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**The Embodiment of Race:
Health Disparities in the Age of Epigenetics**

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Abstract

The role of genetic and environmental influences on race-based health disparities has been a source of heated debate among the public health and clinical medical communities. In this article, the authors review new evidence for developmental and epigenetic origins of common adult metabolic diseases and argue that this field sheds new light on the origins of racial health disparities. African Americans not only suffer from a disproportionate burden of adult chronic diseases such as hypertension, diabetes, and cardiovascular disease, but they also have higher rates of the perinatal health disparities that are 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, working through pathways such as the effects of discrimination on maternal stress physiology. In light of the inverse relationship between birth weight and adult metabolic diseases, there is now a strong rationale to consider developmental and epigenetic mechanisms as links between social and environmental factors and adult race-based health disparities in conditions like hypertension, diabetes, and cardiovascular disease. Their model builds upon classic social constructivist perspectives by highlighting an important set of mechanisms by which social influences can become embodied, having durable and even transgenerational influences on the most pressing health disparities in the United States.

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 (1). Nationally, African Americans have an age-adjusted all-cause mortality rate that is 1.5 times that of whites (2), and cardiovascular diseases (CVD) and their precursor conditions, including hypertension, diabetes, and obesity, contribute heavily to this disparity. The risk of dying from heart disease is 1.3 times higher in African Americans compared to US whites (3), and African Americans are 1.8 times more likely to develop diabetes (4). Hypertension rates are roughly 1.5-2 times higher in African Americans compared to whites (3), and are especially high in certain regions, such as the so-called 'stroke belt' of the American South. In total, nearly half of all African American adults develop some form of CVD, making racial disparities one of the most pressing US public health problems today (5).

During the past 15 years, there has been a concerted effort to understand the underlying determinants of racial disparities (6-8), and explanations have tended to align with one of two models that emphasize either social or genetic causes. Those who argue that social forces drive racial health disparities point to the importance of factors such as economic disadvantage, psychosocial stress, and institutional and interpersonal discrimination as causes of ill health (7, 9-19). Such cultural and structural challenges can impose barriers to healthy lifestyles, limit access to quality medical care, and chronically strain physiological stress systems that are linked to disease (6, 20-24). Together, these social, economic, and contextual factors can have a significant impact on health, and when taken into account, the black-white differential in health is often diminished (9, 21, 25).

Counterposed against this social constructionist position are researchers who attribute some, or all, of the problem of racial health inequalities to differences in an innate genetic predisposition (26-30). This model is founded upon the assumption that human genetic variation can be differentiated into conventional 'racial' clusters (31-37), and that disease-causing alleles are likely to be among those variants that segregate between these groups (28, 29). Evidence to support this model has recently come from genetic studies of population substructure. Using several different types of markers and analyzing hundreds of loci simultaneously, researchers have found that the clustering of genetic information can be used to correctly identify individuals' self-described geographic ancestry (32-34).

The assumptions and interpretations of these racial-genetic models have been questioned. For instance, a recent study found that knowing what continent someone is from explained only 4% of total human genetic variation in a global sample of individuals (33). Even this low number may be partially explained as a statistical artifact of sampling DNA in individuals from relatively inbred populations in the center of continental ranges (38). Thus, critics of the genetic race concept note that nearly the entire range of human genetic variation is found within each of the so-called continental races, with little explained by the continental groups themselves. Nonetheless, even this small fraction of variation is often pointed to as evidence for a genetic reality to conventional racial classifications. In addition, the tendency for race to remain an important explanation for disease in epidemiological studies, even after lifestyle and SES factors have been adjusted for statistically (39-41), is also often interpreted as indirect support for this position (42).

The ensuing debate between these competing models has been described as a "storm" (6), and has led to often heated disagreement (e.g. (28, 43)). The intensity of the debate has been fueled, in part, by what are recognized as high social and political stakes. On the one hand, many

physicians have noted that identification of consistent genetic differences between race/ethnic groups could lead to better targeting of preventive efforts or treatments (28, 29, 44). If race were found to map onto genetic variation, knowing an individual's racial identity could allow clinical diagnosis of genetic conditions and tailored pharmaceutical therapies (28). On the other hand, however, lies the specter of genetic fatalism and concern that genetic theories of health inequality could lead to an erosion of public health efforts to treat diseases perceived as innate and unavoidable. Additionally, scholars worry that assumptions of genetically-based health disparities have the potential to perpetuate beliefs of innate racial inferiority, and at worst, policies of real or *de facto* eugenics (45-47).

Even as this debate has become increasingly polarized, a quiet revolution has been taking place within biology that promises to transform the discourse on the origins of health disparities. Evidence that individuals born as lower birth weight babies have higher rates of metabolic and cardiovascular disease has led to new ideas about the impact of the prenatal environment—and the social, economic and nutritional factors that impact pregnant women—on adult health. These studies are revealing a new type of causal factor in disease – one that traces neither to the environment or DNA alone but to their intersection, manifesting as environmentally-triggered developmental plasticity in the structure and function of biological tissues, organs and systems. Because these influences involve changes in early developmental processes, they can have greater durability than the often transient influence that the environment has on adult biology. By tracing adult metabolic disease risk to prenatal and early postnatal origins, this research is generating new questions about the causes of human biological variation and health. The implications of the findings for understanding the origins of health disparities are potentially profound: African Americans not only have higher rates of CVD as adults, but they also have a higher burden of the antecedent condition of lower birth weight – an early life health disparity believed to trace in part to factors like stress and discrimination experienced by the mother during pregnancy and across her life-course. Thus, in addition to the better-appreciated chronic and cumulative health impacts of social environments, there is a strong rationale to consider a developmental contribution to the pattern of adult health disparities.

In this paper, we develop an epigenetic model of race-based differences in health and biological function, building from new understandings of the developmental and epigenetic basis for environmental influences on biology and disease risk. We first review evidence that early environments have lingering effects on adult biology and health in humans, and describe current understanding of the developmental and epigenetic mechanisms that help explain these associations. We then propose a model to help account for the presence of health disparities between socially constructed race groups, with a specific focus on the most prominent and well-studied US health disparity: the disparate rates of metabolic and cardiovascular diseases among US blacks and US whites.

BACKGROUND

Early environments and adult health

For the past two decades, evidence has been accumulating that stress, prenatal nutrition and other early life factors can influence risk for adult cardiovascular and metabolic diseases. Starting in the late-1980s, David Barker and colleagues at Southampton University published a series of papers showing that the risk of dying from CVD, or of suffering from conditions that precede CVD like hypertension or diabetes, is higher among individuals who were lower weight at birth (48-50). Although studies had previously found evidence for relationships between

deprivation during childhood and higher subsequent adult mortality rates (51, 52), the Southampton group was the first to link these associations to a biological marker that hinted at possible mechanisms to account for them.

Building from the assumption that a baby born small had been poorly nourished prior to birth, they proposed that these relationships were the outcome of adjustments made by the fetus in response to a compromised intrauterine nutritional environment. They reasoned that a fetus faced with undernutrition would not only slow its growth rate to reduce nutritional requirements, but might also modify the structure and function of organs and systems involved with metabolism and physiology, with effects that could linger into adulthood to influence risk of developing chronic disease. Such durable alterations to developmental biology in response to early environments have been described as developmental “programming” (53, 54) or “induction” (55).

The hypothesis that adult metabolism, biology and disease risk could be “programmed” by prenatal nutrition was greeted with skepticism (56, 57), since most early studies merely linked adult health characteristics with birth weight data recorded in birth records and largely ignored other aspects of the social environment, such as socioeconomic status, that might account for the associations (56, 57). Nearly two decades of research have helped push the field beyond this initial skepticism, and the “developmental origins of health and disease”, or DOHaD as it is now called, is a well-established area of study in fields like medicine, public health and anthropology (58, 59). Hundreds of human studies have now replicated findings of developmental programming, many incorporating longitudinal data on a wider range of lifestyle and environmental influences that might confound associations with birth size. These studies find that smaller birth size predicts higher blood pressure (reviewed by (60)), insulin resistance and diabetes (61, 62), abnormal cholesterol profiles (63), an “android” or abdominal pattern of fat deposition (64), and an elevated risk of suffering or dying from CVD (65, 66). Conditions experienced during infancy and childhood have also been shown to predict adult biological and health outcomes. Not unlike birth size, small size in infancy is also associated with higher CVD risk in adulthood, while breastfed infants have lower rates of hypertension, obesity, and diabetes as adults (67, 68). There is also evidence that prenatal and postnatal exposures interact to influence adult health. For instance, being born small but then experiencing rapid weight gain after birth, especially during childhood, predicts the same constellation of adult diseases (69, 70).

While genetic factors account for roughly 40% of birth weight variation in most populations (71), the rest is determined by maternal influences like nutritional status, exposure to stress, or other factors influencing blood flow to the endometrial lining or placenta (72). Given the ambiguities of interpreting birth weight (73), animal model research, which allows the researcher to modify a single aspect of the environment while holding other factors constant, has proven critical to the field gaining wider acceptance. Animal work in the DOHaD literature has confirmed that factors that influence prenatal nutrition and the conditions of the intrauterine environment can lead to physiologic and metabolic changes in offspring that linger into adulthood. For instance, restricting the nutritional intake of pregnant rats, mice, or sheep, or directly restricting blood flow (and thus nutrient transfer) to the fetus increases postnatal blood pressure, cholesterol, abdominal fat deposition, and diabetes risk in offspring (reviewed by (74, 75)).

Maternal psychological stress during pregnancy leads to a similar constellation of biological changes and disease risk factors in adult offspring. The fetus is normally shielded from exposure to stress hormones produced by the mother’s body by an enzyme (11- β HSD) that

is expressed by the placenta where it converts the active form of the hormone (cortisol in humans) to its inactive form (cortisone). This buffering capacity can be exceeded when the mother is stressed, leading to fetal exposure to maternal stress hormones. This in turn can contribute to reduced birth size by directly reducing fetal growth rate. Although the pathways are not fully understood, it can also influence the stress hormone-related cascade that triggers parturition, leading to early pregnancy termination (76). This fetal exposure to excess cortisol induces a similar suite of biological changes in offspring as are observed with dietary restriction, including an elevation in blood pressure, stress reactivity, abdominal adiposity, insulin resistance, and other precursors of diabetes and cardiovascular disease (77). Thus, prenatal stress—whether nutritional or psychosocial in origin—shapes a wide range of traits that influence future risk of developing cardiovascular disease, including how the body manages and distributes glucose and lipids, regulates blood pressure, and responds to stress.

Phenotypic “memory”

The durability of these effects raises the question of what biological mechanisms underlie them: if early environments influence adult biology and health, where in the body are the “memories” of these early experiences stored and maintained? Several types of mechanism are well-documented, all of which demonstrate axes of biological variation that are independent of one’s genotype. The first and most straight-forward involves a change in growth of a tissue or organ, as reflected in the change in size or cell number. As one well-documented example, the kidneys of prenatally-undernourished individuals tend to be smaller and to have fewer nephrons, making them more prone to hypertension and renal failure later in life (78, 79).

In addition to modifications in cellular growth, research is highlighting the importance of processes collectively described as “epigenetics” to many developmental changes induced by early environments. Although ascribed with numerous meanings since Waddington (80) coined the term in 1942, *epigenetics* is increasingly being reserved for the study of processes that modify patterns of gene expression without changing the nucleotide sequences of the DNA (81). The genome is inherited at conception and, other than relatively rare somatic mutations acquired during cell division, remains unchanged in most body cells across the lifecycle. The “epigenome”, in contrast, is a product of that genome interacting with the environment, and can be viewed as the molecular basis for cellular differentiation and development over the lifecourse (Fig. 1).

While growth represents an increase in body size owing to the expansion of the number of cells, development involves the gradual commitment of these expanding cell lineages to the various functionally-distinct cell types present in the mature organism, and the organization of these cells into tissues, organs and systems. Part of what distinguishes cell lines from each other, and what underlies their differences in function, is which of the original full palette of genes present in the genome are silenced, and thus are incapable of being expressed to build its specified protein within that cell (82). Through a complex series of bifurcations at which new patterns of gene silencing are acquired, the single totipotent “stem cell” formed at conception is capable of creating a body with roughly 200 cell types that vary in structure and function, despite the endowment of each of these daughter cells with an identical genome (82).

The epigenetic code

Unlike the nucleotide bases that form the genetic code, the epigenetic code predominantly involves chemical modifications to the structure of the chromatin that scaffolds

the DNA within the chromosomes. If fully stretched, the chromosomes in a single human cell would be roughly 6 feet in length, and thus, a complex process of folding is required to package the complete genome into each cell nucleus where the genes reside and are expressed. In the nucleus, chromosomes must be unwound locally to allow transcription factors to access a particular gene. How the DNA is packaged within the chromatin influences how easy or difficult a gene is to access and thus, whether and how much it may be expressed in that cell. Epigenetic markings have been described as “volume controls” for genes.

An important class of mechanisms of epigenetic gene silencing involves localized chemical modifications to the chromatin and its constituents, which alters how tightly the DNA is packaged in the region of specific genes. The attachment of an extra methyl group (methylation) to so-called “CpG islands” (regions of DNA rich in cytosine and guanine linked by a phosphodiester bond) within the promoter region of a gene typically impedes expression of that gene in that cell (83). The histone proteins that the DNA fibers are wrapped around can also be modified to alter the tightness of DNA packing, and thus the accessibility of that stretch of DNA to enzymes and transcription factors. Methylation of the histone generally impedes gene expression, whereas acetylation loosens the chromatin and promotes gene expression. Although more commonly implicated in cancers than metabolic diseases, another epigenetic mechanism involves so-called “small RNA” or “microRNA” (84) which are produced in large quantities in the cell nucleus. Although not transcribed to make proteins themselves, they block transcription and expression of other genes in a gene-specific fashion (RNA interference or “RNAi”), thus providing another way that gene expression can be modified within specific cells or cell lineages.

Epigenetics and adult health

Current research is showing how environmental factors can modify epigenetic processes, thereby affecting epigenetic marks and downstream patterns of gene expression in specific cells and cell lineages. These effects help explain how early life exposures, such as prenatal nutrition or stress, can induce a phenotypic “memory” that lingers into later ages to influence adult physiological function, health and risk for disease (85-87). Recent experimental studies in animal models demonstrate how epigenetic markings in offspring may respond to maternal factors like diet (88) and rearing behavior (89). In pregnant rats, protein restriction during gestation reduces methylation of the promoter region of the gene that codes for the glucocorticoid receptor (GR)—the receptor that recognizes and responds to the stress hormone cortisol (a glucocorticoid)—in offspring liver cells. Because methylation impedes access of transcription factors to the gene’s promoter region, the reduced methylation triggered by this dietary intervention increases expression of the GR gene, thus increasing the number of receptors expressed in the liver. This results in an amplification of the liver’s metabolic response to stress hormones, for example increasing expression of the downstream gene product PEPCK - the rate-limiting enzyme in glucose production (gluconeogenesis) (90). In this particular animal model, the nutritional experiences of one generation during pregnancy (the pregnant rat dam) influence how the offspring regulate and produce glucose in response to stress as adults.

In yet other instances, the effect of early environments can linger beyond adulthood to be passed on to future generations. Such examples of epigenetic inheritance can occur through several types of pathways (86, 91). There is evidence in some cases that epigenetic markings of germ-line DNA are not erased at fertilization and are thus present in sperm or egg at conception (92, 93). In females, an early rearing environment can also have a lingering effect on adult biology or behavior that replicates the same early rearing environment in the next generation

(94). When the establishment of epigenetic settings in offspring cells is sensitive to environmental exposures during the period of direct dependence on the prior generation, this can recapitulate a pattern of epigenetic marks in offspring in the absence of direct transfer of those marks through sperm or egg.

One well-studied example is rearing style in lactating rats (89, 95). Pups reared by indulgent mothers exhibit changes in methylation of the glucocorticoid receptor gene in specific hippocampal neurons involved in regulating the stress response. This has the effect of reducing reactivity and anxiety in offspring, and encourages them to adopt a similarly-indulgent rearing approach with their own offspring (the grandoffspring). Cross-fostering shows that this effect is not genetic, and the effect is reversed by chemically blocking epigenetic marking showing that it is not simply a learned behavior (89). This study illustrates how a maternal phenotype can construct a rearing environment that tends to replicate the same phenotype in the next generation, operating not through genes or learning, but through epigenetic pathways.

The emerging understanding of the epigenetic mechanisms that build the phenotype represents a revolution in biology that is rapidly gathering momentum (96, 97). Processes such as promoter region methylation reveal why knowing an organism's genotype—the genes inherited by the totipotent zygote at conception—is merely the first frame in the story of how the phenotype is eventually built. An appreciation for the importance of epigenetic processes helps clarify the generally poor results of attempts to identify susceptibility genes for diseases involving complex systems and traits (98).

These findings are helping to reframe the study of biology and health as lifecourse phenomena, with adult outcomes contingent upon environments experienced early in the lifecycle and even by prior generations. By linking maternal experience with fetal biology, this literature is also showing how stressors, such as imbalanced nutrition or psychosocial stress, can perpetuate a certain pattern of changed biological settings in offspring, with effects on such functions as glucose metabolism, blood pressure regulation, fat deposition and the physiologic response to stress. This field is thus blurring the classic dichotomy between genes and environments by showing how environments can have durable effects that linger into adulthood and in some cases may even be passed on to future generations.

THE MODEL

The adult cardiovascular diseases in which epigenetic and developmental processes play a critical role are the very ones that exhibit the most pronounced disparities across racial groups, calling into question simple assumptions about genetic bases for these patterns of difference. As we now review, an epigenetic origin for race-based US health disparities is suggested by the following observations: 1) as is true for a wide range of human populations, birth outcomes are important predictors of adult cardiovascular health for African Americans (AA); 2) African American mothers have higher rates of low birth weight births than white mothers; 3) this racial disparity in birth outcomes is linked to environmental, and particularly psychosocial, factors, and 4) there is evidence that these patterns could have multi-generational consequences.

Birth weight and adult AA health

The finding that low birth weight is associated with subsequent development of adult metabolic and cardiovascular diseases has been widely replicated in populations across the globe (63, 66, 99-105). While comparably few large studies have been conducted among diverse US populations, findings have generally shown that the effects of prenatal environments on African

American health are in agreement with expectations from other populations. Several small US studies have shown that lower birth weight predicts higher blood pressure and early signs of diabetes in older African American children and adolescents (106-108), as well as other related cardiovascular conditions, such as end-stage renal disease, in adults (109). Findings from larger, population-based cohort studies have demonstrated the most consistent evidence for the effects of birth weight on subsequent health among African Americans. In the well-characterized Bogalusa Heart Study, birth weight is inversely related to later systolic and diastolic blood pressure in adult African Americans (110, 111). Biracial analyses from that study suggest that for some cardiovascular risk factors, such as blood pressure, cholesterol levels, and insulin resistance, birth weight may be a stronger predictor for African Americans than for whites (111, 112). Thus, as for other US and global populations, and consistent with experimental findings in animal models, lower birth weights predict elevated future adult risk for adverse cardiovascular outcomes in African Americans.

Lower AA birth weight

It is well established that African Americans have lower average birth weights than US whites. National data show that rates of low birth weight deliveries are twice as high among blacks compared to whites, and very low birth weight births (<1500 g) are 2.69 times more common among blacks (2, 113). This pattern of racial disparity is true for both main categories of low birth weight: preterm (114) and small for gestational age (SGA) births (115). The racial disparity in birth outcomes has been documented for several decades and has shown no signs of significant improvement during that time (114, 116).

Social origins of AA birth weight

Given the association of birth weight with adult cardiovascular diseases across US populations, finding the cause of the lower average birth weights of African Americans compared to other demographic subgroups is a critical question. Like other health disparities generally, hypotheses tend towards either genetic or environmental explanations. While a genetic cause is a theoretical possibility, there is no evidence that genetic differences between groups explain these inequalities, and, as we discuss below, epidemiologic evidence is difficult to reconcile with this interpretation.

Because maternal stressors and the passage of stress hormones across the placenta can lead to both preterm birth and fetal growth restriction (117), research has examined the contribution of psychosocial stress to low birth weight and preterm delivery in African Americans. Several epidemiologic studies have found that potentially stressful life conditions and specific measures of psychosocial stress are associated with increased risk for both preterm birth and fetal growth restriction in black mothers (118). Higher exposure to stressful life events among African American mothers is associated with a higher risk for preterm births and lower birth weight babies (119-123). Additionally, psychological and emotional correlates of stress, such as symptoms of depression and anxiety, have been linked with poorer birth outcomes for African American women (119, 120, 124).

Several factors related to racial and economic inequality in US society have also been found to predict adverse birth outcomes. Factors related to socioeconomic status, such as income, education, and access to prenatal care, which tend to be lower among African Americans, are related to birth outcomes for US blacks in some studies (118, 125). Exposure to racial discrimination (126-128), residential segregation (129, 130), and neighborhood-level poverty

(131, 132) have all been linked with higher risk for low birth weight deliveries. Racial discrimination in particular has been shown to confer a two-fold increased risk, or higher, for poor birth outcomes (120, 127, 128), and in one study that pooled a multi-racial sample this accounted for a substantial portion of the observed racial difference in preterm deliveries (127). Together these findings suggest that social factors, especially those relating to the experience of stress and inequality, contribute to the lower average birth weights in African American pregnancies.

Further evidence for an environmental, rather than genetic, cause of the lower birth weights of African Americans comes from studies of intergenerational trends of birth outcomes. A non-genetic intergenerational influence on fetal growth has long been appreciated in the medical community (133, 134). Maternal fetal growth rate is among the strongest predictors of offspring fetal growth rate (135, 136), and among survivors of the Dutch Famine winter, the *grandoffspring* of pregnant women who experienced the famine had reduced fetal growth (137). Given evidence for effects of the mother's early life and chronic experiences on the intrauterine environment that she provides offspring, women of the same "race" might be expected to give birth to larger or smaller babies, depending on where they were born and raised. There is in fact good evidence for such differences.

Many studies have compared the birth weights and perinatal health of recent immigrants to the US (who were born overseas) to their racial or ethnic counterparts born in the US (138). These studies are remarkably consistent in their findings. Black newborns in general have higher rates of low birth weight (LBW), preterm delivery (PTD) and neonatal mortality. However, these differences are greatly reduced among black offspring born to foreign-born mothers. For instance, in one study of nearly 2.5 million US deliveries, foreign-born black women were 25% less likely to give birth to a LBW baby compared to their US-born counterparts, while there was no difference in birth outcome by natality among whites (139). Several other studies have revealed similar findings, showing that foreign-born blacks giving birth in the US have rates of LBW that are closer to those of US whites than US blacks (140-142).

One study of Illinois birth records not only compared birth outcomes in foreign-born and US-born blacks but also linked these data with information on birth weights across several generations of offspring subsequently born in the US. The patterns present in the first generation were similar to those described above: in contrast to the lower birth weights of US blacks, foreign-born blacks were found to have a birth weight distribution essentially identical to that of US whites upon arrival (143). However, this equivalence was short lived. Among subsequent generations born in the US, the birth weight distribution of the offspring of African immigrants shifted to the left (**Fig 2**), en route to a convergence with the lower African American mean (144). The findings among the European immigrants in this study showed the opposite pattern: their birth weights were originally *lower* than the US white mean, but *increased* with each generation born in the US.

It goes without saying that these opposing biological responses were far too rapid to be due to changes in gene frequencies (145). Instead they reveal that living in the United States has different implications for the intrauterine environments that US blacks and US whites experience prior to birth, as reflected in differences in fetal growth rate, prematurity and birth weight. Regardless of where individuals emigrate from, after several generations the birth weight distribution of their descendents comes to resemble that of their US ethnic counterparts. This convergence is strong evidence that the widely documented black-white difference in birth weight is not due to genes (144, 146).

Transgenerational impacts

In addition to the links between maternal stress and the offspring's future health, there are several pathways through which the effects of a stressful intrauterine environment could be perpetuated, and might even be amplified, across generations. The most straight-forward explanation for a perpetuation of risk involves a continuity of environments. Given the persistence of racial institutional discrimination and economic inequality in US society (9, 147-149), low birth weight infants are likely to experience many of the same psychosocial stressors as adults that their parents did. Thus women who were themselves born small will likely be at high social-environmental risk for delivering low birth weight offspring as a result of the perpetuation of a similar social and economic environment.

It is important to note, however, that the "environment" that a fetus experiences is an expression of maternal phenotype. This opens up possibilities for a mother's own stressful prenatal experience, as reflected in her having been born small, to influence the intrauterine developmental environment she provides for the next generation. Hypertension during pregnancy, for instance, elevates risk for having a preterm birth or low birth weight delivery by as much as two to three times (150-155). Similarly, maternal insulin resistance, hyperinsulinemia, and diabetes encourage the development of a similar state of weight gain and metabolic dysregulation in offspring (156-159). Heightened stress reactivity can not only restrict fetal growth and lead to premature delivery, but can also have direct effects on the development of the fetus's HPA (hypothalamic-pituitary-adrenal) axis. By changing future adult metabolism, the intrauterine environment of one generation (the mother) can influence the intrauterine environment created for her offspring, thus perpetuating certain biological or metabolic states, albeit in a fading fashion, across multiple matrilineal generations (**Fig 3**).

Summary

The evidence above describes the components of a developmental model of race-based health disparities. Few US studies with high quality birth weight data have had sufficiently large samples across race/ethnic groups to empirically test the contribution of birth outcomes to adult racial health disparities. However, a recent analysis of data from the biracial Bogalusa Heart Study cohort has provided strong support for the developmental origins of a key racial health inequality. In this study, the black-white difference in hypertension – one of the most common and widely-studied racial health differentials - was no longer significant after models adjusted for the effects of birth weight (160). This is one of the rare studies that have "explained away" the race disparity in an adult cardiovascular disease risk factor. It is important to note that no genetic factors have been shown to do this, despite considerable effort (98).

DISCUSSION

An epigenetic model of health disparities

The epigenetic and developmental processes that we describe shed new light on the health disparities debate. In the current polarized discourse over health inequality, some interpret the inability of adult socioeconomic factors to account for racial disparities in disease burden as evidence for underlying genetic differences (e.g. (42)). This reasoning can be critiqued for ignoring the substantial residual impact of social and environmental factors not captured in the often low resolution measures employed in epidemiologic research (43). The model and presented here adds a new layer to this critique. As the epigenetic research reviewed here

illustrates, measuring the biological impact of social forces solely at the level of the adult phenotype misses important developmental and epigenetic pathways that likely contribute to racial health inequality. A genetic interpretation of the residual race effect problematically conflates biology with genes, while it ignores evidence that social factors can have durable lifecourse and intergenerational effects on health. Whereas group membership and continental race are poor predictors of genetic variation, these same categories are directly related to the social and structural manifestations of inequality that impact biological systems. A wealth of evidence now shows that the social and economic experiences of race have profound influence on adult health and, beginning in childhood, can have effects that are both chronic and cumulative in their impact. Our model builds upon this social constructivist perspective by highlighting specific developmental pathways through which these same social factors become embodied during early, critical periods in development, with impacts that extend into adulthood and at times even across generations.

Some may be tempted to interpret these new findings as deterministic; implying, for instance, that biological fates, though not decided by genes, are fixed by early developmental processes over which we have no control. Some may also interpret these findings as stigmatizing for pregnant women, shifting blame onto mothers for the long-term health consequences of stressful prenatal environments. The deleterious effects of some maternal behaviors on offspring health, such as smoking or excessive drinking during pregnancy, have long been appreciated (161), and indeed, this literature broadens the scope of offspring health outcomes that might be adversely affected by such behaviors. However, the research reviewed here overwhelmingly points to factors that are symptomatic of structural inequality and discrimination rather than choice. The most important predictors of compromised birth outcomes include such factors as self-perceived discrimination, racism, and chronic stress (118, 127). These experiences are no more the ‘choice’ of the women who experience them than are the many other symptoms of racial discrimination that have been documented in US society, such as African Americans’ lower average incomes (147) and reduced job opportunities compared to whites with equivalent qualifications (162).

Our model points to social and economic change as key to addressing racial differences in disease burden, and underscores the need to implement these interventions across the lifecourse. In particular, this work opens up the possibility for new approaches to encouraging positive health states in future generations. Some sources of social inequality, such as racism, cannot be eliminated by legislation. But societies *can* legislate changes in public spending that benefit pregnant mothers, improve their access to adequate prenatal care and nutrition and help ensure that they are relatively buffered from stress while pregnant and lactating. Promotion of breastfeeding and longer and more secure maternity leave, for instance, are examples of policies that could have long-term health benefits for future generations, and ease race-based health differentials operating through developmental pathways.

A better understanding of the epidemiology of epigenetic processes will be critical to developing effective interventions (163). Although birth weight is routinely collected in epidemiologic research and is thus widely available for such studies, it is at best a highly-general and non-specific indicator of genetic, epigenetic, and other factors. Future research will benefit from incorporation of more nuanced approaches to quantifying stress and other social, cultural and material processes that could influence the prenatal nutritional and endocrine milieu. For instance, ethnographic approaches to understanding the social and cultural contexts of stress may

provide improved insights into the causes and impacts of stress in different communities and demographic subgroups (164, 165).

Additionally, while we have emphasized the importance of the prenatal period, the impact of stress, nutrition and other social-environmental exposures on developmental biology are by no means limited to fetal life. Infancy, childhood, and adolescence are all critical developmental windows during which epigenetic modifications in gene expression and tissue and organ function take place. As mentioned, there is evidence that breast feeding confers protection against developing obesity, diabetes and cardiovascular disease (67, 68). The quality of the rearing environment and emotional attachment can have lasting effects on reactivity of the stress hormone (HPA) axis (166), and are influenced by factors like maternal emotional well-being (167). The pace of growth during childhood, and especially rapid weight gain, can influence adult risk for metabolic and cardiovascular diseases (64, 69). Additionally, brain regions linked to emotional processing and stress reactivity, as well as other aspects of the HPA axis, undergo critical structural development during adolescence (168, 169), suggesting that this age is also an important period during which programming of the physiologic stress response can take place.

Significantly, this flexibility of the phenotype during later developmental periods has been found in animal models to allow for partial or complete reversal of epigenetic responses to prior stressful environments. Recent research has shown that environmental enrichment during adolescence can reverse some of the deleterious effects of early life epigenetic programming (170-172). Similarly, rat models have shown that injection of neonates with leptin (a body fat-derived hormone that signals energy status) completely reverses the adverse metabolic changes triggered by prenatal protein restriction (173, 174), while orally-administering leptin in suckling rats (perhaps mimicking lactation in a well-nourished mother) protects the offspring against developing obesity later in life (175). These studies demonstrate the continued flexibility of biological systems into later stages of development, and hold open the possibility that strategies can be developed to modify disease risk and reverse epigenetic influences established prior to birth. Thus, while the social consequences of race can have durable effects on biology and health, we stress that “durable” need not equate with “permanent”.

The mechanisms of developmental plasticity and epigenetic modification that we describe pose a fundamental challenge to the genetic race concept. Not only are traditional racial identities poor predictors of gene frequencies, but developmental and epigenetic processes illustrate how genes do not determine our biological fates in any simple fashion. Genes code for ranges of biological possibility, with specific phenotypic outcomes often constrained and dictated by the environment. The literatures that we review demonstrate some of the pathways through which these environmental realities can become embodied, contributing to the perpetuation of linked patterns of early and late-life health disparity. Our model should not be understood as replacing genetic race with a concept of epigenetic race; instead, it shows how social environments, defined along lines of constructed racial identities, can drive developmental processes, thereby becoming embodied as biological patterns that influence health and disease. Debates about the causes of racial health disparities have traditionally aligned with the classic model of disease causation, which emphasizes the contrasting roles of genes and social environments, which are recognized as having both transient and cumulative impacts on biological status and health. The research that we review reveals that this model is incomplete, and must be broadened to account for the more durable role that environments have on biology and health when experienced early in the lifecycle.

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Figure Legends

Fig 1. Schematic illustrating the role of epigenetic gene silencing in the differentiation of an initially totipotent stem cell (the zygote) to ‘committed’ daughter cell lineages. Gray horizontal lines indicate genes capable of being transcribed to produce a protein, whereas black lines are genes that have been silenced by epigenetic modifications. The pattern of gene silencing is heritable to daughter cells, leading to the eventual commitment of cell lineages to specialized cell types (e.g. neurons, muscle cells) as epigenetic marks are accumulated. The focus of classical genetics on modeling the determinants and evolutionary change in gene frequencies is concerned with the genes inherited at conception (the genome), while epigenetics focuses on the narrower pattern of gene silencing and expression in the cells of specific tissues, organs and systems (the epigenome). Although the patterns of epigenetic gene silencing are largely regulated themselves by genes, environmental exposures can modify the cellular pattern of epigenetic gene silencing in specific cells lines during growth and development, which partly accounts for the durable effects that early environments have on later biology and disease risk.

Fig 2. Schematic illustrating the intergenerational change in birth weight among recent African immigrants to the US. The first generation in the US, born to foreign-born mothers, has a mean birth weight and birth weight distribution comparable to that of US whites. Second and third generations born in the US have lower birth weights, moving closer to the African American mean. Not drawn to scale (after data in Collins et al 2002).

Fig 3. Model showing the intergenerational transmission of disease states operating through the reciprocal effects of a stressful intrauterine environment on future adult metabolic state, and future metabolic state (in females) on a stressful intrauterine environment in the next generation. The experience of chronic stress can thus have acute and cumulative adverse effects on the present generation, and among women, lingering effects on future generations of offspring operating through durable epigenetic changes (modified after Drake and Walker 2004).

Fig. 1

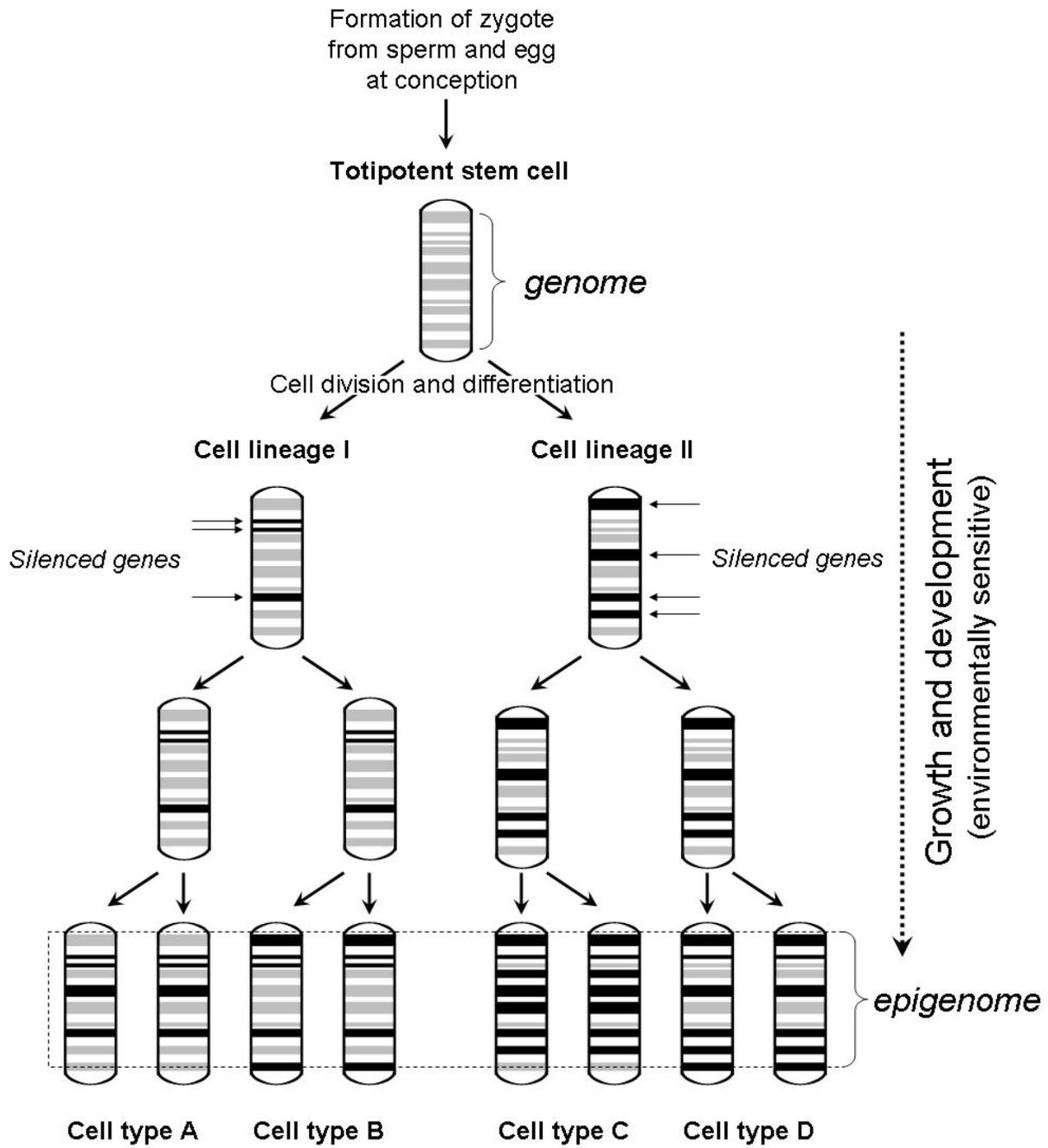


Fig. 2

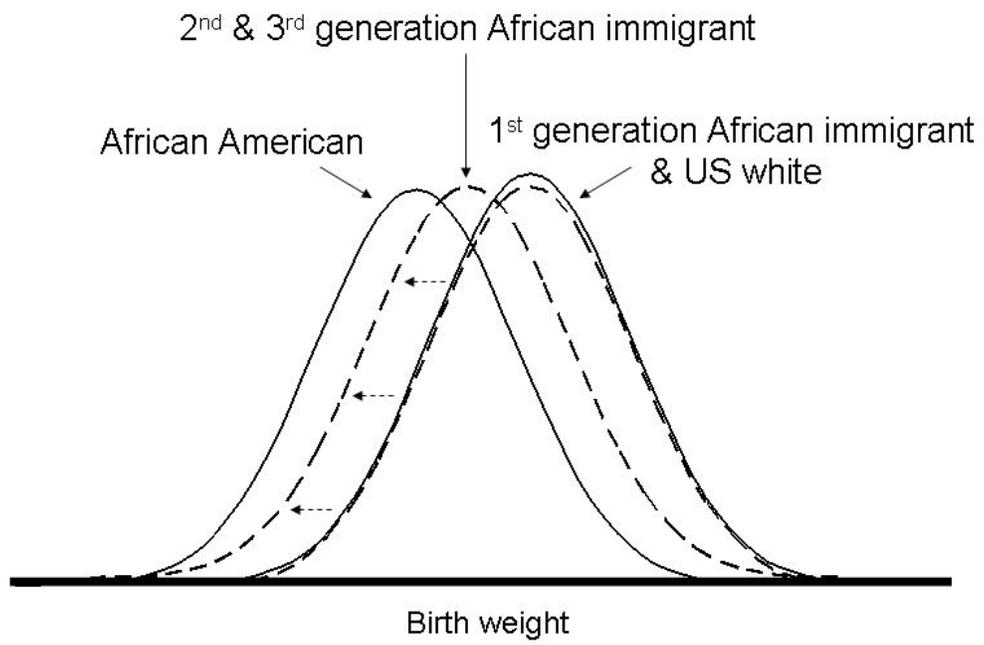


Fig. 3

