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Experiences of Discrimination and DNA Methylation Among Black Nulliparous Women

Sarah E. Harkins[1] · **Arielle K. Hazi**[2] · **Tingting Zhao**[2] · **Paolo Reho**[3] · **Haotian Wu**[3] · **Goleen Samari**[4] · **Ronald Wapner**[1] · **Yihong Zhao**[2] · **Veronica Barcelona**[2]

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Abstract

Exposure to racial discrimination is a well-documented risk factor for adverse pregnancy outcomes. It is hypothesized that this association occurs through epigenetic changes. Researchers have identified associations between perceived discrimination and methylation of stress-response genes among racially and ethnically minoritized women. However, findings are limited by small sample sizes and inclusion of women who are several years postpartum. Little is known about the influence of discrimination on DNA methylation among Black women in pregnancy. Therefore, we conducted an epigenome-wide association study of 897 Black pregnant women who participated in the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) study to examine associations between experiences of racial discrimination and DNA methylation. Racial discrimination was measured using responses to the Experiences of Discrimination scale (range 0–9) completed in the second trimester of pregnancy. We dichotomized responses into low discrimination (0–2) and high discrimination (≥ 3) categories. Whole blood was collected in the first trimester of pregnancy and used for DNA extraction. We identified 130 CpG sites significantly associated with high levels of racial discrimination. There were 17 genes mapped to the 20 most significant CpG sites. Fourteen of those genes have disease-associated phenotypes including cancer (*LCMT2, LINC02753, RARA, HSP90AA1, SMTN, LPCAT1, SPAG4, DAPK1, ZNF500*), cardiomyopathy (*SMTN*), ovarian insufficiency (*DMRT3*), neurodevelopmental disability (*MLPH*, CDC123, *OGFOD3*), and asthma (*STAT6*). We identified novel associations between racial discrimination and disease-related genes among Black nulliparous pregnant women. Future research should include structural racism measures and study epigenetic pathways between racism and adverse pregnancy and birth outcomes.

Keywords Epigenetics · Methylation · Discrimination · Racism · Pregnancy

Introduction

Racial inequities in adverse pregnancy outcomes persist in the United States [1]. Black women have the highest rates of preterm birth, low birthweight, and maternal morbidity and mortality among all racial and ethnic groups [2, 3]. These inequities are not explained by socioeconomic indicators alone as Black women with a college degree or greater education have significantly higher risks of maternal mortality compared to White women with less than a high school diploma [4]. Therefore, socioeconomic factors typically considered protective against adverse perinatal outcomes do not offer the same advantages for Black women. Reproductive health and justice scholars have identified racism, defined as an institutionalized system of policies, practices, and beliefs that discriminates against individuals based on

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✉ Veronica Barcelona
vb2534@cumc.columbia.edu

[1] Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, NY, USA

[2] Columbia University School of Nursing, 560 W 168th Street, New York, NY 10032, USA

[3] Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, NY, USA

[4] Department of Population and Public Health Sciences in the Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

racial group membership, as the primary cause of racial inequities in adverse pregnancy outcomes [5]. For example, discrimination has been associated with increased risks of preterm birth [6, 7], small for gestational age infants [8], and maternal morbidity [9–11] among Black women. In addition, over 95% of Black women reported experiencing discrimination in a recent national study of pregnancy, underscoring how racism is a pervasive and common experience [9].

Understanding the psychopathological pathways through which discrimination affects pregnancy outcomes is important to inform more targeted interventions and eliminate perinatal inequities. Researchers have hypothesized that exposure to racial discrimination results in epigenetic changes that increase the risk of adverse pregnancy outcomes [12, 13]. The most commonly studied epigenetic change is DNA methylation. Methylation of cytosine residues may indicate the addition or removal of a methyl group to CpG dinucleotides that can up- or downregulate gene expression. For example, a study of African American women who were 3–5 years postpartum identified significant associations between perceived discrimination and CpG methylation levels of genes linked to schizophrenia, bipolar disorder, and asthma [14]. Another study of Latina mothers found that discrimination was associated with hypomethylation of stress-response genes, including the glucocorticoid receptor gene (*NR3C1*) and brain-derived neurotrophic factor (*BDNF*) genes throughout pregnancy and the postpartum period [15]. In addition, a study of pregnant Latina women found different methylation patterns of *NR3C1* in participants with high physical and psychological stress compared to participants with low stress [16].

Prior research on discrimination and DNA methylation in the perinatal period has been limited by small cross-sectional study designs, reducing the ability to detect significant findings. In addition, while previous studies have primarily focused on comparisons among Latina women in pregnancy [15, 16] or Black women several years after giving birth [14], there is a paucity of research on the effects of discrimination on DNA methylation among Black women during pregnancy. This is a critical gap in pregnancy health knowledge given that Black women are disproportionately exposed to discrimination, and inequities in adverse pregnancy outcomes continue to increase in the United States [17]. Studying within-group variation among Black pregnant women is essential to identifying epigenetic responses to social stressors and informing more tailored interventions to advance perinatal health equity. Therefore, the purpose of this study was to conduct an epigenome-wide association study among Black pregnant women and to examine associations between experiences of discrimination and DNA methylation.

Methods

Study Sample

We conducted a secondary analysis of data from the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b). A detailed description of the nuMoM2b methods and cohort has been previously published [18]. Briefly, nuMoM2b was a longitudinal, prospective cohort study of nulliparous women conducted across eight academic medical centers from 2010–2014 ($N = 10{,}038$). Women were recruited in the first trimester of pregnancy and were eligible if they were between 6- and 13-weeks of gestation, had a viable singleton gestation, and had no prior history of a pregnancy ≥ 20 weeks of gestation. Women were interviewed during each trimester of pregnancy and again at the labor and birth admission to collect demographic characteristics, medical history, psychosocial history, clinical measurements, and biospecimens. Clinical outcomes were abstracted from electronic health records after birth. The current analysis is part of a study to examine associations between individual-and structural-level racism, DNA methylation markers, and preterm birth among Black nuMoM2b participants, and methods have been published elsewhere [19]. Study procedures for this analysis were approved by the institutional review board at [blinded] University.

Conceptual Model

We present our guiding conceptual model in Fig. 1. It is hypothesized that exposure to structural and interpersonal discrimination results in physiological wear and tear due to increased stress and anxiety from racism [12, 13]. Examples of physiological wear and tear include epigenetic changes such as DNA methylation, which may increase risk of adverse pregnancy and birth outcomes among Black women. Therefore, epigenetic changes may mediate the relationship between racism and adverse pregnancy outcomes. For the present analysis, we only tested the association between interpersonal racism and DNA methylation. Future research should examine the mediation pathway between DNA methylation and adverse pregnancy and birth outcomes.

Measures

Discrimination was measured using the Experiences of Discrimination (EOD) scale. This validated measure (Cronbach's alpha = 0.74) asks respondents if they have experienced discrimination due to their race, ethnicity, or color across nine social settings such as at school, from police, or when receiving medical care [20]. Participants provide their responses (yes/no) to each social setting for a total

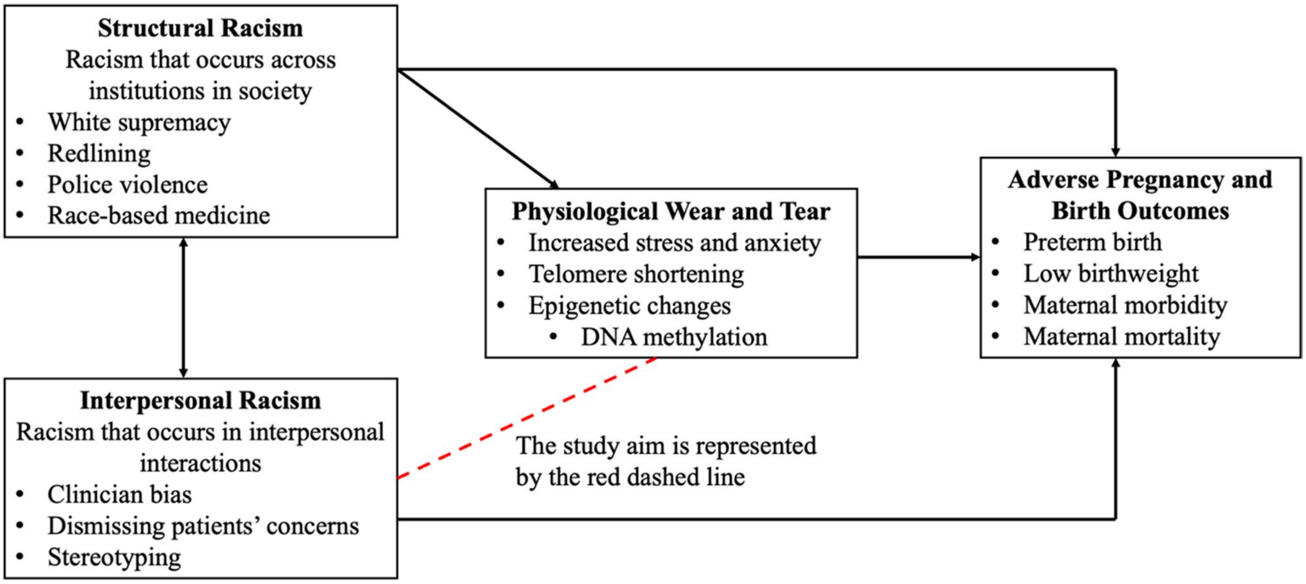


Fig. 1 The dashed line represents the focus of the present analysis in which we examined the association between interpersonal racism and DNA methylation among nulliparous Black women

score range of 0–9, which can be examined as a continuous or categorical variable. However, EOD scores in our study sample were largely skewed toward lower values. Consistent with prior studies, we dichotomized responses into low discrimination (0–2) and high discrimination (≥ 3) categories [21, 22]. EOD responses were collected once in the second trimester of pregnancy in the nuMoM2b cohort.

DNA and Epigenetic Processing

Whole blood (4–8 mL) was collected from participants during the first trimester study visit. Maternal DNA was extracted and frozen at −80 degrees Celsius. Genotyping was completed for Black nuMoM2b participants using the Infinium Multi-Ethnic Global D2 BeadChip [23]. Raw IDAT files ($n = 1{,}073$) were processed using MethylCallR, an EPICv2-aware pipeline for probe and sample quality control. Samples were excluded if median $\log_2$ signal intensity < 10.5 or > 1% of probes failed detection ($p > 0.01$). Probes were removed if they met any of the following: detection $p > 0.01$ in > 1% of samples, bead count < 3 in > 5% of samples, mapped to non-CG sites, located on sex chromosomes, overlapped common AFR SNPs (SeSaMe manifest), identified as cross-hybridizing (BLAT), annotated as low-reproducibility (EPICv2 manifest), or failed alignment to GRCh38/hg38. EPICv2-specific duplicates were also discarded. After filtering, 1,070 samples and 815,165 probes remained.

We used the Noob method for normalization (offset = 100, XY probes excluded). Outliers were identified via Mahalanobis distance, with 11 samples removed. Batch effects (e.g., Sentrix barcode, sample section) were corrected with *MeCall.RemoveBatch()*, preserving preterm birth status. Cell-type proportions (CD8^{+}/CD4^{+} T cells, NK cells, B cells, monocytes, neutrophils) were estimated using *MeCall.CellComp()*.

Epigenome Wide Association Study (EWAS) Analysis

EWAS were performed using the *MeCall.DMP()* function from MethylCallR, which applies a linear modeling framework implemented in the *limma* package. Batch-adjusted beta values from the EPIC v2 arrays were used as input. Models were adjusted for maternal age, smoking during pregnancy (any vs. none), educational attainment, body mass index (BMI) at the first prenatal visit, and infant sex at birth. To account for technical variation and unmeasured confounding, the first 10 principal components from the methylation data were included as covariates, along with estimated proportions of major blood cell types. Participants with missing covariates or poor-quality measurements were excluded. Differentially methylated positions (DMPs) were identified using empirical Bayes moderated t-statistics, and multiple testing corrections were applied using the Benjamini–Hochberg method to control the false discovery rate (FDR). Significant CpGs (FDR < 0.05) annotation was retrieved using the *annotatr()* package [24]. For CpGs reaching epigenome-wide significance, we computed the E-value for the point estimate and the lower bound of the 95% confidence interval to quantify the robustness of our findings to potential unmeasured confounding [25, 26]. All analyses were completed in R.

Functional Enrichment Analysis

We conducted a functional enrichment analysis to determine which biological pathways were enriched by the CpG-annotate genes using the g:Profiler toolkit [27]. This evaluation drew from multiple databases, including Gene Ontology (GO) [28], the Kyoto Encyclopedia of Genes and Genomes [29], and Reactome [30]. The analysis included genes linked to DMPs that met a FDR threshold of <0.05 in the EWAS and was performed using a custom reference background derived from the CpGs available in the study. We retained pathways that met the Bonferroni-corrected threshold of 0.05.

Results

Demographic Characteristics of Participants

This analysis included 897 participants from the NuMoM2b epigenomic sample. We present descriptive statistics for the analytic sample in Table 1. The mean age of participants was 23.5 years and just over half had some college education or greater (57.8%). In addition, 730 participants (81.4%) reported EOD scores of 0–2 and 167 participants (18.6%) reported EOD scores ≥ 3. Participants with higher EOD scores were significantly older ($p<0.001$), had higher education levels ($p<0.001$), were more likely to have a male infant ($p=0.034$), and had a higher BMI ($p=0.012$) compared to participants with lower EOD scores.

Table 1 Demographic characteristics of the study sample by reported EOD scores

Characteristic	Total sample	Experiences of Discrimination Scores		
	N (%)	High (≥3) n (%)	Low (0–2) n (%)	*p*
Total	897 (100.0)	167 (18.6)	730 (81.4)	
Maternal age				<.001[1]
Mean (SD)	23.5 (5.3)	27.4 (6.2)	22.6 (4.7)	
Range	13.0—45.0	16.0—45.0	13.0—42.0	
Smoked during pregnancy				.930[2]
No	804 (89.6)	150 (89.8)	654 (89.6)	
Yes	93 (10.4)	17 (10.2)	76 (10.4)	
Highest level of education				<.001[2]
High school or less	378 (42.1)	37 (22.2)	341 (46.7)	
Some college or college degree	456 (50.8)	99 (59.3)	357 (48.9)	
Education beyond college	63 (7.0)	31 (18.6)	32 (4.4)	
Infant Sex				.034[2]
Female	438 (49.0)	69 (41.6)	369 (50.7)	
Male	456 (51.0)	97 (58.4)	359 (49.3)	
Body mass index				.012[1]
Mean (SD)	28.9 (7.9)	30.4 (8.8)	28.5 (7.7)	
Range	16.0—59.8	16.0—59.8	16.8—59.7	

SD standard deviation. [1] = Wilcoxon rank sum test. [2] = Chi squared test

Differentially Methylated CpG Sites Associated with Discrimination

We present the Volcano and Manhattan Plots of the EWAS in Figs. 2 and 3. We identified 130 CpG sites that were significantly associated with EOD scores (FDR adjusted $p<0.05$). Among the 20 most significant CpG sites (Table 2), 12 sites were found to be hypomethylated and 8 were hypermethylated with increasing levels of discrimination. The top 20 most significant CpG sites were mapped to 17 genes, including leucine carboxyl methyltransferase 2 (*LCMT2,* cg27481594, FDR adjusted $p=0.00028472$, $\Delta B=-0.03119069$), retinoic acid receptor alpha (*RARA*, cg22521767, FDR adjusted $p=0.000590694$, $\Delta B=-0.0079237$), smoothelin (*SMTN*, cg10237442, FDR adjusted $p=0.000590694$, $\Delta B=-0.00820263$), doublesex and MAB-3 related transcription factor (*DMRT3*, cg14495514, FDR adjusted $p=0.00217422$, $\Delta B=-0.01196172$), long intergenic non-protein coding RNA 2753 (*LINC02753*, cg16564733, FDR adjusted $p=0.004819383$, $\Delta B=-0.01738003$), uncharacterized LOC105374282 (*LOC105374282*, cg19257384, FDR adjusted $p=0.006105731$, $\Delta B=-0.00471554$), lysophosphatidylcholine acyltransferase 1 (*LPCAT1*, cg17437086, FDR adjusted $p=0.007738431$, $\Delta B=-0.0045996$), B4GAT1- divergent transcript (*B4GAT1-DT*, cg07602924, FDR adjusted $p=0.007738431$, $\Delta B=0.006078073$), melanophilin (*MLPH*, cg13377901, FDR adjusted $p=0.010359301$, $\Delta B=-0.00853755$), death-associated protein kinase 1(*DAPK1*, cg13876645, FDR adjusted $p=0.010359301$, $\Delta B=-0.01005905$), zinc finger protein 500 (*ZNF500*, cg09338875, FDR adjusted $p=0.013031883$, $\Delta B=0.003578896$), cell division cycle 123 (*CDC123*, cg14674977, FDR adjusted $p=0.013607438$, $\Delta B=0.006344377$), sperm-associated antigen 4 (*SPAG4*, cg16402787, FDR adjusted $p=0.013607438$, $\Delta B=0.004635361$), heat shock protein 90 alpha family class A member 1 (*HSP90AA1*, cg07030774, FDR adjusted $p=0.013607438$, $\Delta B=0.003358299$), 2-oxoglutarate and iron dependent oxygenase domain-containing protein 3 (*OGFOD3*, cg19860459, FDR adjusted $p=0.013607438$, $\Delta B=-0.00351783$), signal transducer and activator of transcription 6 (*STAT6*, cg16156751, FDR adjusted $p=0.013607438$, $\Delta B=-0.00969487$), and TSSK6 activating co-chaperone

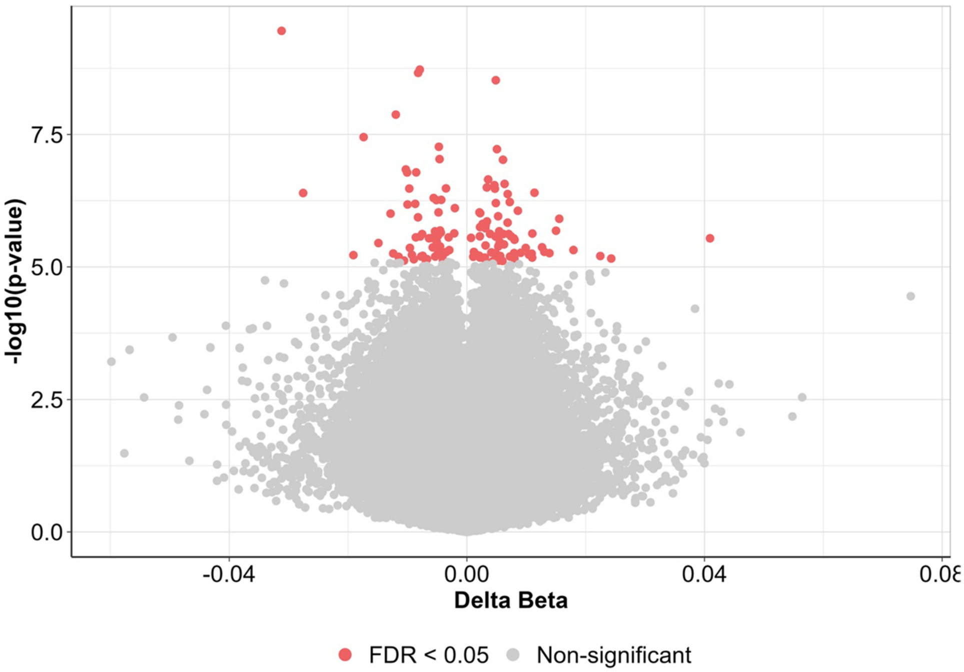


Fig. 2 The volcano plot depicts hypomethylated DMPs to the left of and hypermethylated DMPs to the right of $\Delta B = 0$. Statistically significant sites are displayed in red

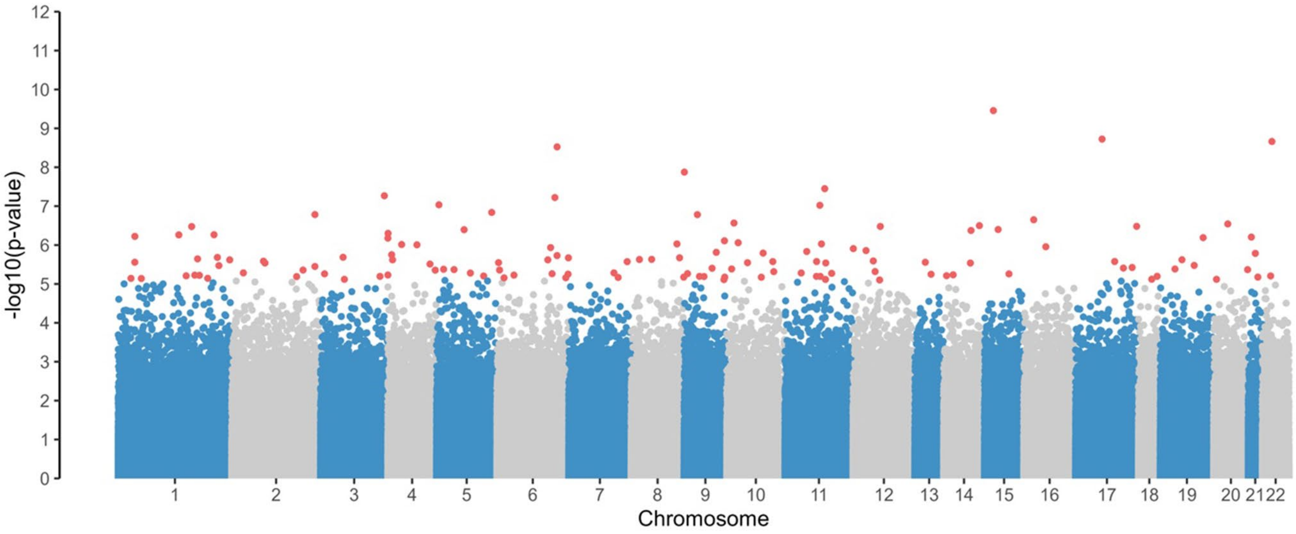


Fig. 3 The Manhattan plot provides the genomic position of each DMP. Statistically significant sites are displayed in red

(*TSACC*, cg18388972, FDR adjusted $p=0.013607438$, $\Delta B=-0.004721452$). Among the top 20 most significant CpG sites, three sites (cg02257090, FDR adjusted $p=0.000609033$, $\Delta B=0.004869344$; cg08712228, FDR adjusted $p=0.006105731$, $\Delta B=0.005059581$; and cg02022425, FDR adjusted $p=0.010359301$, $\Delta B=-0.0102774$) were not mapped to an identified gene.

E-values for the most significant 20 CpG sites ranged from 2.07 to 2.79 and from 1.72 to 2.24 for the lower bound 95% confidence interval limit. Therefore, an unmeasured confounder associated with both the exposure and DNA methylation by risk ratios of at least 1.72, beyond the measured covariates, would be required to fully explain away the weakest observed association.

Functional Enrichment Analysis

We conducted a functional enrichment analysis of 166 genes associated with 130 DMPs linked to racial discrimination in our EWAS. This analysis identified biological processes including cell fate commitment and neuron fate commitment, and molecular functions such as ion binding,

Table 2 The top 20 most significant CpG sites associated with Experiences of Discrimination scores

CpGid	Chromosome	Position	Gene	Functional Region	ΔB	Adjusted *p* value	E-value	E-value lower 95% confidence interval
cg27481594	chr15	43,331,084	LCMT2	TSS1500	−0.03119069	.00028472	2.788675	2.242457
cg22521767	chr17	40,352,172	RARA		−0.0079237	.000590694	2.394535	1.979378
cg10237442	chr22	31,079,136	SMTN		−0.00820263	.000590694	2.548635	2.072678
cg02257090	chr6	148,748,316			0.004869344	.000609033	2.703121	2.161495
cg14495514	chr9	974,533	DMRT3		−0.01196172	.00217422	2.533534	2.039195
cg16564733	chr11	70,068,421	LINC02753		−0.01738003	.004819383	2.551164	2.03472
cg19257384	chr3	193,771,245	LOC105374282		−0.00471554	.006105731	2.488357	1.991639
cg08712228	chr6	139,877,896			0.005059581	.006105731	2.489511	1.99066
cg17437086	chr5	1,473,959	LPCAT1	exon_11	−0.0045996	.007738431	2.415729	1.941132
cg07602924	chr11	66,350,936	B4GAT1-DT		0.006078073	.007738431	2.373265	1.916038
cg02022425	chr5	175,773,398			−0.0102774	.010359301	2.462885	1.960849
cg13377901	chr2	237,534,196	MLPH		−0.00853755	.010359301	2.316886	1.874917
cg13876645	chr9	87,663,092	DAPK1		−0.01005905	.010359301	2.439132	1.945098
cg09338875	chr16	4,768,531	ZNF500	TSS1500	0.003578896	.013031883	2.436409	1.93846
cg14674977	chr10	12,239,323	CDC123		0.006344377	.013607438	2.070975	1.723193
cg16402787	chr20	35,617,005	SPAG4		0.004635361	.013607438	2.347973	1.883936
cg07030774	chr14	102,139,509	HSP90AA1	exon_1	0.003358299	.013607438	2.455344	1.942792
cg19860459	chr17	82,394,443	OGFOD3	exon_9	−0.00351783	.013607438	2.422213	1.923504
cg16156751	chr12	57,102,693	STAT6		−0.00969487	.013607438	2.163707	1.775305
cg18388972	chr1	156,338,383	TSACC	TSS1500	0.004721452	.013607438	2.405774	1.914048

small molecule binding, protein folding chaperone, cytoskeletal protein binding, actin binding, protein binding, voltage-gated chloride channel activity, and metal ion binding. In addition, three cellular components and one REACTOME pathway was identified from the GO database, all of which surpassed the Bonferroni-corrected significance threshold of 0.05 (Fig. 4).

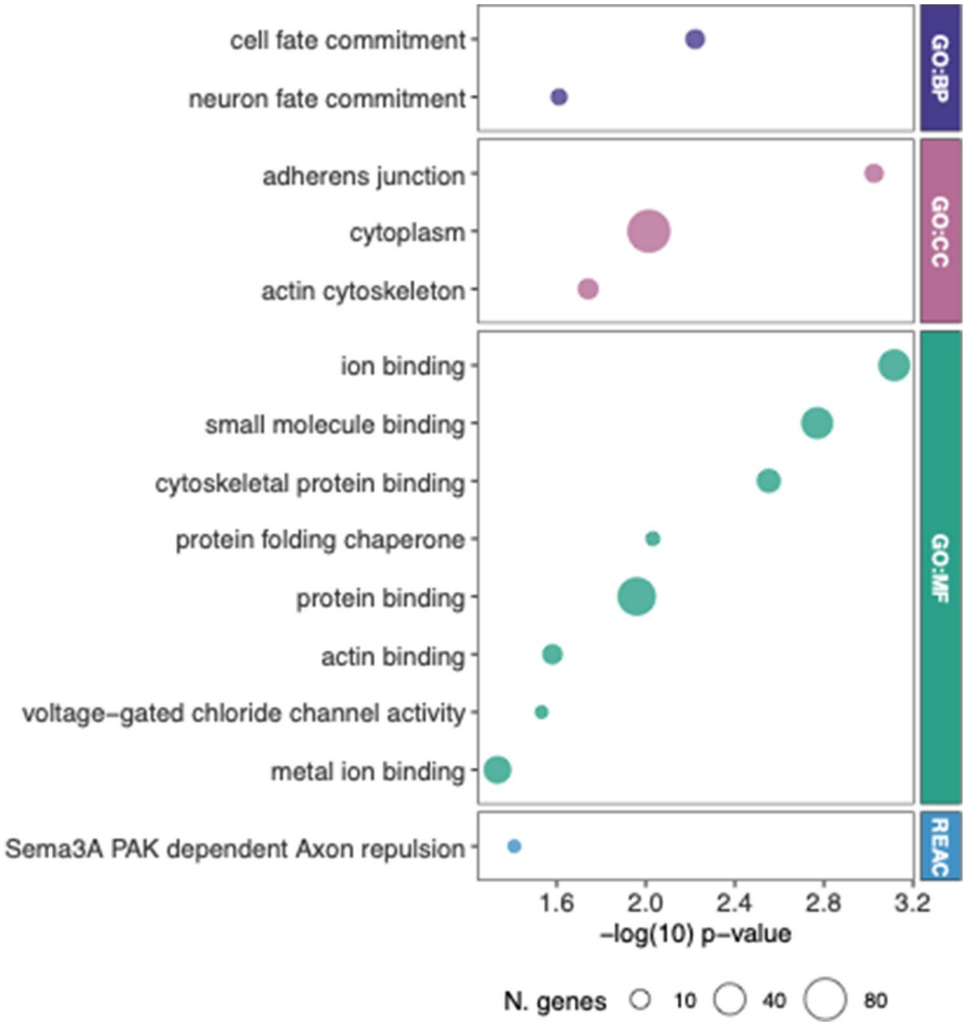
Discussion

The purpose of this analysis was to study epigenomic changes associated with discrimination among Black pregnant women in the nuMoM2b cohort. Our findings provide novel evidence of discrimination-related epigenetic changes, which add to the limited body of previously published research. Specifically, we identified 130 CpG sites that were significantly hypomethylated or hypermethylated with higher levels of discrimination (EOD score ≥ 3). In addition, we identified 17 genes that were mapped to the 20 most significant CpG sites. Furthermore, we observed that these genes were involved in several enriched biological pathways and molecular functions related to cell and neuron development, intracellular signaling, stress responses, and protein stability.

The genes identified in this EWAS have not been previously linked to discrimination. In one study, perceived discrimination was negatively associated with CpG sites mapped to *NR3C1*, a stress-response regulator, and *BDNF*, which has been associated with stress-induced neuroplasticity [15]. Other studies have examined discrimination among Black women outside of the perinatal period. For example, researchers identified significant epigenetic changes associated with perceived racial discrimination among African American mothers across several genes, including *WWOX, LOC101928443, ARGHGAP15, FAT2, MAD1L1, LRRN3, SORCS1,* and *ZXDC* [14], which have been associated with schizophrenia, bipolar disorder, and asthma. In an analysis of the Black Women's Health Study, researchers found significantly higher methylation levels in a CpG Island near *FOXD1* associated with perceived racial discrimination [31]. Our results likely differ from these prior research findings, as earlier studies examined epigenetic changes among Black women several years after pregnancy, while our study captures DNA methylation during pregnancy. Epigenetic profiles shift across the perinatal period [32], thus it is possible that DNA methylation patterns associated with discrimination during pregnancy differ from those observed in postpartum and later adulthood.

Our findings expand upon prior research by identifying several novel epigenetic changes associated with racial discrimination in pregnancy. The genes identified in our study have previously been associated with several disease phenotypes. For example, *LCMT2* [33] and *LINC02753* [34] have been associated with colon cancers, while *RARA* and *HSP90AA1* have been implicated in acute promyelocytic leukemia and other types of hematologic cancers [35, 36].

Fig. 4 Bubble plots display the top enriched Gene Ontology Biological Process (GO:BP), Cellular Components (GO:CC), Molecular Functions (GO:MF), and REACTOME (REACT) pathways derived from genes annotated to differentially methylated positions (DMPs). The x-axis represents enrichment significance (−$\log_{10}$ p-value), and bubble size reflects the number of genes contributing to each term



Hypermethylation of *LPCAT1* has been associated with several cancer types, including colorectal, prostate, lung, and breast cancers [37]. *ZNF500* has been found in women with less aggressive forms of breast cancer [38]. In addition, *SMTN* is a protein coding gene for smooth muscle cell contraction and it has been associated with soft tissue tumors and cardiomyopathy [39, 40]. *DMRT3* has been hypothesized to play a role in primary ovarian insufficiency [41]. *MLPH* [42], *CDC123* [43], and *OGFOD3* [44] have been linked to neurodevelopmental disability. Further, *STAT6* has been implicated in asthma [45]. Future research is needed to better understand how epigenetic changes influenced by racial discrimination contribute to adverse perinatal health outcomes.

Our finding that racial discrimination was linked to DNA methylation of a cardiomyopathy-related gene supports prior research that identified associations between perceived stress and cardiovascular health. In one study, older Black women who reported experiencing higher stressful life events had increased incident cardiovascular disease compared to Black women who reported lower stressful life events [46]. Researchers also found that exposure to high everyday discrimination was associated with significantly higher odds of hypertension among US-born Afro-Caribbean women [47]. These findings are important to consider given known associations between adverse pregnancy outcomes and cardiovascular disease risk in later adulthood [48]. Specifically, the disproportionately high rates of discrimination and adverse pregnancy outcomes experienced by Black women may compound the risk of cardiovascular disease later in life. Future research should examine the epigenetic pathways by which racism increases the risk of adverse pregnancy outcomes such as hypertensive disorders of pregnancy, gestational diabetes, fetal growth restriction, preterm birth, and cardiovascular disease in later adulthood.

In addition, we identified associations between racial discrimination and DNA methylation of several cancer-related genes. Prior studies have reported significant associations between structural racism, including residential segregation and redlining, and adverse breast cancer outcomes, such as higher mortality rates, later-stage diagnosis, and suboptimal treatment [49]. One study of 80 Black and White women with breast cancer identified significant associations between contemporary redlining and hypermethylation of genes implicated in breast tumor development, including *ANGPT1* and *PRG4* [50]. While not fully understood, researchers have reported that parity, pregnancy hormones, and other maternal factors may increase the risk of experiencing a malignancy [51]. Our findings further this work by identifying DNA methylation of several cancer-related genes during pregnancy. Additional epigenomic studies are needed to better understand the underlying mechanisms between discrimination and cancer among parous Black women.

We also found several significant differences in sociodemographic characteristics between women with low and high EOD scores. Women who reported higher levels of discrimination were significantly older, had attained greater education levels, and had higher BMI compared to women who reported less experiences of discrimination. In pregnancy care, social biases rooted in patriarchy and white supremacy devalue and stigmatize women who are older than 35 years of age (e.g., ‘advanced’ maternal age) and those with higher body weight [52]. Therefore, our findings may reflect intersectional experiences of racism, ageism, and weight stigma. Future research should study how intersectional experiences of discrimination may be associated with epigenetic changes in pregnancy.

In addition, the pathways identified in our study highlight the critical role of these genes in discrimination-related maternal stress responses [7]. Specifically, the genes we identified have a significant impact on intracellular signaling, protein stability, and how cells differentiate during development, particularly in the nervous system. We also found that the identified genes influence cytoskeletal dynamics and cell adhesion, which are essential for placental structure and function, as well as neuronal connectivity.

This study has both strengths and limitations. One strength of this study is that it includes the largest sample size to date when compared to prior studies that have examined epigenetic changes among pregnant Latina women or Black women outside of the perinatal period. The focus on Black women is another strength, as reproductive justice scholars have called for within-group analyses to better identify the influence of risk factors such as racism on perinatal health. One limitation of this approach is that findings do not reflect between-group comparisons, and future research should explore associations among other minoritized populations. In addition, while most participants reported low EOD scores in the study sample, this response bias consistent with prior research [53]. However, anti-Black racism is a significant exposure associated with adverse pregnancy outcomes and examining within-group variation is needed to adequately address racial and ethnic inequities in perinatal health [5–11].

Additional study limitations include the relatively young, healthy, highly educated, nulliparous sample, and the low levels of self-reported racial discrimination, which may have limited our ability to identify stronger associations and reduced generalizability of the findings to multiparas and other higher-risk populations. We also could not examine site-level differences as these data were not available in the nuMoM2b dataset. In addition, the Illumina MethylationEPIC array captures only a subset of CpG sites across the human genome, thus we may have missed other potentially significant CpGs. Environmental factors potentially influencing methylation, such as vascular comorbidities, hormonal levels, and alcohol intake were not controlled for in this analysis. Further, although blood-derived DNA methylation can capture systemic influences of psychosocial stress and has been widely used in epigenetic studies [7], it may not represent epigenetic changes occurring in target tissues that more proximally shape pregnancy outcomes, such as placental tissue. The relatively small effect sizes are another limitation. However, effect sizes were statistically significant after controlling for multiple testing and are comparable to prior EWAS findings among Black women [14]. Larger, prospective cohorts of Black women are needed to replicate study findings and researchers should use more precise measures of racism to improve measurement of the exposure. Indeed, racism operates across multiple levels of society, and our findings are limited to lifetime exposure to interpersonal racism. Future research should examine epigenetic changes associated with pregnancy-specific discrimination and structural racism.

Conclusion

In sum, we identified methylation changes significantly associated with high levels of racial discrimination among Black women in pregnancy. Findings contribute to the dearth of research on the biological impact of racism in perinatal populations. Future research should incorporate measures of structural discrimination and include a larger, nationally representative sample of multiparous Black women in the United States. Future epigenetic studies are needed to examine methylation patterns associated with racial discrimination and adverse pregnancy outcomes, as well as their relationship to other health outcomes.

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Data Availability NuMoM2b phenotype data are publicly available through the Eunice Kennedy Shriver National Institute of Child Health and Human Development Data and Specimen Hub NICHD (DASH). Epigenomic data are publicly available through the NIH Database of Genotypes and Phenotypes (dbGaP) repository under accession number phs003992.v1.p1. Both are controlled access repositories.

Declarations

Ethics Approval and Consent to Participate Study procedures were approved by the Columbia University Institutional Review Board (#AAAU0215) and informed consent was obtained from all participants prior to enrollment.

Competing interests The authors declare that they have no conflict of interest.

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