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Racial disparities in pregnancy outcomes: genetics, epigenetics, and allostatic load

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Preterm birth (PTB) has a complex etiology that includes genetic heritability, lifestyle and health, socioeconomic status, and psychosocial stress. Racial disparities in pregnancy outcomes are reported in many countries, but an especially marked contrast is evident in the United States. Because of the size of the problem, considerable research has investigated the involvement of genetic and social factors. However, race is a social construct and evidence suggests that in the United States the effect of Black race on PTB is environmental, not genetic. This derives since stress accumulates throughout a lifetime and across generations leading to a large accumulated allostatic load that is mediated by epigenetic mechanisms. Epigenetic mechanisms can however be reversed and therein lies future hope.

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Introduction

Preterm birth (PTB), defined as birth before the 37th week of gestation, is a complex syndrome that affects 15 million babies each year worldwide. Of these, 1.1 million do not survive [1,2]. Those who do survive may face a spectrum of lifelong disabilities, including cerebral palsy, intellectual impairment, chronic lung disease, vision and hearing loss [3]. Babies born weighing less than 2500 g and 1500 g are considered low birth weight (LBW) and very low birth weight (VLBW), respectively [4]. Globally, PTB complications are the greatest cause of death for children under five years of age, and in developed countries PTB is the greatest cause of newborn mortality and disability [1,2]. The etiology of PTB remains largely unknown in spite of decades of research, with the cause of nearly half of all preterm births unexplained [5]. Social factors such as socioeconomic status (SES), past traumatic events, marital or relationship issues, abuse, discrimination, loss of a close friend or family member, and natural disasters have been identified as risk factors for PTB and LBW [6,7].

Racial disparities in pregnancy outcomes

Considerable racial disparities in birth outcomes have been reported around the world, but an especially marked contrast is evident in the United States. Health disparities subsist between White Americans and all ethnic minorities, but the imbalance is especially prominent between Non-Hispanic White and Non-Hispanic Black populations. Black women are more than 50% more likely to have a PTB and nearly twice as likely to have a LBW baby [8,9]. Moreover, the perinatal mortality rate of Black infants is 3.5x higher than White babies [10], and Black infants are 2.3 times more likely to die within their first year of life [11].

In Pelotas, Southern Brazil, trajectories of inequalities are uniquely well demonstrated through a series of birth cohorts in 1982, 1993, 2004 and 2015 [12•,13–16]. The PTB rate increased sharply over time, from 5.8% to 13.8%, whereas LBW incidence increased from 9.0 to 10.1%. This inflation in PTB was disproportionately experienced by women who were Black, Mixed-race, or from a low-SES household. Another Brazilian study compared birth outcome data of women with African and European origins from 15 different cities, calculating PTB rates of 18.9% and 15% and LBW rates of 12.4% and 8.1%, respectively [17]. Similarly, women with African or Caribbean ethnicity in London, UK, had a 33% higher incidence of PTB [18]. PTB rates of Black women in Canada are 30% lower than in the US, but remain higher than White Canadians [19]. Hence the question derives, do women of Black race possess a risk allele that increases their risk for a PTB?

Race is a social construct, not a biological variable

Researchers around the world have been pursuing the identification of a genetic variant responsible for PTB for decades, but they have only had modest success so far due to the complex etiology of PTB. Nevertheless, progress towards answering this question has been made in recent years using techniques such as whole exome sequencing [20], genome-wide association studies [21–23], and large

meta-analyses [24•,25,26]. Summaries of a selection of recent studies are presented in Table 1.

Non-White people are consistently underrepresented or systematically excluded in genetic studies, resulting in a very limited understanding of the role of genetic variants in adverse pregnancy outcomes in non-White individuals. Although there is some genetic heritability involved in PTB [27], genetics are likely not a leading contributor to the existing racial disparities in birth outcomes. Nearly two decades have passed since editorials were published in both the New England Journal of Medicine and Nature

Table 1

Recent studies depicting genetic variants associated with PTB

Study	Discovery cohort	Replication cohort	Data Collection	Outcome
Zhang *et al.* [21]	$n = 43\,568$ women with European ancestry (database from 23andme)	3 Nordic data sets, $n = 8643$ mothers and 4090 infants.	Genome-wide association study (GWAS) of discovery and replication data sets. Maternal-fetal genetic association analysis was completed in replication data set	Genetic variants significantly associated with duration of gestation: *EBF1*, *EEFSEC*, *AGTR2*, *WNT4*, *ADCY5*, *RAP2C.* Genetic variants significantly associated with PTB: *EBF1, EEFSEC, AGTR2*. Association analysis concluded variants act at the level of the maternal genome
Modi *et al.* [20]	Neonates of African American mothers in Richmond, Virginia, $n = 76$ with pPROM and $n = 43$ healthy controls.	$n = 188$ cases and 175 controls (Richmond and Detroit)	Whole exome sequencing of neonatal DNA of original cohort. Targeted genotyping of 35 selected candidate gene variants in replication cohort.	Mutations detected in 10 genes involved in innate immune and host response: *CARD6*, *CARD8*, *NLRP10*, *NLRP12*, *NOD2*, *TLR10*, *AOAH*, *DEFB1*, *MBL2*, *FUT2*. Mutations occurred more often in pPROM pregnancies.
Tiensuu *et al.* [22]	$n = 247$ infants born <36 weeks, and 419 term controls	$n = 260$ infants born <32 weeks and 9630 term controls.	Genome-wide association study pathway analysis, localization of tissue expression, qPCR to confirm difference in mRNA expression.	*SLIT2* was significantly associated with sPTB in discovery and replication cohorts. Pathway analysis found association with retinal ganglion cell axon guidance, telencephalon development, and negative chemotaxis. SLIT2 and its receptor ROBO1 are localized to villous and decidual trophoblasts, and mRNA expression is higher in sPTB placentas compared to placentas at term or elective preterm.
	Oulu and Tampere University Hospitals	1000 Genomes phase3 data (Finland)		
Rappoport *et al.* [23]	Ancestry-matched control population from Health and Retirement Study, 1000 Genomes dataset	1) Genes-environments and Admixture in Latino American babies (GALA II) study	Genome-wide association study, testing over 2 million SNPs in each 'population group' separately. 1000 Genomes dataset to map cases and controls to five populations (African, Americas, European, South Asian, East Asian).	Only two genetic variants were statistically significant, rs17591250 on chromosome 1 in the African group and rs1979081 on chromosome 8 in the Americas group. Neither of these were validated in all replication cohorts. The authors suggested that PTB is 'likely explained by interactions of multiple common variants, race variants affected by environmental influences, all not detectable by GWAS alone.'
	1349 preterm infants (born 25–30 weeks gestation), 12 595 ancestry matched controls.	2) Inova Translational Medicine Institute (800 mother, father, infant trios)		
		3) Boston Birth Cohort (African American, 698 preterm infants, 1035 term controls)		

Genetics delineating the scientific opinion that race is not a biological variable, but rather a social construct [28•,29–31]. Race is not a proxy for genetic ancestry, but ancestral populations are often conflated with race or misinterpreted as racial classifications. Genetic ancestry is determined based on the prevalence of certain genetic variations and does not take into account predetermined sociocultural groupings [32]. Fujimura and Rajagopalan emphasize the importance of maintaining an unambiguous distinction between ancestry and race in biomedical research, as results can be easily misconstrued by the media and public [32].

Many studies have demonstrated that racial disparities in the United States are a result of environmental and not biological influences. A seminal study in 1997 established that infants born to US-born Black mothers have worse birth outcomes than African-born immigrant Black mothers living in the US [33]. Even when the authors analyzed the data of only the lowest risk group of women (women with no previous pregnancy losses, gravida 2–3, first trimester initiation of prenatal care, ages 20–39, and educated), US-born Black women still had an inflated LBW incidence of 7.5%, compared to 3.6% of African-born Black women and 2.4% of US-born White women [33]. Another group employed biometric genetic models to measure the influence of genetic versus environmental factors on the phenotypic variation in gestational age in Americans of European and African origin in Virginia from 1989 to 2008 [34••]. In European-Americans, 35.2% of the variation in gestational age at birth could be explained by fetal genetic factors, whereas in African–Americans that value was negligible (3.7%). Black women had twice the variation in gestational age at birth, and 82.5% of this variation was explained by environmental influences [34••].

A Brazilian study determined that 63% of the racial disparities in PTB were a result of the unequal distribution of wealth presenting in fewer prenatal care visits, with Black families making only 44% of the family income of White Brazilians [17]. However, an American study concluded that only 27.5% of the variation in US PTB rates could be appropriated to the SES of the parents [35]. Black women with a lifelong residence in a high-income Chicago neighborhood were still found to have 1.2x the rate of PTB and 2.4 times the rate of LBW [36]. In California, Black women have a 1.56x higher chance of preeclampsia. Although high SES was found to be protective in White women, further reducing the risk of preeclampsia, it had no effect in Black women [37]. This concept has been termed *diminishing returns*, which is defined by Black individuals not receiving the same gain or benefit from belonging to a high SES group [37,38]. In a population of US Military where all women had equal access to healthcare and insurance, VLBW, LBW and neonatal mortality rates were still higher in Black women [39]. When compared directly to White women, Black women in the military had a 3.6x higher chance of placental abruption, a rare but potentially serious pregnancy complication [40]. Clearly, racial disparities in the US are not a result of socioeconomic disadvantage alone, and other social factors must be considered.

Interpersonal racism is a chronic stressor that impacts birth outcomes

Perceived stress has physiological impacts and can disrupt a person's overall health and ability to self-regulate, cope, learn, and perform [41••]. As pregnancy is an especially vulnerable time for both mother and child, stress during this period can lead to adverse birth outcomes [42–47]. Racial discrimination is a form of chronic stress experienced by many African Americans. A calculation of the number of Google searches using the N-word was used to form an 'internet query-based measure of area racism' experienced by Black mothers over a period of three years. The authors accounted for all variability in SES and demographics, and concluded that both PTB and LBW incidence increased by 5% with each increasing standard deviation of measured area racism [48•]. Experiences of personal and group racism, structural racism, and chronic worry or unease about racial discrimination have all been found to significantly increase the odds of PTB or LBW in Black women [49–52]. The accumulation of such stressors leads to adverse pregnancy outcomes.

Stress accumulates throughout the lifespan

Psychosocial stress accumulates throughout a person's lifespan. The impact of stressful major life events (LEs) throughout a person's lifetime are typically measured using an additive scale, however many stressors are deeply interrelated, increasing the complexity. Women with one or more highly stressful LEs have a 76% higher chance of PTB [53]. Adverse childhood experiences (ACE), typically involving abuse, household dysfunction, and neglect, can negatively influence adult health later in life [54]. Exposure to two adverse experiences as a child increased a woman's odds of PTB by a factor of 2.09; this value increased 18% with each additional ACE exposure [55]. When these data were combined with experiences of adult abuse to form a combined lifetime abuse score, each subsequent adverse event increased the risk of spontaneous PTB by an additional 30% [55].

African American women that reported encountering extensive racial discrimination over their lifespan were found to be 3.1x and 5x more likely to have a PTB or a LBW infant, respectively [56]. Further, another study demonstrated that Black women who experience three or more different domains of racism in their lifetime have a 3.2-fold greater chance of delivering a VLBW infant. Interestingly, in this study population, experiences of racism during pregnancy did not increase rates of

LBW, possibly signifying that stress accumulation throughout the lifetime is more impactful than recent exposures [57]. Recently, hierarchical clustering analysis was used to analyze stressful LEs experienced in the year preceding delivery in a population of pregnant mothers, resulting in three distinct groups of stressor landscapes: a protected stressor landscape (PSL), isolated stressor landscape (ISL), and toxic stressor landscape (TSL) [41••]. The stress landscapes impacted health outcomes differently depending on the intersection of race and income. Outcomes of this study are presented in Table 2.

Environmental toxin exposure: prevalence and susceptibility

Environmental exposures to toxins and chemicals also increase PTB rates [58]. In Ningbo, China, short-term exposure to four different ambient air pollutants ($PM_{2.5}$, PM_{10}, SO_2, and NO_2) in the week before delivery increased the PTB risk by 3.6 to 6.5-fold [59]. In San Joaquin Valley, California, exposure to the highest measured quartile of the same four pollutants during the second trimester and end of pregnancy increased early PTB between 20 and 27 weeks of gestation by 1.4–2.8x [60]. Urban minority neighborhoods in the US are exposed to higher levels of environmental toxins due to closer proximity to high-traffic zones and factories [61,62]. In every metropolitan area of the country with a population greater than 1 million, Black individuals are more likely than White individuals to be living in census tract areas with high toxic air levels [63]. A study analyzing all natality data from 48 states in 1998–99 found that Hispanic, African–American and Asian/Pacific Islander pregnant mothers were more than two times more likely to live in the most polluted counties compared to White mothers [64].

However, disparities are evident not only in the prevalence of exposures, but also in the altered vulnerability to that exposure. Chronic stress, such as racial discrimination or poverty, can induce immune alterations that modify the ability of an individual to manage their exposure to future stressors. There are many examples of this interaction in the literature, a selection of studies is summarized in Table 3 [60,65,66•,67–70].

Table 2

Hierarchical clustering analysis of stressful life events (LEs) preceding delivery, from Koning *et al.* [41••]

Study	Koning *et al.* [41••]		
Data source	CDC PRAMS (Pregnancy Risk Assessment Monitoring System) Working Group		
Population	$n = 111\,330$ mothers; US Births from 32 states and New York City, 2011–2015.		
Data collection	Administration of standardized self-administered questionnaires before, during, and after pregnancy. Total duration of assessment: one year preceding delivery. Subject: maternal experiences, risk factors, and health care. Data is linked to child's birth record.		
Outcome	3 groups of stressor landscapes identified based on maternal life events (LEs): 1) Protected stressor landscape (PSL) 2) Isolated or illness stressor landscape (ISL) 3) Toxic stressor landscape (TSL)		
	Protected stressor landscape (PSL)	Isolated stressor landscape (ISL)	Toxic stressor landscape
Stressor landscape characteristics	Low frequency of LEs	Low frequency of acute LEs, 81% reported illness of close relative	High frequency of LEs, often traumatic in nature
Population characteristics	Overrepresentation of high-income and White mothers. Higher proportion of married mothers, advanced maternal age	Higher proportion of married mothers	Disproportionate distribution of minorities, low-income, and unmarried mothers: 46% of mothers are also in the lowest-income quartile
Birth outcomes	LBW: 5.8%	LBW: 6.2%	LBW: 8.3% Compared to PSL: 1.3x PTB, 1.5x LBW, 1.6x VLBW
Intersection of race and income	White women are most affected by LEs if they are also in the lowest income quartile (high income is protective). In Black and Hispanic women, income is not protective. Black women had higher rates of adverse pregnancy outcomes in all stressor landscapes, but the greatest racial disparities are actually demonstrated in the upper middle class.		

Table 3

Chronically stressed individuals exhibit a higher susceptibility to environmental toxin exposures

Study	Data source	Population	Data collection	Outcome
Clougherty *et al.* [65]	East Boston Neighborhood Health Center (EBNHC)	$n = 417$ children from 1987 to 1993. EBNHC, Boston, Massachusetts.	Traffic-related pollution exposures, residential retrospective exposure estimates (trajectory for each child), violence exposure assessment, and child's asthma diagnosis.	Children with a higher than median level of violence exposure were 1.6–2.4x more likely to develop asthma following air pollution exposure.
Padula *et al.* [60]	Study of Air Pollution, Genetics and Early Life Events (California Dept of Health)	$n = 263\,204$ births from 2000 to 2006, San Joaquin Valley, California.	Geocoding of maternal residence, Ambient Air Quality Data (EPA Database), traffic density, socioeconomic status (SES), birth outcomes.	During the 2nd trimester: High CO_2 and NO_2 exposure increases early PTB (from 20–23 wks) by 60% and 92%. PM exposure increases early PTB (from 20–27 wks) $>2\times$. If residence is in a low SES neighborhood, PTB risk increases by an additional 50%.
Padula *et al.* [66•]	Office of Statewide Health Planning and Development (OSHPD), linked hospital discharge birth cohort database	$n = 53\,843$ births from 2009 to 2012, Fresno County, California.	19 environmental and population indicators (pollution burden and population characteristics, using screening tool CalEnviroScreen2.0), merged OSHPD birth records by census tract.	The highest 3 quintiles of pollution burden and the highest quintile of drinking water contamination are both associated with a significant increase in PTB. The risk of early PTB was increased further in low SES neighborhoods and in non-White and non-Hispanic mothers.
Ponce *et al.* [67]	Linked LA county birth records, 1990 US Census, California Department of Transportation, and South Coast Air Quality Management District	$n = 37\,347$ births from 1994 to 1996, LA county, California. 112 of 269 LA county zip codes within 3.2 km of a freeway and monitoring station	Traffic count info, ambient air pollution data, birth records, US census data. Neighborhood SES stratification into high, mid, and low based on unemployment, income from public assistance, and family poverty.	The interaction of upregulated traffic-related air pollution in winter months (thermal inversion) and economic hardship increased the odds of PTB 2.2–2.6x in African-American women compared to White women. The association between air pollution and PTB was highest in low SES neighborhoods, no effect on PTB in high SES areas.
Casey *et al.* [68]	California Department of Public Health Birth Statistical Master Files, US Census Data	$n = 57\,005$ births from 2001 to 2011 in California. Last menstrual period 2 yrs before plant retirement or within 1 yr of plant retirement.	Geocoded maternal addresses, km distance from coal and oil power plant, time of exposure, gestational age, demographic and SES data per census block	The closure of 8 coal and oil power plants resulted in the decrease of PTB rates from 7.0 to 5.1% in women residing within 5 km of the plant. These effects were most pronounced in Black and Asian mothers.
Pereira *et al.* [69]	Connecticut Department of Health Birth Records and Environmental Protection Agency Monitoring Stations	$n = 61\,688$ infants born to 29 175 mothers (longitudinal study of births in Connecticut 2000–2006, at least 2 births per mother)	Weekly averages of $PM_{2.5}$ measurements from EPA monitoring stations used to compute exposures per trimester, birth records for birth outcomes	$PM_{2.5}$ exposure in the 1st trimester was associated with a 10% increase in PTB risk with each $PM_{2.5}$ interquartile range increase. The association was stronger in Black and Hispanic mothers, with a 39% and 31% increase in PTB risk in response to whole-pregnancy exposure to $PM_{2.5}$.

Table 3 (*Continued*)

Study	Data source	Population	Data collection	Outcome
Ferguson *et al.* [70]	TIDES Pregnancy cohort (The Infant Development and the Environment Study)	$n = 783$ infants born between 2010 and 2012	Phthalate exposure measured through analysis of urinary metabolites at 3 time points during pregnancy, self-report of stressful LEs during pregnancy, birth outcomes	Exposure to ΣDEHP during the 3rd trimester increased the risk of PTB by 2.09 if the women had experienced a stressful LE during pregnancy. Women who did not experience LEs during pregnancy only increased risk of PTB by 1.04 with ΣDEHP.

Allostatic load and the 'Weathering Hypothesis'

Allostasis is the process by which the body maintains physiological homeostasis as it encounters external stressors. It is closely regulated by the brain, and involves both the autonomic nervous system and the hypothalamic pituitary adrenal axis [71–73]. Acute stress activates allostasis, stimulating the release of inflammatory cytokines, adrenal hormones (cortisol) and neurotransmitters to adapt to the stress. Once the stressor is resolved, the system returns to baseline. If the stressor is chronic, these systems are activated repeatedly until overloaded and unable to return to baseline, causing wear and tear on the body and mind. This accumulation of stress over time is allostatic load (AL), which can lead to an increased susceptibility to infection and adverse health outcomes [6,71]. AL is the missing physiological mechanism that explains the presentation of poor health outcomes in chronically stressed populations. These individuals have a reduced capacity to withstand future stressors as a result of their stress burdens, increasing their vulnerability to future exposures [71,74–76]. The 'Weathering Hypothesis', first proposed by Geronimus *et al.* in 1992, interprets the widening differential between Black and White health outcomes over time as a direct result of the accumulating effects of socioeconomic inequalities on the body [77]. This model works in concert with the AL hypothesis. There is an increased probability in all age groups for Black Americans to have a higher AL score; this gap widens with increasing age and is the most pronounced in women [78•]. By age 64, 80% of Black women had a high AL score, whereas the proportion of White women with a high AL score never surpassed 60%. After adjusting for the poverty income scale, White Americans considered 'poor' were still less likely than non-poor Black Americans to have a high AL score [78•].

Telomeres, located at the end of every chromosome, are a biomarker of cellular aging and AL. Telomere length acts as a biological aging clock for the body's cells as the length shortens with each cell division cycle [6,79–81]. Stress exposures such as air pollution and psychosocial stress can increase the rate of telomere shortening [82,83]. Placental tissues of Black American women have shorter telomere lengths than those of White women. Decreased telomere lengths were measured in the amnion, chorion, villus, and umbilical cord of Black women, but the distinction was particularly prominent in the chorion [84•]. A population-based study of 981 adults determined that after adjusting for income, education, smoking, physical activity, diet, and BMI, Black and Hispanic Americans demonstrated more pronounced telomere shortening with age compared to White Americans, proportionate to 6–10 years of additional aging. This racial difference was more pronounced in women than men [85].

Pregnancy itself is a stressful event, so it is conceivable that women who begin their pregnancy with an already elevated allostatic load score may have a higher likelihood of PTB or LBW. However, as summarized in Olson *et al.* [6], studies thus far have presented conflicting results when examining the significance of the association between allostatic load and adverse pregnancy outcomes. These researchers measured a series of AL-related clinical biomarkers in the preconception period, during pregnancy, or postpartum [86–88,89•,90–92]. Since then, additional researchers have demonstrated a significant association between postpartum increases in AL and a history of adverse pregnancy outcomes [93–95]. Nevertheless, prospective work comparing pre-pregnancy AL scores and PTB remains quite limited. Morrison *et al.* determined that commonly used AL-related biomarkers, although appropriate for use in non-pregnant women, are not relevant measures of chronic lifetime stress during pregnancy [89•]. Researchers have emphasized the critical need for prospective longitudinal studies employing a number of different measures to assess AL, including an assessment of lifetime psychosocial stress and abuse [6,96,97]. As AL disparities are evident in ethnic minority populations, it is important that prospective studies enroll women with diverse genetic ancestries.

Notably, although race is a social construct, environmental stressors such as ACEs and LEs can modify gene expression through epigenetic mechanisms. Gene activity can be altered through DNA methylation, histone modification, and small noncoding RNAs without generating any change to the DNA sequence. Through a process termed *transgenerational epigenetic inheritance*,

modifications induced by social factors can be transmitted to future generations. This concept is explained in detail in Jawaid *et al.* [98]. Exposure to maternal trauma during residential schools [99], ACEs [100,101], natural disasters [102–106], famine [107], the Holocaust [108], and sexual slavery [109] can be passed on epigenetically to the next generation resulting in biological changes to health and behavior later in life. Studies in animal models have demonstrated that maternal (or paternal) stress during pregnancy can affect offspring behavior, birth timing, metabolism, and molecular processes even after multiple generations [110–116], and an allostatic load score can be developed to predict those at risk [117•]. In addition to present day discrimination and systemic racial bias [118], African Americans were subjected to centuries of cultural trauma, termed *Posttraumatic Slave Syndrome* [119,120]. Epigenetic mechanisms are expected to be involved in this transmission of AL through generations.

Concluding remarks

Many African Americans as well as people of other races and cultures are exposed to systemic and interpersonal racism throughout their lives. These psychosocial, physical environment, and socioeconomic inequalities all contribute to increased allostatic load. It is clear that the lifelong accumulation of these and other stressors increase an individual's vulnerability and negatively influence pregnancy outcomes [121]. High allostatic load of mothers without compensatory resilience can be transmitted to future generations through epigenetic mechanisms thereby negatively impacting offspring health. Fortunately, recent animal studies have demonstrated that an enriched environment reverses the negative effect of epigenetically transmitted adverse health outcomes [122•]. Perhaps with time and a more equitable social environment, there will be hope to reverse the adverse health effects of centuries of endemic racism.

Conflict of interest statement

Nothing declared.

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