Developmental Origins of US Race-Based Disparities in Cardiovascular Health

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US health disparities

Hypertension

Source: NCHS 2004
**Major US health disparities:**
Disproportionate burden among African Americans

<table>
<thead>
<tr>
<th>Early life</th>
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Classic model of disease causation

Genes  Environment

Trait
Racial disparity in the frequency of recurrence of preterm birth

Zachary A.-F. Kistka; Lisanne Palomar; Kirstin A. Lee, MD; Sarah E. Boslaugh, PhD; Michael F. Wangler, MD; F. Sessions Cole, MD; Michael R. DeBaun, MD, MPH; Louis J. Muglia, MD, PhD

OBJECTIVE: We examined the hypothesis that black race independent of other factors increases the risk for extreme preterm birth and its frequency of recurrence at a similar gestational age.

STUDY DESIGN: We conducted a population-based cohort study using the Missouri Department of Health’s maternally linked database of all births in Missouri between 1989 and 1997 for factors associated with recurrent preterm delivery.

RESULTS: Recurrent black preterm births occurred at increased frequency (adjusted odds ratio 4.11 [95% confidence interval 3.78 to 4.47]) and earlier gestations (31 versus 33 weeks’ median age) than white births. Black siblingships also had higher multiplicity of prematurity (odds ratio 2.14 [95% confidence interval 1.49 to 3.07] and 5.09 [95% confidence interval 1.26 to 20.51] for 3 and 4 preterm births). Additionally, 47% of women delivered recurrent preterm infants within 2 weeks of the gestational age of their initial preterm infant.

CONCLUSION: Overrepresentation of preterm births in blacks occurs independently of maternal medical and socioeconomic factors. Furthermore, the grouping of timing for preterm birth in different pregnancies of the same mother implicates important genetic contributors to the timing of birth.

Key words: epidemiology, parturition, population-based cohort, preterm birth, racial disparity

In race disparities research, “genes” are often the default explanation for group differences, even in absence of evidence.

Study Points to Genetics in Disparities in Preterm Births

By NICHOLAS BARTOLCAR
Published: February 27, 2007

Black women have significantly higher rates of premature birth than white women, and a new study suggests there may be underlying genetic factors even when other known risks are taken into account.

The researchers, who published their findings this month in The American Journal of Obstetrics & Gynecology, say that even though preterm birth is not a desirable outcome, it may provide some advantage, perhaps protection against diseases -- in somewhat the same way the gene for sickle cell confers protection against malaria.

"We have to think of everything in the context of what's been evolutionarily advantageous," said Dr. Louis J. Muglia, a professor of pediatrics at Washington University in St. Louis, who was the senior author of the study.

Dr. Muglia noted that during a normal pregnancy, certain immune responses are suppressed, and that cytokines, the molecules involved in healthy immune response, are heavily involved in preterm birth.

"The same things that select for a robust immune response," he said, "may also confer a

Is greater tissue activity of creatine kinase the genetic factor increasing hypertension risk in black people of sub-Saharan African descent?

Brewster LM, Clark JF, van Montfrans GA.

Department of Neurology, University of Cincinnati, Ohio 45267-0525, USA. mail@lizzybrewster.net

We postulate that the genetic factor increasing the propensity of black people of sub-Saharan African descent to develop high blood pressure is the relatively high activity of creatine kinase, predominantly in vascular and cardiac muscle tissue. Such greater activity of
The African gene? Searching through history for the roots of black hypertension
- Cover Story

Science News, Oct 19, 1991 by Kathy A. Fackelmann
Classic model of disease causation

Genes ➔ Trait ➔ Environment
New perspective:
The developmental origins of adult health

The roots of adult health trace (in part) to experiences during intrauterine and early postnatal life
Example of early environments and adult health in Philippines

Cebu Study, Philippines
Enrolled 3,327 pregnant women in 1983
Offspring now 26 yrs old
Adult waist circumference and diabetes risk (Philippines)

Males

<table>
<thead>
<tr>
<th>Adult waist circumference</th>
<th>Insulin (μg/ml)</th>
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<tbody>
<tr>
<td>WC 1</td>
<td>5.6</td>
</tr>
<tr>
<td>WC 2</td>
<td>5.6</td>
</tr>
<tr>
<td>WC 3</td>
<td>6.4</td>
</tr>
<tr>
<td>WC 4</td>
<td>9.2</td>
</tr>
</tbody>
</table>
Adult waist circumference and diabetes risk (Philippines)

Highest diabetes risk: born small + adult weight gain

Males

Adult waist circumference

Insulin (ug/ml)

Birth weight 1
Birth weight 2
Birth weight 3
Adult waist circumference and blood pressure (Philippines)

Highest blood pressure: born small + adult weight gain

Males

- WC 1
- WC 2
- WC 3
- WC 4

Adult waist circumference

Systolic blood pressure (mm Hg)
Outline of talk

PART I: Overview of developmental pathways linking early environments with adult health
British women: Birth weight and CHD Mortality

Developmental Origins of Adult Health

Fetal Stress or Undernutrition

→ Slow growth rate

→ Low birth weight
Developmental Origins of Adult Health

Fetal Stress or Undernutrition → Developmental response → Cardiovascular Disease

- Stress hormones or nutrient restriction
- "programming"
- Cholesterol
- Insulin resistance
- Visceral fat
- Hypertension

Barker, DP (1997) *Nutrition*: 13(9) 807-13
Cortisol response to psychosocial stress by birth weight

Trier Social Stress Test

Wüst et al (2005), Psychoneuroimmunology, 30(6)591-98
Lambs: effect of 15% maternal dietary restriction on stress response in offspring

Where does the biological “memory” of early life nutrition and stress reside?
Mechanisms of biological “memory”

- Change in growth of organ or tissue
- Change in types of cells present
- Changes in cellular gene expression

“epigenetic” changes
Two biological codes

Genetic code: sequence of DNA (nucleotide sequences) that tells a cell how to build one protein. Set for life.

Epigenetic code: chemical modifications in the structure of the chromosomes that influence which genes can be expressed and in which tissues. Potentially altered in response to environments (especially early environments).
Components of the epigenetic code

- **DNA methylation**
  - Methyl marks added to certain DNA bases repress gene activity.

- **Histone modification**
  - A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.
Example of how early environments influence biology via methylation:

*Maternal nutrition and diabetes risk in offspring*
Prenatal protein restriction (rats): effects on liver glucocorticoid receptor (GR) in adult offspring

(target gene: PEPCK)

protein restriction (pregnant mother) → Methylation

Glucose (offspring)

Maternal dietary group

Summary: early environments, development, and adult health

• Developmental biology is sensitive to prenatal and early postnatal conditions.

• Maternal psychosocial and nutritional stressors lead to durable biological changes in offspring that elevate future risk for cardiovascular and other common diseases.

• Allows maternal experience of environment to have lingering impact on adult health disparities in offspring generation.
Outline of talk

→ **PART I:** Overview of developmental pathways linking early environments with adult health

→ **PART II:** Evidence for contribution of developmental and intergenerational processes to US race-based health disparities.
How important are developmental and epigenetic processes to US "racial" health disparities?
## Major US health disparities:
Disproportionate burden among African Americans

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US health disparities

Low birth weight

Source: NCHS 2004
Might birth weight differences among “race” groups trace to genes?

Evidence: birth outcomes in inter-racial marriages
Risk of LBW in interracial marriages
Black mother (vs. White mother)

Parker (2000) Epidemiology 11(3) 242
Might birth weight differences among “race” groups trace to genes?

Evidence: birth outcomes in inter-racial marriages
Evidence: birth outcomes in recent US immigrants
Intergenerational birth weight trends

Intergenerational birth weight trends
Descendents of foreign-born blacks

Collins et al (2002), Am J Epidem, 155(3)210
Poor birth outcomes in African American women are predicted by social and economic factors:

**Examples:**

- Education
- Residential segregation
- Neighborhood level poverty
- Racism
- Discrimination
Racial discrimination and LBW

Self-reported racial discrimination

Odds ratio

No events    1-2 events    3+ events

1.0          2.0           4.8 *

Mustillo et al 2004 Am J Pub Health
Racial discrimination and LBW

Odds ratio

Black (vs. White)

Mustillo et al 2004 Am J Pub Health
Relative risk of LBW birth in Arabic-named women post-Sept 11 compared to prior year

Source: California birth records

<table>
<thead>
<tr>
<th>Group</th>
<th>RR</th>
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<tbody>
<tr>
<td>Non-Hispanic White</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>1.00</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>1.03</td>
</tr>
<tr>
<td>Native American</td>
<td>1.19</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.99</td>
</tr>
<tr>
<td>not ethnically distinctive</td>
<td>1.16</td>
</tr>
<tr>
<td>name ethnically distinctive</td>
<td>2.25</td>
</tr>
</tbody>
</table>

Lauderdale 2006 Demography 43: 185-201
Durable biological changes

Hypertension
Central obesity
Diabetes
Heart attack
Stroke

Adulthood
Stress reactivity
Hypertension
Central obesity
Diabetes
Heart attack
Stroke

Prematurity, IUGR & low birth weight

SES
discrimination
racism

“STRESS”

Long-term effects:

Short-term effects:

Durable biological changes
Bogalusa Heart Study
Black & White participants

Mzayek et al 2004, Annals Epidemiology 14(4)258
Birth weight and blood pressure in black and white adolescents

\[ \beta \text{ mmHg/kg} \]

Oberg et al 2007 *Am J Hypert.* 20: 1235
Durable biological changes

Hypertension
Central obesity
Diabetes
Heart attack
Stroke

Long-term effects:

Adulthood
Stress reactivity
Hypertension
Central obesity
Diabetes
Heart attack
Stroke

“STRESS”

SES
discrimination
racism

Durable biological changes
Evidence for social-developmental origins of racial health disparities

- US blacks have lower birth weight
- LBW traces to social causes
- LBW negatively impacts adult health
Durable biological changes

Hypertension
Central obesity
Diabetes
Heart attack
Stroke

Long-term effects:

Adulthood
Stress reactivity
Hypertension
Central obesity
Diabetes
Heart attack
Stroke

"STRESS"

SES
discrimination
racism

Durable biological changes
Stressful prenatal environment

Generation #2

SES discrimination racism

“STRESS”

Durable biological changes
Maternal blood pressure during pregnancy and fetal growth

Maternal pre-pregnancy hypertension increases risk of intrauterine growth restriction

<table>
<thead>
<tr>
<th>Type of IUGR</th>
<th>Odds Ratio</th>
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<tr>
<td>Mild IUGR</td>
<td>2.24 (1.47, 3.39)</td>
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<tr>
<td>Severe IUGR</td>
<td>3.45 (2.18, 5.46)</td>
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Kramer et al (1999), Pediatrics, 103: 599-602
Gestational diabetes in mother predicts diabetes in offspring

Age 10-22 years

Odds of having been exposed to gestational diabetes (diabetic vs. control offspring)

Dabelea et al 2008 Diabetes Care 31: 1422
Major US health disparities

**Early life**
- Prematurity
- Low birth weight
- IUGR

**Adulthood**
- Heart attack
- Stroke
- Diabetes
- Hypertension
Intergenerational, life course health model

Maternal health

Fetal health
- Prematurity
- Low birth weight
- Perinatal mortality
- High reactivity

Infant health

Adult health
- Hypertension
- Diabetes
- Stress
- Heart attack
- Stroke

Childhood health

Kuzawa (2008) in Trevathan et al
Evolutionary Medicine: New Perspectives, Oxford UP
Wrap-up
Evidence for social-developmental origins of racial health disparities

- US blacks have lower birth weight
- LBW traces to social causes
- LBW negatively impacts adult health
  - Adult health → LBW in next generation
  - Cycle continues, reinforced by ongoing stress

Social environments influence health disparities (in part) via lifecourse and intergenerational pathways.
Research & policy questions

• How important are early environments relative to traditional (adult) risk factors?

• How do we measure the relevant early life exposures (e.g. prenatal nutrition or stress)?

• Designing interventions: How important are maternal/intrauterine environment, infancy, and childhood? Where are opportunities to intervene?

• How “durable” are these effects? Can early life effects be reversed?
Reversability?


Fetal undernutrition

Fetal undernutrition + postnatal leptin

Rats
Research & policy questions

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The embodiment of race disparities

Genes → Trait

Environment → Trait

Developmental & Epigenetic → Trait

“Race”
Feature Article

Epigenetics and the Embodiment of Race: Developmental Origins of US Racial Disparities in Cardiovascular Health

CHRISTOPHER W. KUZAWA* AND ELIZABETH SWEET
Department of Anthropology, Northwestern University, Evanston, Illinois 60208

ABSTRACT The relative contribution of genetic and environmental influences to the US black-white disparity in cardiovascular disease (CVD) is hotly debated within the public health, anthropology, and medical communities. In this article, we review evidence for developmental and epigenetic pathways linking early life environments with CVD, and critically evaluate their possible role in the origins of these racial health disparities. African Americans not only suffer from a disproportionate burden of CVD relative to whites, but also have higher rates of the perinatal health disparities now known to be the antecedents of these conditions. There is extensive evidence for a social origin to prematurity and low birth weight in African Americans, reflecting pathways such as the effects of discrimination on maternal stress physiology. In light of the inverse relationship between birth weight and adult CVD, there is now a strong rationale to consider developmental and epigenetic mechanisms as links between early life environmental factors like maternal stress during pregnancy and adult race-based health disparities in diseases like hypertension, diabetes, stroke, and coronary heart disease. The model outlined here builds upon social constructivist perspectives to highlight an important set of mechanisms by which social influences can become embodied, having durable and even transgenerational influences on the most pressing US health disparities. We conclude that environmentally responsive phenotypic plasticity, in combination with the better-studied acute and chronic effects of social-environmental exposures, provides a more parsimonious explanation than genetics for the persistence of CVD disparities between members of socially imposed racial categories. Am. J. Hum. Biol. 21:2–15, 2009. © 2008 Wiley-Liss, Inc.

The disproportionate disease and mortality burden of African Americans is among the most challenging of US public health problems. It is now broadly known that an African American man in Harlem is less likely than a man in Bangladesh to survive to the age of 65 (McCord and Freeman, 1990). Nationally, African Americans have an age-adjusted all-cause mortality rate that is 1.5 times that of Tang et al., 2005), and that disease-causing alleles are likely to be among those variants that segregate between these groups (Burchard et al., 2003; Risch et al., 2002). Evidence to support this model has recently come from genetic studies of population substructure, in which the analysis of thousands of loci simultaneously has produced clusters of genetic information that can be used to cor-
Thank you!
Genes Show Limited Value in Predicting Diseases

By NICHOLAS WADE
Published: April 15, 2009

The era of personal genomic medicine may have to wait. The genetic analysis of common disease is turning out to be a lot more complex than expected.
New York blacks: risk of mortality by place of birth
Cardiovascular disease

SMR

Birth place

New York blacks: risk of mortality by place of birth
Coronary Heart Disease

SMR

Birth place

Prenatal stress

Induced changes in metabolism and physiology

Perpetuation of changes to next generation via intrauterine environment, e.g.
- maternal cortisol
- maternal insulin
- maternal BP

Further perpetuation of biological changes
Questions

• How important are early environments compared to traditional (adult) risk factors?

• How do we measure the relevant early life exposures (e.g. prenatal nutrition or stress)?
  – How important are maternal/intrauterine environment, infancy, and childhood?

• Can early life effects be reversed?

• Most work to date has been in UK, Europe: How are these processes different in developing countries or in populations in transition?