US Black vs White disparities in foetal growth: physiological or pathological?

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Background Birthweight for gestational age is lower in US Black infants than in US White infants. It is unknown, however, whether this difference is ‘normal’ (i.e. physiological) or reflects pathological foetal growth restriction.

Methods We applied an analytic approach based on foetuses at risk to compare gestational age-specific rates of live birth, ‘revealed’ small-for-gestational-age (SGA), and neonatal mortality among singleton infants >22 weeks of gestation and >500 g born in 1998–2000 to US White (n = 9 012 194), US-born Black (n = 1 554 382), and foreign-born Black (n = 200 395) mothers. Graphical methods and Cox proportional hazards regression analyses were used to compare outcomes in the three ethnic groups.

Results Rates of live birth and neonatal mortality were highest at all gestational ages in US-born Blacks, lowest in Whites, and intermediate in foreign-born Blacks. The revealed SGA pattern cohered much more closely with the observed pattern for neonatal mortality when SGA was defined based on a single, overall standard of birthweight for gestational age than when based on ethnic group-specific standards.

Conclusion The closer coherence of revealed SGA and neonatal mortality rates based on a single standard and the intermediate pattern among foreign-born Blacks strongly suggest that Black–White differences in birthweight for gestational age are pathological, rather than physiological.

Keywords foetal growth; small-for-gestational-age; intrauterine growth restriction; racial/ethnic disparities

Introduction Birthweight is widely recognized as an important indicator of newborn health, both in individual infants and for populations.1 Birthweight for gestational age is often used as an indirect measure of foetal growth, although true ‘growth’ depends on serial increases in size over two or more time points during gestation. In the absence of valid and precise ultrasound or other non-invasive measures to assess true foetal growth in utero, birthweight for gestational age is used as an overall index of foetal growth from the time of conception to the moment of birth.2 Despite the indirectness of this measure, birthweight for gestational age is strongly associated with foetal, neonatal, and even postneonatal mortality, infant and child morbidity, and long-term growth and development.1,3 In recent years, numerous studies have associated low birthweight for gestational age with several long-term chronic diseases in adults, including hypertension, coronary heart disease, and type 2 diabetes.4

When using birthweight for gestational age for evaluating growth in individual infants, or across populations, the question arises to what is the appropriate standard to use.5 There is general agreement that sex-specific foetal growth standards are appropriate, since female foetuses and newborns are smaller at a given gestational age than males, yet are at lower risk for mortality and morbidity.1,3

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Black infants in the US have had consistently lower birthweight for gestational age than Whites, a disparity that has persisted for decades.\(^6\)-\(^8\) This disparity has been overshadowed by differences in preterm birth rates between the two ethnic groups,\(^9\) and few investigators have examined the reasons for the persistent differences in birthweight for gestational age. We recently evaluated race-specific foetal growth standards in US Blacks and Whites\(^10\) using an analytic approach based on foetuses at risk.\(^11\)-\(^13\) We observed that the frequency of foetal growth restriction as a function of gestational age cohered more closely to the gestational age-specific pattern for perinatal mortality when small-for-gestational-age (SGA) was defined based on a single, rather than an ethnic-specific, standard of birthweight for gestational age. This coherence strongly suggested that the observed Black–White differences in SGA were pathological, rather than physiological. In this paper, we explore this issue further by comparing birthweight for gestational age in US-born and foreign-born US Blacks and US Whites and by using a more quantitative multivariate analytic approach that adjusts for potentially confounding differences among these ethnic groups.

**Methods**

This study was based on 11.5 million Black and White singleton live births \(\geq 22\) completed weeks and \(\geq 500\) g in the United States from 1998 to 2000, derived from the National Center for Health Statistics (NCHS) linked birth-infant death cohort files for those calendar years. This study was confined to live births, because for stillbirths maternal birthplace is not forwarded by the U.S. Vital Statistics.\(^1\) The replacement of menstrual-based gestational age was incompatible with birth-weight, a clinical estimate of gestation (also recorded on the birth certificate, calculated as the difference between the date of the last menstrual period and the date of delivery. In a small fraction of births (approximately \(< 5\%\)) that did not contain a valid date for the last menstrual period, or when the menstrual-based gestational age was incompatible with birth-weight, a clinical estimate of gestation (also recorded on the birth certificate) was used instead.\(^14\) If a valid month and year of the last menstrual period were available but the date was missing, gestational age (also in completed weeks) was imputed.\(^15\) The replacement of menstrual-based gestational age by a clinical estimate as well as imputation of missing gestational age were performed by NCHS prior to public release of the data.

The main comparisons among White (\(n = 9012\) 194), US-born Black (\(n = 1\) 554 382), and foreign-born Black (\(n = 200\) 395) mothers are based on the following three perinatal outcomes: live birth, neonatal death (death within the first 27 days of life), and ‘revealed’ SGA. Rates for each of these outcomes are calculated using the number of foetuses at risk as the denominator, i.e. the number of foetuses who remain alive \(\text{in utero}\) at a given number of completed weeks of gestation.\(^11\)-\(^13\)\(^16\)-\(^18\) All foetuses who remain alive at that gestational age are at risk to be live-born within the next week and hence to die within a month following a live birth, or to be born SGA. ‘Foreign-born’ is defined as a maternal birthplace outside of the United States. Note, however, that because maternal birthplace is not contained in NCHS’s foetal death files, the denominator used in the present study does not include all foetuses at risk, but only those who are eventually born alive, since foetal deaths at or subsequent to a given gestational age are excluded. Thus for the present study, foetuses at risk were calculated as the number of live births at a given gestational age plus all live births at subsequent gestational ages.

We have previously shown that risks based on the number of foetuses at risk, rather than the number of total births, provides greater coherence between birth rates (and thus risks of preterm birth), foetal growth restriction, and perinatal mortality; it also eliminates the ‘paradoxical’ cross-over in gestational age-specific perinatal mortality curves.\(^10\)-\(^13\) One important consequence of using foetuses at risk rather than live births or total births as the denominator for calculating rates of gestational age-specific pregnancy outcomes is that perinatal mortality rates (and stillbirth and early neonatal mortality rates as well) rise with advancing gestational age. This may at first seem counter-intuitive, but conventional ‘rates’ are actually ratios of deaths to live births or total births at a given gestational age. They are not true proportions, because the denominator does not include all subjects (unborn foetuses) at risk for the events denoted by the numerator; all living foetuses are at risk for stillbirth, live birth, and early neonatal death in the succeeding week. Neonatologists are (appropriately) concerned with mortality among live-born births at a given gestational age, but neither the pregnant woman carrying a live foetus at a given gestational age nor her obstetrician, family physician, or midwife has any way of knowing whether or not her foetus will be born in the next week. From the woman’s and her unborn foetus’s perspective, the risk of stillbirth or live birth and early neonatal mortality in the succeeding week does indeed increase with advancing gestation, because the likelihood of birth (either a live birth or a stillbirth) rises as gestation advances.\(^13\)

Because SGA cannot be determined among unborn foetuses (i.e. those remaining \(\text{in utero}\)), and because the weight of stillbirths may underestimate the foetal weight at the (earlier) time of foetal death, we have developed a proxy measure, ‘revealed SGA’, that provides a tip-of-the-iceberg indication of foetal growth restriction. The revealed SGA rate is the number of live-born SGA infants at a given gestational age divided by the number of foetuses at risk,\(^11\)-\(^13\) where SGA is defined as a birthweight below the 10th percentile birthweight at the given gestational age for this dataset (i.e. an internal standard). Since the revealed SGA rate depends on both the birth rate and the SGA rate among live births, it is far below 10\%, except in the last gestational age category (42+ weeks) when all remaining foetuses are born. It thus relates the number of live-born SGA infants to the number of foetuses at a given gestational age who were at risk for both SGA and birth during the subsequent week.

We used two different internal standards to define revealed SGA: (i) a single standard comprising all three study groups and (ii) a group-specific standard for each of the ethnic groups. We then graphically compared the patterns of gestational age-specific rates of live birth, revealed SGA, and neonatal death among the three study groups and compared the coherence of the patterns using the single vs group-specific SGA standards.
In addition to these graphical methods of comparison, we also carried out Cox proportional hazard regression analyses to compare rates of live birth, neonatal mortality, and revealed SGA among the three study groups after adjusting for calendar year (1998, 1999, 2000) to control for temporal trends in group differences, maternal age (<20, 20–24, 25–29, 30–34, ≥35 years), gravidity (primigravid vs multigravid), education (<12, 12, ≥13 completed years), and lack or delayed initiation of prenatal care (late/none vs first trimester).

Most analyses were carried out using SAS version 8.2 (SAS Institute, Cary, NC, USA) operating on a UNIX operating system. Hazard proportionality was examined graphically using Stata version 8.0 and S-Plus version 6.2.19

Results
Maternal characteristics and pregnancy outcomes for the three study groups are shown in Table 1.

Figure 1 compares the live birth rate per 1000 foetuses at risk on a logarithmic scale and shows a clear separation among the three study groups in the preterm period (<37 weeks), with the highest rates among US-born Blacks, the lowest among Whites, and an intermediate rate for foreign-born Blacks.

Figure 2 compares the three groups for neonatal mortality per 1000 foetuses at risk, again on a logarithmic scale. At all gestations, US-born Blacks again show the highest rates, followed by foreign-born Blacks, and Whites having the lowest rates. The downturn in the curves at 42 1/2 weeks is likely an artefact due to systematic overestimation of true gestational age based on menstrual dates at 42 1/2 weeks20 and the fact that all foetuses remaining in utero at 42 weeks are born in that gestational age category.

Figure 3 shows the mean birthweight for gestational age among the three study groups. Differences among the three groups begin to emerge after about 34 weeks of gestation, with the highest means in Whites, lowest among US-born Blacks, and intermediate among foreign-born Blacks.

Figure 4 compares the revealed SGA rate (on a logarithmic scale) among the three ethnic groups based on a single (internal) standard for birthweight for gestational age. The pattern is similar to those seen for the neonatal mortality rate (Figure 2): US-born Blacks > foreign-born Blacks > Whites throughout gestation. This pattern contrasts with the pattern seen in Figure 5, however, where the revealed SGA rate is based on subgroup-specific standards for birthweight for gestational age. The pattern in Figure 5 differs substantially from the pattern for neonatal mortality in late gestation (Figure 2) but closely resembles that for the live birth rate shown in Figure 1; the subgroup-specific revealed SGA is in fact a constant multiple (10%) of the birth rate.

Table 2 shows the crude (unadjusted) and adjusted hazard ratios for the three study groups for the outcomes depicted in Figures 1, 2, 4, and 5. As in the graphical analyses, the revealed SGA results cohere much more closely with the neonatal mortality results when SGA is defined using a single standard, rather than an ethnic-specific standard. As shown in Figure 6, the hazards for neonatal mortality were not proportional among the three study groups. Hazard ratios (vs Whites as the reference group) declined with advancing gestational age. Thus, the overall hazard ratios for neonatal mortality shown in Table 2 represent weighted averages, rather than constant values.

Discussion
The overall differences we observed between US Blacks and Whites in rates of live birth, SGA, and neonatal mortality are consistent with those reported previously.6–10,21–24 What is new in our study is the comparison of single vs ethnic-specific

Table 1 Description of maternal characteristics and infant outcomes by maternal race

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Whites (n = 9012194)</th>
<th>US-born Blacks (n = 1554382)</th>
<th>Foreign-born Blacks (n = 200395)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>11.0</td>
<td>22.7</td>
<td>6.7</td>
</tr>
<tr>
<td>20–24</td>
<td>24.1</td>
<td>33.4</td>
<td>19.9</td>
</tr>
<tr>
<td>25–29</td>
<td>27.9</td>
<td>22.2</td>
<td>26.7</td>
</tr>
<tr>
<td>30–34</td>
<td>23.6</td>
<td>13.6</td>
<td>27.1</td>
</tr>
<tr>
<td>≥35</td>
<td>13.5</td>
<td>8.1</td>
<td>19.6</td>
</tr>
<tr>
<td>Primigravida (%)</td>
<td>33.8</td>
<td>30.6</td>
<td>29.0</td>
</tr>
<tr>
<td>Maternal education (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>18.8</td>
<td>25.1</td>
<td>16.6</td>
</tr>
<tr>
<td>12</td>
<td>39.5</td>
<td>48.4</td>
<td>44.6</td>
</tr>
<tr>
<td>≥13</td>
<td>41.7</td>
<td>26.5</td>
<td>38.6</td>
</tr>
<tr>
<td>Late/no prenatal care (%)</td>
<td>14.4</td>
<td>23.7</td>
<td>22.9</td>
</tr>
<tr>
<td>SGA birth (single standard) (%)</td>
<td>8.3</td>
<td>15.9</td>
<td>11.4</td>
</tr>
<tr>
<td>Preterm birth &lt;37 weeks (%)</td>
<td>9.3</td>
<td>16.6</td>
<td>12.6</td>
</tr>
<tr>
<td>Preterm birth &lt;32 weeks (%)</td>
<td>1.3</td>
<td>3.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Neonatal mortality (per 1000)</td>
<td>2.4</td>
<td>4.7</td>
<td>3.6</td>
</tr>
</tbody>
</table>
Figure 1  Gestational age-specific live birth rate in three study groups (logarithmic scale)

Figure 2  Gestational age-specific neonatal mortality in three study groups (logarithmic scale)
**Figure 3** Gestational age-specific mean birthweight in three study groups

**Figure 4** Gestational age-specific ‘revealed’ SGA rate in three study groups based on single standard for SGA (logarithmic scale)
standards for birthweight for gestational age as a way of assessing the physiological vs pathological differences in birthweight for gestational among the ethnic groups. As in our previous work, we have used the gestational age-specific revealed SGA rate as a ‘tip of the iceberg’ that reflects foetal growth restriction among foetuses remaining in utero at the given gestational age. The fact that the gestational age-specific pattern of revealed SGA coheres better with the pattern for neonatal mortality when SGA is based on a single standard suggests that the single standard is appropriate, i.e. that differences in birthweight for gestational age among the three groups under study are pathological, not physiological. That the observed hazard ratios for all three study outcomes (rates of live birth, revealed SGA, and neonatal mortality) are not strongly confounded by group differences in maternal age, gravidity, education, or prenatal care (Table 2) adds further support to our results and conclusions.

The subdivision of US Black infants into those whose mothers were born in the US vs those whose mothers were born abroad has further strengthened our inference that the Black–White disparities are unlikely to reflect ‘normal’ physiological differences. Genetic or other biologically based explanations for the observed patterns in birthweight for gestational age should theoretically show US-born Blacks being intermediate between foreign-born Blacks and US Whites, given the intermarriage and genetic admixture that has occurred in US-born Blacks over many generations.25

Previous studies have reported lower rates of low birthweight and very low birthweight among recent Black immigrants from the Caribbean or Africa.21–24 Our results confirm and extend those reports by analysing gestational age-specific rates of birth, SGA, and perinatal mortality and by relating the rates to

Figure 5 Gestational age-specific ‘revealed’ SGA rate in three study groups based on the group-specific standard for SGA (logarithmic scale)

<table>
<thead>
<tr>
<th>Maternal race</th>
<th>Hazard ratio (95% confidence interval) vs Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth rate</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.12 (1.11–1.13)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.14 (1.13–1.15)</td>
</tr>
<tr>
<td>Revealed SGA (single standard)</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.16 (2.15–2.17)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>2.05 (2.04–2.06)</td>
</tr>
<tr>
<td>Revealed SGA (ethnic-specific)</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.10 (1.09–1.11)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.05 (1.04–1.06)</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.10 (2.05–2.16)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>2.05 (1.99–2.11)</td>
</tr>
</tbody>
</table>

a Hazard ratios were derived from fitting Cox proportional hazards regression models and are adjusted for the confounding effects of birth year, maternal age, gravidity, maternal education, and lack of or initiation of prenatal care after the first trimester.

b Hazards for neonatal mortality are non-proportional (hazard ratios decline with advancing gestational age—see text and Figure 6).
foetuses at risk, rather than conditioning on live birth. We did not compare outcomes among US-born vs foreign-born Whites, because the available evidence does not suggest that pregnancy outcomes differ in these latter groups.\textsuperscript{24}

The lower rates of live birth, revealed SGA, and neonatal mortality among foreign-born vs US-born Blacks raise the question of a ‘healthy migrant’ bias among the foreign-born Blacks. The fact that the outcomes under study were more favourable among foreign-born than among US-born Blacks is consistent with findings from previous studies and probably does reflect the more favourable socioeconomic and health status among these immigrants \textit{vis à vis} US-born Blacks. Nonetheless, if differences in foetal growth (as reflected by GA-specific mean birthweights and revealed SGA rates) were truly physiological, rather than pathological, we would expect patterns that were more coherent with those observed for neonatal mortality when the definition of SGA was based on ethnic-specific standards, rather than a single standard, for birthweight for gestational age.

One potentially important limitation of our study stems from the fact that the NCHS foetal death files do not contain information on maternal birthplace. Our definition of ‘foetuses at risk’ in the present study differs from that used in our previous studies, since we cannot study stillbirths or perinatal deaths as outcomes (numerators) and cannot include pregnancies that end in stillbirth in the denominator of foetuses at risk. Nonetheless, our previous work has demonstrated extremely similar patterns in ethnic and other comparisons, whether the outcomes compared were stillbirths, perinatal deaths, or neonatal deaths, and we are confident that similar patterns to those reported here would have been observed had we be able to separate stillbirths in US-born Blacks from those in foreign-born Blacks. Similarly, our inability to include foetuses with eventutal stillbirth in the denominator of foetuses at risk probably had little impact on our results and conclusions. Further limitations include the potential for errors in menstrual-based estimates of gestational age\textsuperscript{26} and some inevitable misclassification of race based on mothers’ self-identification.

Our findings do not provide any clues about the pathophysiological mechanisms underlying the differences we observed. The trivial differences in the magnitude of crude vs adjusted associations with maternal race (Table 2) suggest that birth year, age, and gravidity do not confound those associations and that maternal education and lack of or late entry into prenatal care (which are potential causal intermediates) do not mediate them. The results argue against a genetic mechanism, but our inference that the observed differences in birthweight for gestational age are ‘pathological’ does not elucidate which environmental exposures are most important, nor whether they are primarily related to social (e.g. racism), behavioural, health care, or other factors. Our results and conclusions should therefore be placed in the overall context of helping to elucidate reasons for observed racial disparities, without attempting to minimize the biological, social, and political complexities behind the concept of ‘race’.\textsuperscript{27–29}

We infer that differences in birthweight for gestational age among both US-born and (to a lesser extent) foreign-born Blacks in the United States are due to pathological restriction in foetal growth, reflecting a more adverse intrauterine environment. Whether that adverse intrauterine environment reflects low-grade infection, prolonged and repeated exposure to racial discrimination\textsuperscript{30,31} or other sources of psychological stress, or some other pathological mechanism remains to be determined. Regardless of the mechanism, however, our findings and inferences imply that observed differences in birthweight for gestational age are potentially preventable with appropriate modification of the pathological determinants.
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KEY MESSAGES

- Foreign-born Blacks in the US had live birth rates, mean birthweights, SGA rates, and neonatal mortality rates that were intermediate between those of US Whites and US-born Blacks.
- The gestational age-specific patterns of SGA among the three racial/ethnic groups cohered much more closely with the pattern for neonatal mortality when SGA was defined based on a single standard of birthweight for gestational age than when based on ethnic group-specific standards.
- The smaller size of US Black infants thus appears to be pathological rather than physiological.

References

