

# Racial disparities in preterm birth in USA: a biosensor of physical and social environmental exposures

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## INTRODUCTION

The infant mortality rate in USA exceeds that of most other developed nations, ranking 26th among Organisation for Economic Co-operation and Development countries.<sup>1</sup> Non-Hispanic black infants in USA die more than twice as often as non-Hispanic white infants (11.4 vs 4.9 per 1000 live births).<sup>2</sup> This disparity reflects disparities in preterm birth (PTB) rates, since two-thirds of infant mortality occurs in preterm infants.<sup>3</sup> The PTB rate is 52% higher for black (13.8%) than white (9.0%) women. Efforts to reduce PTB and its disparities have failed (figure 1). We propose that racial disparities in PTB are a cumulative biosensor of exposures that vary by race, arising from long-standing inequities.

## PTB disparities are not due to genetic sequence variation between racial groups

While some monogenic diseases track (incompletely) with race, such as sickle cell anaemia and cystic fibrosis, the vast majority of health conditions cannot be mapped to genetic variation between racial groups. Most human genetic variation is found within ancestral groups with only 5%–10% of gene frequencies differing between ancestral groups.<sup>4</sup> Nonetheless, different frequencies of single nucleotide polymorphisms (SNPs) by race have led some investigators to

search for genetic differences that cause racial disparities in PTB. However, SNPs explain an exceedingly small portion of PTB risk, and are often not replicated.<sup>5,6</sup> Some strong evidence supports that disparities in birth outcomes are largely attributable to environmental, as opposed to genetic variation. One example is the phenomenon of erosion of immigrant health over generations. Birth weight (BWT) distributions of infants born to African-born black women and US-born white women nearly overlap, whereas infants born to US-born black women were substantially smaller.<sup>7</sup> Indeed in a study of 27 states' births in 2008, foreign-born black women had significantly lower odds of PTB than US-born black women even after adjustment for sociodemographic, health behavioural and medical risk factors (adjusted OR 0.727; CI 0.726 to 0.727).<sup>8</sup> Others have used twin and kinship studies to analyse the genetic versus the environmental contributions to PTB. These find that the pooled genetic contribution (<35%) is dwarfed by non-genetic or broadly defined environmental influences, particularly when self-identified African-Americans are compared with self-identified European Americans.<sup>9,10</sup> Further, PTB is a heterogeneous phenotype comprised

of distinct pathophysiological pathways. Spontaneous PTB results from premature cervical remodelling and/or myometrial contractility, whereas medically indicated PTB occurs when providers elect to deliver a fetus due to maternal or fetal conditions such as pre-eclampsia or intrauterine growth restriction. Black women are at higher risk of both spontaneous and medically indicated PTB,<sup>11</sup> and it is unlikely that a set of genetic sequences that track with race would lead to such different phenotypes. Given the small contribution of genetics to PTB, coupled with the very small differences in genetic sequences between racial groups in USA, broadly defined environmental factors must be responsible for racial disparities in PTB.

## Environmental factors must play a role in black-white disparities in PTB

We propose a framework wherein microenvironmental and macroenvironmental factors shape the likelihood of a healthy, term delivery (figure 2). Microenvironmental factors include behavioural factors where an element of individual choice can be made, such as smoking and diet. Macroenvironmental factors include social and physical environmental exposures such as neighbourhood violence, air and water pollution, heavy metals, and other exposures that are not directly due to an individual's decisions, but are present in the environment. Both microenvironmental and macroenvironmental exposures can affect an individual woman's physiology, and alter the likelihood of delivering preterm. We will argue that the macroenvironment plays a significant and underappreciated role in population-level disparities.

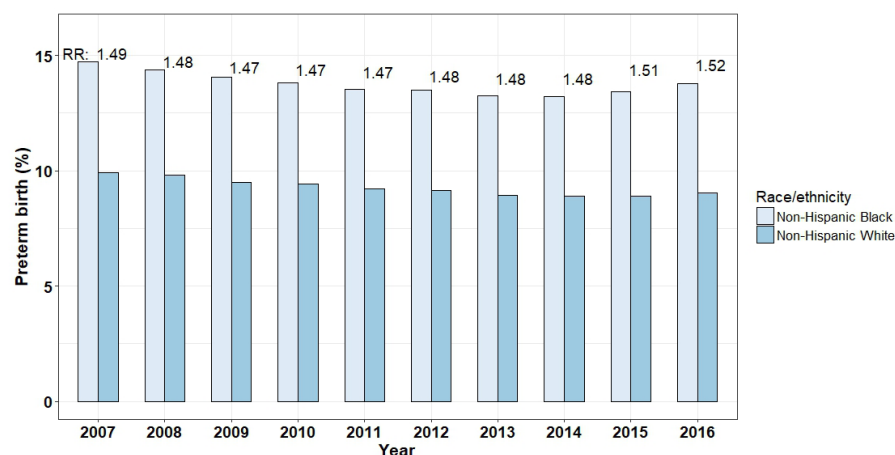


Figure 1 Black-white disparities in preterm birth over 10 years in USA.<sup>64,65</sup> RR, relative risk.

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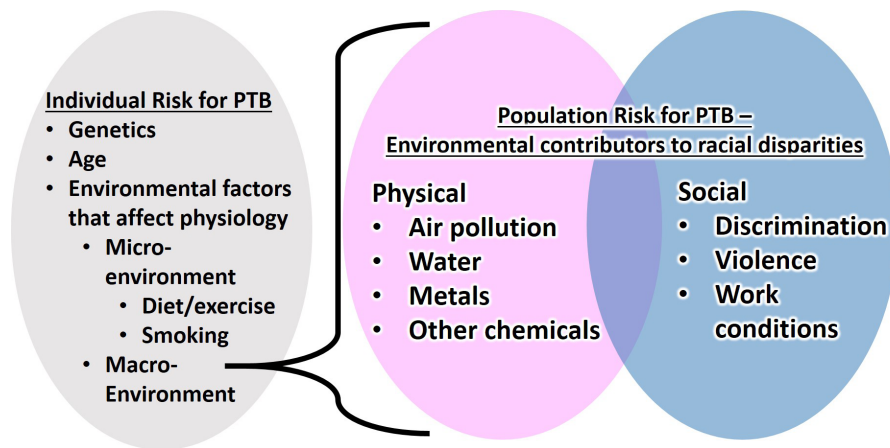
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**Figure 2** Expanded framework for environmental exposures that shape racial disparities in preterm birth (PTB).

### MICROENVIRONMENTAL FACTORS INCOMPLETELY EXPLAIN BLACK-WHITE DIFFERENCES IN PTB

To implicate an exposure as a contributing factor to black-white disparities, it must be more highly prevalent among black women. Smoking is one of the strongest risk factors for PTB.<sup>12</sup> Differences in smoking rates do not explain differences in PTB risk. Only 5.6% of non-Hispanic black women report smoking in pregnancy, compared with 10.1% of non-Hispanic white women.<sup>13</sup> White women who smoke have similar PTB rates (12.9%) to black women who do not smoke (13.5%), suggesting that while smoking increases individuals' risk of PTB, differential PTB rates between races is not due to smoking.

Diets are culturally patterned practices that can differ by race/ethnicity.<sup>14</sup> No single dietary practice has been implicated in PTB. A key micronutrient during pregnancy hypothesised to be involved in racial disparities in health is vitamin D. Unlike smoking, vitamin D deficiency is more common among black women; lighter pigmented skin is more efficient at synthesising vitamin D from sunlight.<sup>15</sup> While some observational studies have shown associations between vitamin D deficiency and PTB,<sup>16</sup> intervention trials have not. In a trial in South Carolina, 257 women were randomised to three different doses of vitamin D supplementation and while 25(OH)D levels increased according to dose, there was no difference in PTB.<sup>17</sup> In a recent, large trial of 1164 women randomised to high doses of monthly vitamin D versus placebo in Bangladesh, there were no differences in birth outcomes.<sup>18</sup> These results suggest that supplementing vitamin D for black women is unlikely to mitigate disparities in PTB.

Iron deficiency and anaemia, which are more common among African-Americans,<sup>19 20</sup> has likewise been associated with PTB in observational studies,<sup>21</sup> but randomised controlled trials of iron supplementation have been disappointing.<sup>22</sup> In a recent study, over 15 000 women were randomised to one of three interventions: folic acid alone, folic acid with iron and multiple micronutrients.<sup>23</sup> While the last group had a significant decrease in spontaneous PTB, there was no difference in the folic acid with iron group compared with the folic acid only group. Simply treating iron deficiency is unlikely to mitigate racial disparities in PTB.

### MACROENVIRONMENTAL FACTORS THAT MAY HELP TO EXPLAIN RACIAL DISPARITIES IN PTB

A large body of evidence has connected neighbourhoods to health.<sup>24</sup> This is particularly relevant due to residential racial segregation and environmental inequity between black and white neighbourhoods.<sup>25 26</sup> The extent to which segregation and disproportionate exposure to toxic environments among black families contributes to racial disparities in PTB is unknown. Yet, evidence is mounting to connect physical and social environmental exposures to PTB risk. Most implicated exposures are concentrated in black neighbourhoods, and black women living in racially segregated black neighbourhoods have higher risk of PTB than black women living in integrated neighbourhoods.<sup>27</sup>

#### Physical environmental exposures

Several physical environmental exposures have well-documented associations with PTB risk and disproportionately affect

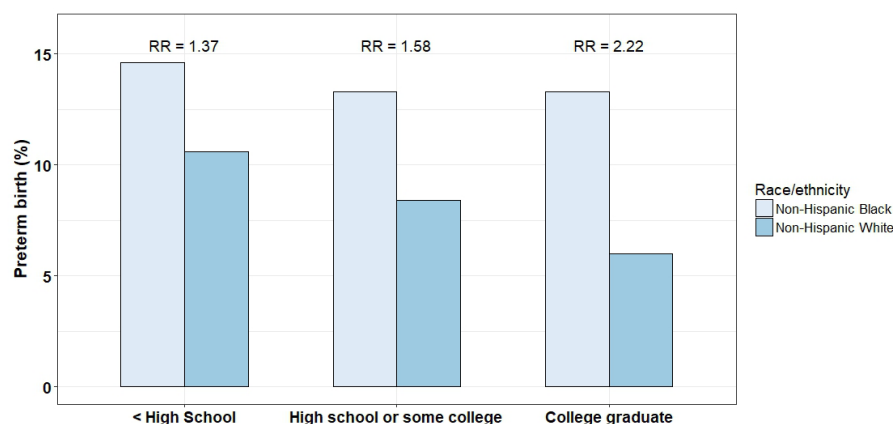
black families. Air pollution exposure increases the risk of PTB<sup>28 29</sup> and black Americans are more highly exposed due to residential proximity to industrial facilities,<sup>30</sup> traffic<sup>31</sup> and other sources. One recent study of over 37 000 births in China demonstrated that as IQR of short-term exposure to gases (SO<sub>2</sub> and NO<sub>2</sub>) and particulate matter (<2.5 [PM<sub>2.5</sub>] microns and <10 [PM<sub>10</sub>] microns in diameter) increased, the odds of PTB were 3.7–6.5 times higher.<sup>32</sup>

Lead exposure also disproportionately affect black families.<sup>33</sup> According to the Environmental Protection Agency's biomonitoring programme, regardless of poverty level, black children (1.1 µg/dL) have higher median lead levels than white children (0.8 µg/dL) and are twice as likely to have elevated levels (>5 µg/dL).<sup>34 35</sup> Lead has been shown to be associated with increased risk of PTB.<sup>36</sup> A recent case-control study (n=102 preterm cases and 306 term controls), also in China, found that infants in the highest tertile of lead levels, versus the lowest, had higher odds of being born preterm (adjusted OR 2.96, CI 1.49 to 5.87).<sup>37</sup>

Phthalates have also been shown to increase the risk of PTB.<sup>38</sup> These ubiquitous chemicals are used as plasticisers, and are components of personal care products, fast food packaging and building materials (eg, flooring). Phthalate metabolite levels can vary by race/ethnicity due to microenvironmental<sup>39</sup> as well as macroenvironmental exposures.<sup>40</sup> In a prospective, nested case-control study (n=130 cases, 352 controls) in Boston, women with higher levels of several phthalate metabolites had higher odds of spontaneous PTB (ORs 1.22–1.67 per ln-unit increase).<sup>38</sup> While evidence that physical environmental exposures contribute to PTB risk is accumulating, it is not yet clear what proportion of racial disparities in PTB is attributable to differences in the physical environment.

#### Social human environmental exposures

Social environments (human interactions) also strongly affect PTB risk. Exposure to racism and discrimination is associated with increased risk of PTB.<sup>41 42</sup> In a case-control study of 312 black women (104 cases and 208 controls) in Chicago, women who reported high levels of exposure to lifetime interpersonal racism were more likely to have delivered a very low BWT (<1500 g) infant than an infant >2500 g (adjusted OR 2.6, CI 1.2 to 5.3).<sup>41</sup>



**Figure 3** Black-white disparities in preterm birth according to maternal education in USA. Data from the Centers for Disease Control and Prevention (CDC) Wonder, singleton births from 2016.<sup>13</sup> RR, relative risk.

Violent crime, a severe chronic urban stressor, is often concentrated in lower-income and minority neighbourhoods,<sup>43</sup> and has been shown to affect birth outcomes. A study in North Carolina found that among over 30 000 live births, neighbourhood exposure to violent crime was associated with PTB;<sup>44</sup> notably, the range of violent crime counts near black women was higher than for white women with so little overlap, that race-specific tertiles were necessary for analysis. Recently, investigators used a natural experiment to perform a population-based longitudinal analysis of BWT in Mexico before and after the rise of the Mexican drug war. Increase in violent crime was associated with lower BWT after adjustment for maternal and community confounding variables.<sup>45</sup> Like physical environmental exposures, the extent to which differential social exposures by race may explain racial disparities in PTB is unknown.

### Interaction of physical and social environments

In 1992, Geronimus proposed an analytical framework to explain why black women had increased risk of adverse perinatal outcomes.<sup>46</sup> She postulated that the black-white infant mortality differential among infants born to older (versus younger) women was due to the cumulative effects of socioeconomic disadvantage. One potential mechanism transmitting socioeconomic disadvantage to racial disparities is through increasing susceptibility to physical exposures through chronic stress and related physiological impacts on immune and metabolic function (allostatic load).<sup>47</sup> Indeed there is evidence that social and physical environments interact to result in differential

birth outcomes.<sup>48</sup> Ponce *et al* analysed birth certificate data for 37 347 deliveries in California, and found that air pollution was associated with odds of PTB only among women in the lowest socioeconomic stratum.<sup>49</sup> A recent analysis of 53 843 mother-infant pairs in California used an exposure index to include air, land and water pollution sources.<sup>50</sup> Women in the highest quintile of exposure had twice the odds of PTB versus women in the lowest quintile, and when dichotomising the index, only women in the low socioeconomic stratum had elevated odds of PTB with higher pollution exposures.<sup>50</sup> These data suggest that socioeconomic disadvantage changes susceptibility to physical environments.

Social and physical inequity is not limited to residential life. Employment opportunities vary by race in USA resulting in differential physical occupational exposures<sup>51</sup> and higher levels of job strain defined as high demand and low control in the workplace,<sup>52</sup> among black workers.<sup>53</sup> In a case-control (1242 preterm cases, 4413 term controls) study in Quebec, Croteau *et al* found that women with high levels of job strain, including physically demanding postures and lack of control at work, had higher odds of PTB.<sup>54</sup> Further in a study of black and white women in North Carolina, job strain was associated with higher odds of PTB, specifically among black women (OR 1.8, 95% CI 1.1 to 3.1) compared with white women (OR 1.0, 95% CI 0.5 to 2.0).<sup>55</sup> Taken together, given that race often tracks with socioeconomic position that determines where women live and work, interactions of physical and social environments likely explain much of the racial disparity in PTB.

### Improving education alone will not solve disparities

One way to improve socioeconomic position is through education. However, education alone does not eliminate birth outcome disparities. In 1992, Schoendorf demonstrated that racial disparities in infant mortality existed even among infants born to college-educated women and that the disparity was entirely explained by differential risk of low birth weight (<2 500 g) (7% and 3% among black and white infants, respectively).<sup>56</sup> This phenomenon persists today. Disparities widen as education levels rise, as shown in figure 3, which displays PTB rates by education level in 2016 in USA.<sup>13</sup> These data suggest that education alone does not mitigate exposures that differ by race over a lifetime. Whether racial disparities among well-educated women are due to earlier life exposures (or even exposure to prior generations that could be passed along through epigenetic phenomena) or due to ongoing exposure to racism or other environmental stressors which are not eliminated with education, remains unknown.

### THE STUDY COMPLEXITY NEEDED TO ADDRESS RACIAL DISPARITIES IN PTB

Tackling racial disparities in PTB will require rigorously quantifying the relative contribution of adverse environmental factors that are disproportionately concentrated in black communities. One way this could be studied is by analysing inter-racial couples with one black parent and one white parent. A recent population-based study of over 1.6 million live births in California demonstrated that couples where one parent is black and the other is white have lower risk of spontaneous PTB than when both parents are black; the risk reduction was greater when the woman was white (adjusted OR 0.7, 95% CI 0.7 to 0.8) than when the man was white (adjusted OR 0.9, 95% CI 0.8 to 1.0).<sup>57</sup> While the risk reduction may be due to unmeasured socioeconomic position differences between couples who have inter-racial marriages compared with black couples, understanding which exposures differ among these families may shed light on environmental causes of PTB. Investigation into how the environment may shape racial disparities in PTB requires interdisciplinary collaboration between perinatal and environmental scientists, sociologists and other social scientists, biostatisticians, epidemiologists, and public health professionals. Identifying priorities for environmental exposure reduction is a critical step to motivate

policy efforts to reduce racial disparities in PTB.

### The importance of phenotyping PTBs

Due to the small impact of any individual environmental exposure on PTB, it is critical to clarify which subtype of PTB is affected, and to have large study populations. Otherwise, associations can be missed (type II error). Theoretically, if a toxic chemical affects the risk of preterm labour (one presentation of spontaneous PTB) with a relative risk of 1.4, but not preterm pre-eclampsia (one presentation of medically indicated PTB) with a relative risk of 0.9, the overall relative risk of PTB from the chemical might be 1.2 with a CI that crosses 1. In this case, the chemical might be deemed falsely benign with respect to PTB. Phenotyping PTBs is resource intensive, but will be required for detecting PTB subtype-specific environmental effects.

### Consideration of mixtures

Because many physical and social environmental exposures co-locate, considering the effects of mixtures is also extremely important given the small impacts of single exposures. For example, a single elevated phthalate may not alone cause spontaneous PTB, but combined with air pollution, lead and violence, the phthalate could be the last necessary stressor to trigger premature myometrial contractility or cervical remodelling necessary for spontaneous PTB.

### Getting closer to causation

Given the many variables that potentially confound an environmental exposure's effect on PTB, demonstrating that a toxic chemical affects the risk of a specific PTB phenotype among black women within an educational or income stratum would help to identify true targets. Better causal inference modelling, including mediation may also facilitate a better understanding as to the relative contributions of multiple exposures.<sup>58</sup> Multilevel modelling can also clarify the relative contribution of neighbourhood factors versus individual-level factors.<sup>59 60</sup> Additionally, collaborating with translational scientists and toxicologists to identify biological pathways by which toxic chemicals could lead to a specific PTB phenotype in animal models or in vitro can help to clarify whether an association is more likely to be truly causal.

### REALISING POLICY CHANGE

It is important to focus on social and environmental determinants of health in order to reduce disparities, as opposed to simply

improving medical care for all which can sometimes widen black-white gaps.<sup>61</sup> Once the targets that are likely both causative agents for PTB and disproportionately concentrated in black communities are identified, policy changes could reduce disparities. The built environment can affect physical activity through walkability and recreational resources. Local food environments can affect diet quality. Together these factors can affect likelihood of diabetes and hypertension<sup>24</sup> which can be associated with the risk of medically indicated PTB.<sup>62</sup> Additionally, clean-up efforts can improve birth outcomes. Recently, a study of over 57 000 births within 20 miles (36 kilometers) of coal power plants that were retired between 2001 and 2011 demonstrated significant reductions in PTB after the closures with the largest impact among black women.<sup>63</sup> Ultimately, exposure reduction of multiple implicated exposures will be required to narrow the racial gap in PTB that has persisted for decades.

### CONCLUSION

Long-standing racial disparities in PTB are likely largely due to social and physical exposures that vary by race due to enduring inequity in USA. The next frontier in tackling perinatal health disparities will require studying and rectifying the injustices of unequal environments. Only then will black families have an equal chance of healthy, full-term births.

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