical Center, Department of Obstetrics and Gynecology, Columbia University, New York, New York, USA

Contributors VB: conceptualisation, methodology, writing–original draft, writing–revision, funding. MR: writing–original draft, methodology. YZ: writing–original draft, writing–revision, methodology. GS: writing–original draft, methodology. HW: writing–review and editing, methodology. PR: writing–review and editing, methodology. RM: formal analysis, writing–review and editing, methodology. UMR: writing–review and editing. Guarantor is VB.

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Competing interests None declared.

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ORCID iD
Veronica Barcelona http://orcid.org/0000-0003-3070-1716

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