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REVIEW ARTICLE

Gaining a deeper understanding of social determinants of preterm birth by integrating multi-omics data

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In the US, high rates of preterm birth (PTB) and profound Black–White disparities in PTB have persisted for decades. This review focuses on the role of social determinants of health (SDH), with an emphasis on maternal stress, in PTB disparity and biological embedding. It covers: (1) PTB disparity in US Black women and possible contributors; (2) the role of SDH, highlighting maternal stress, in the persistent racial disparity of PTB; (3) epigenetics at the interface between genes and environment; (4) the role of the genome in modifying maternal stress–PTB associations; (5) recent advances in multi-omics studies of PTB; and (6) future perspectives on integrating multi-omics with SDH to elucidate the Black–White disparity in PTB. Available studies have indicated that neither environmental exposures nor genetics alone can adequately explain the Black–White PTB disparity. Preliminary yet promising findings of epigenetic and gene–environment interaction studies underscore the value of integrating SDH with multi-omics in prospective birth cohort studies, especially among high-risk Black women. In an era of rapid advancements in biomedical sciences and technologies and a growing number of prospective birth cohort studies, we have unprecedented opportunities to advance this field and finally address the long history of health disparities in PTB.

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IMPACT:

- This review provides an overview of social determinants of health (SDH) with a focus on maternal stress and its role on Black–White disparity in preterm birth (PTB).
- It summarizes the available literature on the interplay of maternal stress with key biological layers (e.g., individual genome and epigenome in response to environmental stressors) and significant knowledge gaps.
- It offers perspectives that such knowledge may provide deeper insight into how SDH affects PTB and why some women are more vulnerable than others and underscores the critical need for integrating SDH with multi-omics in prospective birth cohort studies, especially among high-risk Black women.

OVERVIEW: PRETERM BIRTH (PTB) DISPARITY IN US BLACK WOMEN AND POSSIBLE CONTRIBUTORS

Worldwide, about 11% of infants are born preterm (defined as birth before 37 weeks gestation) and 1 million die annually.[1–3] In the US, there have been not only persistently high rates of PTB for decades but also a prolonged and profound racial disparity in PTB among Black women. In 2018, the rate of PTB among Black women (14%) was about 50% higher than the rate among White women (9%).[3] Even more concerning is the finding of 40% excess risk for late PTB and 2.2 times higher risk for early PTB in Black women compared to White women.[4] Early PTB is known to be associated with myriad perinatal and postnatal complications and sequelae.[5–8] To date, the underlying mechanisms of PTB have remained elusive despite more than half a century of research. This has been partly explained as due to the fact that PTB is a complex trait determined by multiple environmental and genetic factors[9] and because of the significant heterogeneity and complexity of biological pathways that could lead to PTB.[10,11] This lack of progress after years of investigation underscores a critical need to go beyond traditional approaches to tackle PTB.

The earliest studies on PTB were primarily focused on uncovering socio-demographic, environmental, and clinical factors, and a number of them have been identified, including maternal race/ethnicity,[12–14] age,[15–17] education,[18,19] income,[20,21] place of birth,[22] smoking,[23–25] stress,[26–28] (see section "Social determinants of health (SDH) and the role of maternal stress in the persistent Black–White disparity of PTB" below), social support,[29,30] air pollution,[31–34] and malnutrition.[35,36] Two of the strongest risk factors appear to be a history of prior PTB[37,38] and a woman's own PTB outcome.[39] Our early study showed that these two factors in combination greatly increased the risk of PTB or low birth weight.[40] There are by now hundreds of studies, and reviews of those studies, pointing to the role of environmental and psychosocial exposures in PTB, though their findings and even their conclusions are still in some way limited by our incomplete understanding of the causes of PTB.

The field is confronted by persistent challenges. Foremost among these is that these identified factors still only explain a fraction of all PTB cases, and the identified associations vary by studies, populations, and individuals. At the same time,

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intervention trials focused on major risk factors aiming to reduce PTB have also yielded disappointing results. For most social-epidemiological studies, there has been an absence of biomarker data that would allow for further explorations of underlying biological mechanisms.

Over the past two decades, with rapid advancements in human genetics and high-throughput biotechnology, an increasing number of genome-wide association studies (GWAS), epigenome-wide association studies (EWAS), and other omics studies of PTB have been or are being conducted (see sections "Epigenetics: the interface of genes and environment in mediating the stress response," "Role of the genome in modifying maternal stress–PTB associations," and "Recent advances in multi-omics studies of PTB").[41–52] However, most GWAS have failed to yield promising results that can be replicated in other populations, including Black populations. The largest study to date identified some significant genes associated with PTB,[43] but this study was limited to White populations. The role of genes in the continued disparities seen in Black populations still remains to be determined, though it has been suggested that genetic variation may not be the main cause of the Black–White disparity in PTB.[53] The value of searching for gene-by-environment (G×E) interactions, which are typically overlooked in existing genetic studies, has been demonstrated by our studies.[52,54–56] We have shown that maternal risk factors such as smoking,[54] maternal pre-pregnancy obesity,[55] and maternal perceived stress[52] can interact with individual genetic variants to affect the risk of PTB. Such studies help to identify individuals at significantly higher risk of PTB in the presence of these risk factors. This is an important step forward for precision risk assessment and prevention as compared to a "one size fits all" approach.

In the following sections, we discuss the social determinants of PTB, with an emphasis on the role of maternal stress in PTB risk and the persistent Black–White disparity, as well as its biological embedding in the context of multi-omics. In this report, the terms African American and Black are used interchangeably, unless otherwise specified.

SOCIAL DETERMINANTS OF HEALTH (SDH) AND THE ROLE OF MATERNAL STRESS IN THE PERSISTENT BLACK–WHITE DISPARITY OF PTB

The ongoing search for modifiable factors that result in racial disparities in PTB has been broad in scope; this review will focus on SDH, as defined by the Centers for Disease Control.[57] More specifically, SDH are "the economic and social conditions that influence individual and group differences in health status,"[58] which influence an individual's ability to engage in health promoting activities, and are themselves "shaped by the distribution of money, power, and resources at global, national, and local levels."[59–61] The growing list of SDH under study today is extensive and includes food security, housing stability, homelessness, violence exposure, structural racism, and immigration-related policies. While a comprehensive review of SDH and their roles in the Black–White disparity of PTB is beyond the scope and allowed space, here we primarily discuss one major component of SDH, maternal stress, and its relationships with PTB.

In general, stress, as defined by Cohen et al., is a process in which environmental demands exceed a person's adaptive capacity to respond and results in changes that put a person at risk for disease.[62] Key elements of stress include its timing, type, severity, and length of exposure, as well as the response to the stressor. Black populations have been shown to be disproportionally subject to psychosocial stressors and poor health outcomes, including PTB.[63,64] One form of stress that consistently varies by race is the experience of discrimination and racism.[65,66] Exposure to discrimination showed a twofold or higher risk for adverse birth outcomes related to residential segregation and neighborhood-level poverty.[67] Since the release in 2004 of the report "Unequal treatment: confronting racial and ethnic disparities in health care" from the Institute of Medicine,[68] an even greater focus on racism as a factor driving higher PTB rates in Black women has emerged. The report's findings were clear—racism is one of the single most important factors in health disparities for African Americans as it relates to the provision of low-quality care and high burden of preventable causes of death including PTB. The relationship between racism and adverse birth outcomes may also be mediated by stress.[69] These findings should not be surprising. However, many questions remain to be answered. Below we highlight a few.

There is a lack of consensus about the extent to which stress may account for the racial disparity in PTB.[70] For example, a study by Grobman et al.[69] demonstrated that Black women were more likely to have greater psychosocial burden across almost all domains compared to White women and that such racial/ethnic differences cannot be fully mitigated by income status. Such racial/ethnic disparity in psychosocial burden may mirror the disparity observed in birth outcomes, including PTB. In comparison, Almeida et al.,[12] using data from the Pregnancy Risk Assessment Monitoring System, found that Black women had a higher risk of PTB relative to White women. While accounting for stress reduced the risk of PTB by 22%, this, however, did not fully explain the Black–White disparity in PTB. However, the study by Lu et al. did not support that maternal stress contributed significantly to racial disparities in PTB.[71]

Investigators working as far back as the 1940s have explored the association of maternal stress with birth outcomes.[12,26–28,71–92] However, after decades of studies such an association has not consistently been found. For example, some reported that mothers experiencing self-reported higher stress, stressful life events, and/or emotional disorders[27,77–79,81–87,92–94] were at a higher risk of PTB, but others did not find such associations.[71,80,88,90,91] It has been proposed that such inconsistency may be at least partly due to methodological variations in stress measurements across studies.[28,80,87,93,94] Furthermore, a combination of different stressors, or stress plus other environmental exposures (i.e., smoking, air pollution, and heavy metal exposure),[95] was found to have an even more profound impact on birth outcomes, including PTB.

Moreover, there is limited understanding of the biological embedding of SDH in PTB. Maternal stress during pregnancy can lead to a series of biochemical changes that may underlie the psychological and physiological consequences of maternal stress. The hypothalamic–pituitary–adrenal (HPA) axis is the principal endocrine system that is activated in response to stress. Specifically, maternal stress is thought to trigger norepinephrine and cortical release, activating placental corticotropin-releasing hormone gene expression, and leading to a cascade of events ending in PTB.[96,97] Hyperactivity of the HPA axis in mothers and/or in the fetus was found to be associated with an altered risk of PTB,[98,99] indicating a potential physiological link between stress exposure and risk of PTB. It is also likely that elevated maternal stress may contribute to PTB via inflammation/infection.[100,101]

Taken together, maternal stress is a socially based but biologically plausible risk factor for PTB. In the following sections, we summarize the current literature on the interplay of maternal stress with key biological layers (e.g., genome, epigenome, metabolome) in response to environmental stressors. Such knowledge may provide deeper insight into how maternal stress affects PTB and why some women are more vulnerable than others, to help move the field beyond studies focused on the identification of risk factors, and should also help to inform more targeted, precise, and effective interventions.

EPIGENETICS: THE INTERFACE OF GENES AND ENVIRONMENT IN MEDIATING THE STRESS RESPONSE

Epigenetics—a mechanism for regulating gene expression without changes occurring in the DNA sequence—may represent a

critical interface between individual genetic susceptibility and responses to environmental or psychosocial exposures.[102,103] In contrast to the consistency of the genome, the epigenome is characterized as having dynamic and flexible changes in response to intra- and extra-cellular stimuli that can serve as modifiable biomarkers for environmental exposures.[104] Epigenomic variations are largely established in utero, a period that is most sensitive to environmental perturbation and a critical time for the establishment of epigenetic variability.[105–108] The major epigenetic mechanisms include DNA methylation (DNAm), histone modification, and non-coding RNAs (ncRNAs).[109,110] DNAm, an addition of a methyl group to cytosines, occurs predominantly in cytosines located at 5′ of guanines (known as CpG dinucleotides). Although its function may vary, DNAm, when it occurs in promoter regions, generally is associated with gene silencing and repressing gene expression.[111] Histone acetylation directly remodels chromatin rather than affecting messenger RNA (mRNA), which may affect nucleosome positioning, DNA wrapping, accessibility of chromatin to transcription factors, and regulate gene expression. ncRNAs could silence gene expression via RNA interference, which is commonly associated with posttranscriptional modification of mRNA. Among these mechanisms, DNAm has been studied most extensively in human studies because DNA is relatively stable compared to chromatin or RNA, and because recent technological advances make epigenome-wide DNAm profiling feasible in large cohorts.

As reviewed previously,[112] a growing number of candidate-gene and epigenome-wide studies have showed that different forms and severity of maternal psychosocial stress have an influence on fetal DNAm (measured in cord blood or placental DNA),[113–140] which may lead to an altered risk of PTB. Candidate-gene studies of this kind have mainly targeted specific genes involved in the human HPA axis.[113–117,120–123,129–131,138] In particular, the *NR3C1* gene, which encodes glucocorticoid receptors that mediate the stress response in humans, was found to have altered methylation levels at the promoter region in newborns whose mothers were exposed to stress and/or depression during pregnancy.[113–116,121,131,138] Mulligan et al., in cord blood samples from 25 mother–newborn dyads, demonstrated a significant correlation between maternal stress, newborn methylation in the promoter region of the *NR3C1* gene, and newborn birth weight, suggesting a potential role of *NR3C1* DNAm in mediating the impact of prenatal stress exposure on birth outcomes.[121] Maternal stress may also be associated with altered DNAm of other genes that are involved in the HPA axis, such as *FKBP5*,[116,120,122,123] which encodes FK506-binding protein 51 that plays an important role in the negative feedback loop, *OXTRs*,[139] which encode the receptors of oxytocin (OXT) that have stress-buffering effects, and *HSD11B2* that encodes hydroxysteroid 11-beta dehydrogenase 2.[123,130] It may also be associated with altered DNAm of other genes not in the HPA axis but that may be implicated in PTB such as *IGF2*[132,133] and *SLC6A4*.[119] Further studies to explore how these promising DNAm markers mediate the impact of maternal stress on the risk of PTB may contribute to our understanding of the biological mechanisms underlying PTB.

Several epigenome-wide associations with maternal stress have also been reported, although their findings await further validation and replication.[124–128,135–137,140] Vangeel et al., by enrolling 22 versus 23 newborns who were exposed to the lowest or highest degree of maternal anxiety, respectively, identified and verified a differentiated methylated region (DMR) in the GABA-B receptor subunit 1 gene (*GABBR1*) in newborns that was associated with pregnancy anxiety. DNAm level of the *GABBR1* gene was significantly associated with HPA axis response to a stressor.[124] Burnst et al., in 207 subjects, investigated epigenome-wide placental DNAm in relation to maternal experiences of traumatic and non-traumatic stressors over her lifetime, which led to differential DNAm at 112 CpG sites. They also identified some significant pathways that play important roles in multiple physiological functions necessary for proper fetal development.[125] Cardenas et al., in Project Viva, measured DNAm profiles in 479 infants at birth and found that newborns exposed to antidepressants in pregnancy had decreased DNAm levels in the gene body of *ZNF575* (a gene involved in transcriptional regulation but with unknown specific functions), which was replicated in the Generation R study.[126] Nemoda et al. performed genome-wide DNA methylation profiling in CD3+ T lymphocytes from 38 antepartum maternal and 44 neonatal cord blood samples via Illumina HumanMethylation 450K and reported that maternal depression was significantly associated with DNAm alteration at multiple CpG sites in newborns, most of which are involved in the immune system.[127] Rijlaarsdam et al. conducted an epigenome-wide association meta-analysis of prenatal maternal stress, which, however, did not identify any Bonferroni-corrected DMRs associated with prenatal stress exposure, suggesting that there are no large effects of prenatal maternal stress exposure on neonatal DNA methylation.[136]

Maternal stress may also affect a mother's own epigenetic profile, as supported by both animal models[141,142] and human studies.[120,143–146] Maternal *FKBP5* methylation was inversely correlated with threat-based adverse childhood experiences and maternal posttraumatic stress disorder (PTSD) symptoms during pregnancy,[120] which was independent of maternal *FKBP5* rs136780 genotypes. Schechter et al. reported that maternal PTSD severity and parenting stress were negatively correlated with the mean percentage of methylation of the *NR3C1* gene in mothers.[147] A few epigenome-wide studies were also reported in mothers.[127,148] Nemoda et al. identified no maternal CpG sites with altered DNAm levels in women exposed to depression.[127] A recent study by Surkan et al. in the Boston Birth Cohort (BBC) showed that, although maternal perceived stress displayed no significant associations with maternal DNAm alterations, social support during pregnancy was significantly associated with maternal DNAm changes at multiple genes.[148]

Epigenetics is also posited as a potential mechanism driving racial disparities in PTB.[70] First, the social construct of race and the propensity to use it as the means to determine how to treat others and develop policy makes it such that Blacks are more likely to experience stress and other adverse SDH than Whites,[69] which could induce epigenetic changes (as described above) that may explain racial differences in PTB. Second, epigenetic levels at certain genes may vary across different ethnic populations, some of which may lead to differences in response to maternal stress and/or represent precursors for future disease risk. Findings from previous studies offer evidence for this. Salihu et al. studied umbilical cord blood DNAm of genes implicated in PTB from 22 Black neonates and 69 non-Black neonates and found differential DNAm in *TNFAIP8* and *PON1* genes among Black vs. non-Black infants.[149] Soubry et al. reported a significant hypermethylation of the *IGF2* H19 DMRs in newborns of Black mothers who reported use of anti-depressive drugs during pregnancy,[150] while such associations were not observed in White mothers. Furthermore, differential risks for PTB were noted among recent African immigrants compared to U.S.-born Black women,[22,151] which could not be explained by known risk factors.[22] This finding may further indicate the role of acquired epigenetic inheritance in the underlying biology of prematurity, although further studies are needed.

As summarized above, although available research suggests that maternal stress can lead to epigenetic changes and that epigenetics may play a role in PTB etiology,[152–156] these existing studies (especially EWAS) have had limited sample sizes and the data remain fragmented. Furthermore, the identification of stress-related DNAm signatures in mothers and newborns raise new questions about when and how these changes might occur and whether maternal stress affects fetal DNAm through changes in

their own DNAm. There is also considerable interest in the possibility that environmental and psychosocial exposures result in epigenetic effects that can then be transmitted from one generation to the next, but so far there is no direct evidence for this in humans.[157]

ROLE OF THE GENOME IN MODIFYING MATERNAL STRESS–PTB ASSOCIATIONS

Human development is known to be shaped by a complex interplay of the social environment with genetic potential, as are birth outcomes including PTB.[158,159] It has been hypothesized that the inconsistent findings for the relationships between maternal stress exposure and birth outcomes, as reported previously,[27,77–79,81–87,92–94] are at least partly due to differences in individual genetic susceptibility to stress. Boyce has proposed the "orchid vs. dandelion" theory,[160] which suggests that certain genetic variants can increase a person's susceptibility to stressors. This plausibility was further supported by previous studies that demonstrated the significant impact of the interaction between maternal genes and perceived stress on multiple child health outcomes, as discussed below.

Multiple genetic variants in the stress response pathways, including those in the HPA axis, may lead to individual differences in response to stress[161,162] and then modify the relationships between stress exposure and different health outcomes, including birth outcomes. Increasing evidence has suggested the existence of gene × maternal stress interactions that may impact multiple child health issues, such as adolescent disruptive behavior,[163] negative emotionality,[164] child internalizing symptoms,[165] childhood intelligence quotient,[166] and bronchiolitis.[167] A recent study showed that the HPA axis multi-locus genetic profile score, which reflects the additive risk of three candidate genes (*CRHR1*, *FKBP5*, and *NR3C1*) and maternal prenatal perceived stress, interacted to affect risk of adolescent depression.[168]

The existence of G×E interactions in PTB etiology has also been supported by studies from us and others, such as maternal obesity × gene interactions,[55] maternal smoking × gene interactions,[54,56,169] and bacterial vaginosis × gene interaction.[170] However, a limited number of studies have been performed to identify the impact of gene × stress interactions on PTB or related birth outcomes. The study by Mparmpakas et al. suggested an interaction between maternal stress (or maternal negative attitude toward the pregnancy) and *NR3C1* polymorphisms on fetal weight.[171] It is believed that genome-wide analyses of gene × stress interactions may have the potential to identify novel pathways underlying the stress–PTB relationships. Our recent study in the BBC was the first to demonstrate a genome-wide significant *PTPRD* × stress interaction on the risk of spontaneous PTB in African Americans. In that study, Hong et al. performed genome-wide screening to identify the gene × stress interactions on the risk of spontaneous PTB (sPTB) in 1490 Black women.[52] The authors reported that rs35331017, a T-allele insertion/deletion polymorphism in the *PTPRD* gene, was genome-wide significantly interacted with overall lifetime stress on the risk of sPTB ($P_{G\times E} = 4.7 \times 10^{-8}$): maternal lifetime stress was dose-responsively associated with an increased risk of sPTB in mothers carrying the II (insertion/insertion) genotype; but the opposite trend was observed in mothers carrying the heterozygous or DD (deletion/deletion) genotypes. This interaction was validated in both Black ($P_{G\times E} = 0.088$) and White mothers ($P_{G\times E} = 0.023$) from another independent cohort.[52] These findings, if further confirmed, may provide new insight into individual susceptibility to stress-induced sPTB.

RECENT ADVANCES IN MULTI-OMICS STUDIES OF PTB

Besides genomics and epigenomics, an increasing number of other omics studies, including transcriptomics,[172,173] microbiomics,[174,175] metabolomics,[176,177] and proteomics,[178,179] have been performed in association with PTB. Overall, such single-omics studies, once again, could not fully capture the entire biological complexity of PTB. Recent significant technological advances and the rapidly decreasing costs of such high-throughput technologies have made it feasible to conduct multi-omics profiles in a single study cohort. An increasing number of analytical tools have also been developed to analyze and integrate multi-omics data. So far, a few reviews on multi-omics integration have been published to discuss its potential advantages over single-omics studies, analytical approaches and challenges, and its utility in clinical diagnosis and treatment.[180–182]

To our knowledge, only a very limited number of studies have performed multi-omics integration in PTB research, although with promising findings. Chien et al., in 10 full-term and 8 PTB infants, conducted integrative analyses of transcriptomics and proteomics. They found that 29 genes/proteins had consistently altered regulation in PTB. This study indicated that such dual-omics analyses can provide new insight into molecular mechanisms and identify candidate biomarkers associated with PTB.[183] Chabrun et al., in 36 placental samples, performed combined analyses of methylomics and transcriptomics in association with intra-uterine growth restriction and related phenotypes, including PTB. They built machine learning models that had a high capacity for predicting PTB, with r^2 of 0.83 between the predicted and the actual PTB score.[184] Ghaemi et al., in 51 samples from 17 pregnant women who delivered at term, built multivariate predictive models for gestational age using the Elastic net algorithm to integrate the multi-omics datasets including transcriptomics, microbiomics, proteomics and metabolomics, which can significantly increase predictive power compared to models based on single-omics datasets.[185] However, as with the other types of studies reviewed above, these currently available studies had limited samples sizes, and their findings call for replication in large populations.

FUTURE PERSPECTIVE: INTEGRATION OF MULTI-OMICS WITH SDH TO ELUCIDATE PTB DISPARITY

Available studies to date have indicated that neither social–environmental risk factors nor genetics/epigenetics alone can adequately explain the persistent and striking Black–White PTB disparity. The preliminary yet promising findings of single-omics and multi-omics studies underscore the need to bring these pieces of puzzle together to gain a better and fuller understanding of the causes and underlying mechanisms driving PTB and racial disparities. The value of integrating SDH with multi-omics in prospective birth cohort studies lies in the following. From a scientific discovery and innovation perspective, this will ensure a strong foundation of basic science and methodology research in the field of SDH, including rigor and reproducibility. From a translational perspective, it will provide critically needed sensitive and objective evidence of SDH to inform public policy, social reform, health service organization and delivery, and clinical and public health programs.

As this review highlights, many gaps remain to achieve integration. First, there is no widely accepted methodology to measure SDH, including maternal stress. Research methodologies must account for the pervasive, chronic, and multidimensional experiences of interpersonal and structural racism throughout the life course. Second, the impact of SDH on PTB disparity is likely mediated by the joint effects of DNAm at multiple CpG sites and/or modified by numerous genetic factors, each of which only have a small effect size. The detection of such small effect markers in GWAS and EWAS requires very large sample sizes or innovative methodologies. Third, the potential involvement of both maternal and fetal genomes, epigenomes, and other omics (such as transcriptomics, proteomics, metabolomics, and microbiomics) underlying the pathogenesis of PTB requires future studies to

include both maternal and fetal biospecimens for analyses. Fourth, although the importance of SDH and individual genetics/epigenetics in health and disease are well recognized, few have considered all these factors as well as other omics in the same study. A successful systems biology approach requires that multi-omics data be generated from the same set of samples to allow for data integration. Furthermore, few studies conducted to date have been longitudinal by design, which make them less likely to clarify temporal and causal relationships. Of greatest concern is that there has been a lack of multi-omics studies conducted among disadvantaged US minority populations including Black mothers and children who bear a disproportionally high burden of social adversities and disparate health outcomes.

We end this review by highlighting our aspiration to connect multi-level, multi-dimensional SDH data with multi-omics to better understand PTB and address health disparities in PTB. Given the growing recognition of the importance of SDH, the rapid advancement of biomedical sciences and technologies, and growing number of prospective birth cohort studies, we have unprecedented opportunities to advance this field both in terms of scientific discoveries and clinical and public health translation. Ultimately, these efforts may allow us to move beyond risk factor analysis to a deeper understanding of the underlying causes of the persistent disparity in PTB, finally leading to improved individual and population health for Black women and children and for all people.

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All the authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; drafted the article or revised it critically for important intellectual content; and gave final approval of the version to be published.

ADDITIONAL INFORMATION

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