Race, Skin Color and Genetic Ancestry: Implications for Biomedical Research on Health Disparities

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Abstract

Defining race continues to be a nemesis. Knowledge from human genetic research continuously challenges the notion that race and biology are inextricably linked, with implications across biomedical and public health disciplines. While it has become fashionable for scientists to declare that race is merely a social construction, there is little practical value to this belief since few in the public believe and act on it. In the U.S., race has largely been based on skin color and ancestry, both of which exhibit large variances within communities of color. Yet biomedical studies continue to examine black / white group differences in health. Here we discuss why using race in biomedical studies is problematic using examples from two U.S. groups (African and Hispanic Americans) which transcend 'racial' boundaries and bear the burden of health disparities.

Keywords: genetics, race, skin color, health disparities

Race is an accepted socio-cultural concept that lacks supportive genetic evidence. When race is used in biomedical research it is often self-reported (self-identified race/ethnicity or SIRE), and used as a proxy for measurable indicators of group differences such as diet, socioeconomic status, cultural lifestyle and biology (Figure 1). Reducing each of these contributors into a composite called race precludes independent analysis of important variables such as genetics, which vary significantly within populations.

Human genetic variation is structured by the history of our species. The pattern of this structure however is not bounded or discrete, but continuous, resulting from the demographic history of populations which include such forces as natural and social "mate" selection. Our knowledge of human genetic variation has grown enormously over the past few decades. Single-nucleotide polymorphisms (SNPs) are the most common form of DNA variation in the human genome. At present, there are more than 10 million SNPs in the human genome (Crawford, Akey, and Nickerson 2005; Hinds et al. 2005). A large fraction of these SNPs are

found at a frequency less than 5% and thus are private or common in only a single population (Hinds et al. 2005). Genetic polymorphisms, such as SNPs have been used to explore how genetic variation is structured within and between human populations. Allocating individuals into clusters based on genotypes which reflect shared ancestry is possible depending on which genetic markers are used (Collins-Schramm et al., 2002; Rosenberg et al., 2002; Rosenberg et al., 2003; Shriver 2004; Tang et al., 2006). The use of ancestry informative markers (called AIMs), which have large allele frequency differences between continental groups such as Western Europeans and West Africans and are powerful for estimating biogeographic ancestry, is becoming more and more popular among biomedical researchers who understand that self-reported race is not a strong proxy for biology (Shriver 2004).

Since a large fraction of genetic variation may be localized to particular geographic regions much attention has been focused on whether geographic ancestral origins contributes to the

differential distribution of disease and mortality (Kiefe 2002). Too many studies continue to utilize sociopolitical constructs that are inappropriate for investigations on genetic contributions to the etiology of complex disease, drug response, and more importantly, health disparities. While race may be an important determinant to monitor health status and health care quality (LaVeist 1994) it lacks biological integrity. In fact, the use of race to identify groups may confound biomedical studies. This is because race reflects deeply confounded sociocultural as well as biological factors, especially when one examines "Black/ White" differences. In 2003, age-adjusted mortality rates for Blacks exceeded Whites by 43% for stroke,

31% for heart disease, and 23% for cancer (CDC, 2006). In the U.S. population Blacks have the highest rates of obesity at 33% compared to 26% in Hispanics and 22% in Whites (CDC, 2006). Data on health insurance status also show inequalities among the ethnic groups. In increasing order of uninsured status, Blacks (18.5%), Hispanics (34.7%) and Native Americans (35.0%) are more likely to be uninsured than whites (16.0%) (CDC, 2006). It is not clear that these SIRE groupings are really social demographic groups in the U.S. In many cases the presentation of differences in health status across these groups suggest biological or "racial" differences and say little about social determinants.
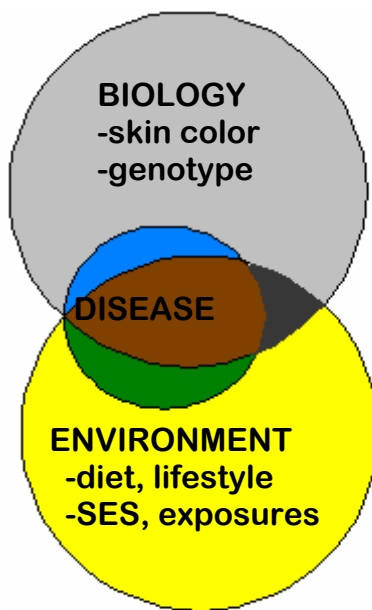

Figure 1
Race is a proxy for shared biology and environment. The Venn diagram depicts the relationship of biology, environment and disease. Disease is due to effects from biology, the environment, and the interaction of biology and environment.

Race in the U.S has largely been based on skin color and ancestry. Descriptions of African Americans and Hispanic Americans in much of the biomedical and social literature are

predicated on the assumption that people of African descent, no matter where they reside, constitute a biological race. Similarly, Hispanic Americans are grouped based on language. Of

course this would mean that genetic and phenotypic variation within this group is less than variation between this group and others (i.e., European Americans, etc.). Here we show the biological ambiguity of socially classified race using data on African and Hispanic Americans.

Genetic and Social Histories of African Americans

It is important to examine the genetics of African Americans within the context of the socio-political history of the U.S. African Americans are an extremely heterogeneous macro-ethnic group due to their unique population history (Jackson, 1993). While biologically, the U.S. is widely considered a melting pot of various ethnicities, the sociopolitical history however has fostered the black/ white dichotomy predicated on slavery, segregation, anti-miscegenation laws, and the Rule of Hypo-descent (one-drop rule). The vast majority of contemporary African Americans are descendants of enslaved Africans kidnapped and transported to America during the transatlantic slave trade from ~1619 to 1850. The sources of enslaved Africans encompassed a wide geographic range of coastal regions from Senegal to Angola and eastern Africa along the coast of Mozambique and Madagascar (Curtin, 1969). The systematic kidnapping of indigenous Africans led to significant differences in the ethnic and geographic ancestry of African Americans (Shriver and Kittles, 2004).

The African American population exhibits high levels of gene diversity for several reasons. The first reason is due to its African ancestry. The African continent is rich in biological diversity and is most likely the place of origin of modern humans. Studies have consistently shown that for most genetic systems, diversity for African populations is greater than that of non-African populations (Jorde et al., 1995; Jorde et al., 2000; Kittles and Weiss, 2003; Tishkoff and Williams, 2002). The second reason is its recent (within the last 400 years) admixture (gene flow) in North America with Europeans and Native Americans (Mays, Coleman, and Jackson 1996; Parra et al. 1998; Parra et al., 2001). It was estimated that by 1860 there were 4.5 million

people of African descent in the U.S., of which 600,000 were of mixed ancestry or "mulattos" (Frazier, 1957). The offspring of these matings between African Americans and other ethnic groups were considered African American due to the socially constructed classification system called the rule of hypo-descent or the "one-drop rule" (Harris, 1964) The one-drop rule was unique since it ignored the various degrees of admixture between populations in America. And since it was only applied to American Blacks, it increased even higher, the level of phenotypic and genetic heterogeneity that existed among early Africans in the America.

The pattern of biological variation among African American communities varies across geographic regions within North America, mainly because diverse populations of indigenous Africans were brought to different areas in North America during the period of enslavement. Also levels of gene flow from European and Native American communities varied considerably across different geographic areas of the country. Gene flow and the recent migrations of African Americans from rural to urban areas following World War II increased heterogeneity within the African American population. The extent of gene flow between various African American communities and specific non-African groups is strongly correlated with geographic region of residence (Jackson, 1997; Parra et al., 1998; Parra et al., 2001). This is important both from the historic and epidemiologic point of view.

The present use of AIMs to estimate ancestral contributions (continental) in admixed populations (Shriver and Kittles, 2004) has brought to focus the fluidity of genotypes and ancestry within traditional U.S. "racial" groups. Figure 2 details a map with estimates of the European genetic contribution in 23 African Americans communities from different geographic areas in the United States. These estimates are based on between 10-60 AIMs. Levels of European admixture in African American populations range from 3.5% among the Gullah sea-island community along the coast of South Carolina to 35.0% in Washington State. Several features of the geographic distribution in

ancestry are important to note. First there are significant differences in European ancestry between self-reported African Americans along the west coast versus African Americans in the deep south of the U.S. Differences are also observed between urban African Americans in the cosmopolitan north when compared to African Americans in the rural south (except for some cities like New Orleans, Louisiana which exhibit higher levels of European genetic

ancestry ~22.5%). The striking differences in European admixture between the pacific NW and the rural SE are mainly due to differences in social norms, mate-selection and historical interactions between African Americans and European Americans in those communities. The social histories not only differed across African American communities but they also play a role in the genetic and environmental background of the communities and likely health status.
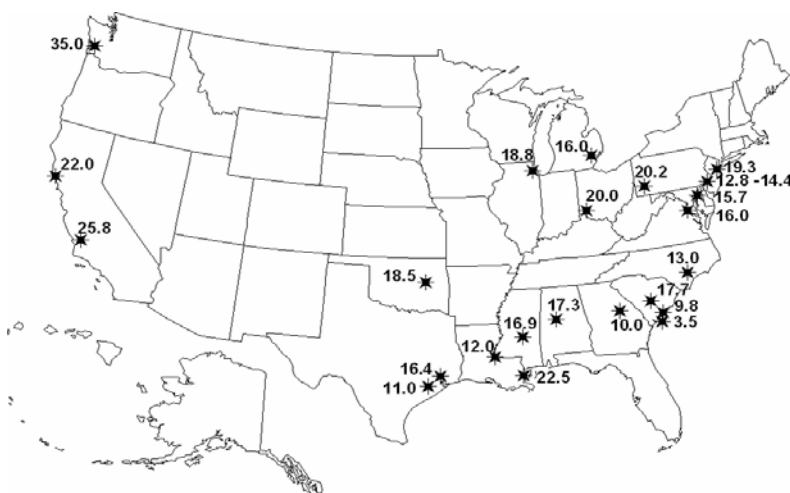

Figure 2
European genetic contribution in African American populations living in different geographical areas of North America.
[Data from Parra, 1998; Parra, 2001; and Kittles et al. unpublished.]

The observed distribution of ancestry should be interpreted in terms of well-known historical and demographic events that have played an important role in African American history (see Para et al. 1998 and 2001 for details). Research using sex-based lineage markers, such as mitochondrial DNA, have observed that, for African Americans along the east coast as well as in most of the Caribbean, there is low Native American genetic ancestry (Parra et al. 1998; Parra et al., 2001). Similar estimates have been observed for European maternal lineages (mtDNA) within the African American population. In contrast, over 30% of African

American paternal lineages (as estimated by the Y chromosome) are of European ancestry, thus most of the gene flow from European Americans into the African American population is male-directed (Kayser et al., 2003; Lind et al., 2007).

African American biological variation has been significantly shaped by periods of intermixture with non-African populations creating high heterogeneity, and selective pressures emanating from the unique and particularly adverse social, economic, and political conditions in the U.S. (Jackson, 1993). All of these factors likely contribute to health disparities.

The Hispanic Conglomerate
The term "Hispanic" has been coined mainly for governmental demographic purposes, and is generally employed to identify persons of Latin American origin or descent, living in the United States, who speak Spanish. Although this definition lumps together people with very different historical, cultural and genetic backgrounds, this classification has been widely used. Even though Central America, the Caribbean, and South America have been for centuries under the domination of the Iberian imperial powers (Spain and Portugal), they have had quite different regional histories, both before and after the Colonial period. Populations from three continents, North and South America, Europe, and Africa, have contributed to the formation of contemporary Hispanic populations. Our main objective here is to discuss the anthropological background of the three main Hispanic groups currently residing in the United States: Mexican Americans, Puerto Ricans and Cubans, which together makeup more than 80% of the total U.S. Hispanic population.

Each of these groups has been exposed to a particular set of experiences that have influenced their integration into mainstream society. Mexican Americans tend to be more generationally and socioeconomically diverse than other Hispanic groups due to their longer history in this country. Initially they became part of the U.S. as a result of the conquest of the Southwest, and later through continuous immigration from Mexico (Campa, 1979). As with Mexican Americans, the Puerto Rican migratory movement was essentially one of wage labor but unlike the former, which started out as an agricultural experience, Puerto Ricans concentrated in the cities of the Northeast since the very beginning. Even though Puerto Ricans are U.S. citizens by birth and their entry to the mainland is not regulated they have not been accepted more into the recipient society than Mexicans (Bean and Tienda, 1987). The Cuban case is quite different from those of the Mexican Americans and Puerto Ricans, mostly because the host society was more willing to accept political rather than economic refugees. Early waves of migrants consisted of individuals from

the upper and middle classes who were able to succeed economically in the new environment. As a result, Cubans have been the least segregated of the three Hispanic groups (Bean and Tienda, 1987). Following migratory waves included people of lower socioeconomic strata, younger and less well educated, elements that make the recent Cuban immigration more similar to that of other Hispanics.

According to Bean and Tienda (1987), three defining features of the Hispanic population are rapid growth, regional concentration, and diversity with respect to social, demographic and economic characteristics. The geographic distribution of this population shows a concentration of individuals of Mexican ancestry in the Southwestern states (Texas, Arizona, California, Colorado and New Mexico), Puerto Ricans are found generally in the Northeast (states of New York, New Jersey and Connecticut), while Cubans reside mainly in the state of Florida.

Mexican Americans show the highest Amerindian contribution of the three aforementioned groups. Soon after the Spanish conquest of Mexico, at the beginning of the 16th century, intermixture of the Spanish men with Amerindian women resulted in an increasingly important mixed population (Mestizos), and this admixture continued through the three centuries of Spanish domination in "New Spain", configuring the Mexican population both biologically and culturally. The majority of estimates have indicated an Amerindian component in Mexican Americans range between 30% and 40% (Bonilla et al., 2005; Bonilla et al. 2004; Bonilla, Shriver et al., 2004; Hanis et al., 1986; Merriwether et al., 1997). It is interesting to point out, as well, that some studies have shown an inverse correlation between Amerindian ancestry and socioeconomic status (Chakraborty et al., 1986; Mitchell and Stern, 1992). There was also a substantial African presence in the Mexican territory during the Spanish rule. Curtin (1969) has estimated the total number of West Africans enslaved in Mexico during the entire period of Slave Trade to be around 200,000. Their contribution to the Mexican gene pool, however,

has been estimated to be much lower than the European and Amerindian contribution, ranging from zero to 10% (Hanis et al., 1991; Lisker and Babinsky, 1986; Lisker et al., 1986).

In the Caribbean colonies (Cuba and Puerto Rico), the situation was very different from the mainland. The Native American population was far smaller there, and was decimated by slavery and disease very soon after the first contact with the Europeans. Nevertheless, the rate of admixture during the initial phases of the colonization was high enough to result in an appreciable genetic contribution (about 18%) from the Arawaks and Caribs, the original inhabitants of the Spanish Caribbean (Hanis et al., 1991; Lisker and Babinsky, 1986; Lisker et al., 1986). Another distinctive feature of this region is a significant African influence, which is also reflected in many aspects of the present societies of countries like Cuba, Puerto Rico, and the Dominican Republic. Enslaved west Africans were forced to work in the sugar plantations in large numbers, even outnumbering the population of European origin. Accordingly, the percentage of African genetic contribution in contemporary Cubans (20%) and Puerto Ricans (37%) is significantly higher than in other Hispanic populations (Hanis et al., 1991).

Genetic Ancestry, Skin Color and Why Self-Reported "Race" Does Not Work
The existence of genomic regions that differ significantly among human groups raises two important questions. Can we reliably allocate humans into ancestral groups according to genotypes? Most importantly, how much do genes within these divergent regions contribute to differences in health or health disparities?

The answer to the first question is yes (Bamshad et al., 2004). Recently 377 autosomal microsatellite loci in 1056 individuals from 52 populations were examined in order to explore human population structure (Rosenberg et al., 2002). It was found that within group differences accounted for 93-95% of genetic variation, while differences among groups represented only 5-7%. Without using prior information about the origins of individuals, these investigators observed six main genetic clusters, five of which corresponded to the major geographic regions (i.e., continents) with sub-clusters corresponding for the most part to individual populations. Does this mean that there are biological races? No, in fact a recent re-analysis of the Rosenberg et al. data revealed that when individuals are sampled homogeneously from around the world the pattern observed is one of gradients (clinal distribution) of allele frequencies rather than discrete continental clusters (Serre and Paabo, 2004).

The answer to the second question is still unknown. Using population genetic models we know that natural selection on disease variants can greatly influence the pattern of genetic variation across human populations depending on the geographic distribution of the selective pressure. An evolutionary framework for common disease would suggest that old genetic variants reflect ancient adaptations to the lifestyle of old-world populations. However, with changing environment and lifestyle these same variants now increase risk for common disease in modern populations (DiRienzo and Richard, 2005). Several examples of this have been shown for variants in the APOE and PPAR genes which influence risk for Alzheimer's disease and type 2 diabetes, respectively.

The traditional paradigm of using race (self or investigator described) as a proxy for ancestral background in biomedical research is slowly shifting given the heterogeneity that exists in U.S. populations. This is especially the case for research on African and Hispanic Americans which vary considerably for the reasons discussed in the previous section.

We have shown in past work that individual ancestry varies considerably within African American and Hispanic American populations. Figure 3 depicts a triangular representation of % individual ancestry using AIMs and a maximum likelihood estimation method (Shriver et al., 2003). It is clear that there is a wide range of individual ancestry values for each population. Notably, there is significant overlap in ancestry estimates between self-reported African Americans and European Americans. It is also

clear that there is not a significant amount of Native American ancestry in both populations. The diversity in genetic ancestry among individuals classified as Hispanic in the U.S. is quite broad. Higher levels of African ancestry are evident among Puerto Ricans than the other Hispanic groups in contrast to extremely high levels of Native American ancestry observed for Mexicans. Contrasting distributions in genetic ancestry among Hispanic populations has also been observed by others (Choudhry et al., 2005; Choudhry, Coyle et al. 2006; Choudhry, Burchard et al., 2006; Martinez-Marignac et al., 2007; Salari et al., 2005).
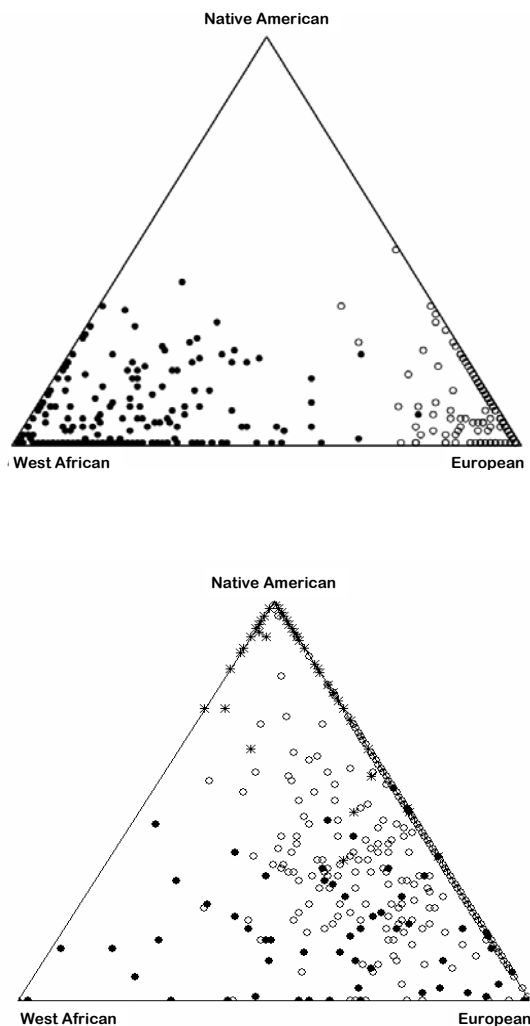
Figure 3

Triangular plots depicting individual genetic ancestry (%) from west African, European American and Native American parental populations. A) African Americans from Washington, DC (closed circles) and European Americans from State College, PA (open circles). B). Hispanics from San Luis Valley, CO (open circle), Puerto Rico (closed circle), and Mexico, City (star). [Data from Bonilla, 2005; Bonilla, 2004; Bonilla, 2004; and Shriver, 2003]

Understanding Genetic Ancestry has Broad Implications for Biomedical Studies

A popular approach to determining genetic effects on disease has been case-control association studies. However, while case-control association studies may be powerful for detecting the non-random association between an allele and a trait, they are prone to problems due to population stratification (PS) created by admixture (Chakraborty and Weiss, 1988; Lander and Schork, 1994). This is especially the case for the African and Hispanic American populations that due to their unique population histories represent a mixture of diverse ancestries. This problem is compounded when the disease of interest is more prevalent in one of the populations, as is the case with prostate cancer, cardiovascular disease (CVD), or type 2 diabetes. Any alleles that are more common among African Americans will tend to be associated with the disease, even if it is completely unlinked to the disease-causing locus.

Thus, in order to control for association error due to confounding many now introduce individual genetic ancestry as a covariate in genetic analyses. This approach has been used to limit spurious associations that are the result of differences in ancestral proportions (admixture). Statistical tests for association which adjust for individual genetic ancestry in order to control for confounding due to recent admixture are now becoming routine for biomedical studies on admixed populations (Bonilla et al., 2005; Chen et al., 2006; Hoggart et al., 2003; Kittles et al., 2006; Lamason et al., 2005; Peralta et al., 2006; Reiner et al., 2005; Salari et al., 2005; Shriver et al., 2003; Tsai et al., 2006; Ziv et al., 2006).

In addition, genetic ancestry has implications for pharmacogenetics. On our path towards personalized genetic medicine we have recently stopped unexpectedly at race-based therapeutics. The recent controversy surrounding the use of the drug BiDil in Blacks with heart failure is a perfect example of the need for understanding genetic background within the widely considered SIRE groups in order to effectively improve drug efficacy (Haga and Ginsburg,

2006; Sankar and Kahn, 2005; Taylor et al., 2004). SIRE was used as a surrogate for the basis of improved mortality in African Americans over European Americans. In fact it was a loose surrogate given that not all African Americans responded to the adjunct treatment. Interestingly, the clinical investigators stressed in their New England Journal of Medicine article that their trial using only African Americans, "represents a departure from the recent approach to the design of cardiovascular trials. Rather than studying a large heterogeneous population, we examined a specific population" (Taylor et al., 2004). They then stated that "A heterogeneous population may have substantial variations in genetic and environmental factors that influence disease progression and the response to therapy." These statements are completely opposite from what we know about genetic heterogeneity among African Americans. In the end, the BiDil fiasco represented a clear departure off the path of personalized medicine back to the traditional paradigm of race.

This is particularly important because drug efficacy is influenced by genes and environment not skin color. In American society, skin color has been used to demarcate race. Interestingly enough, while skin color is strongly hereditable and influenced by ancestry, the correlation with genetic ancestry varies considerably across communities of color and should not be used as a proxy for ancestry (Parra, Kittles, and Shriver, 2004). For instance, Figure 4 shows the correlation between skin pigmentation and West African ancestry in African Americans from Washington, DC. Increasing West African ancestry is correlated with increased skin pigmentation. However, only about 21% of the variance in skin color is due to West African ancestry. We should note that among African Americans with 100% West African ancestry there is still a wide range of skin color exhibited. This is not surprising given that throughout West Africa there exists a wide range of individual variation in skin pigmentation. In addition, the correlation between skin color and ancestry varies considerably across populations (Parra, Kittles, and Shriver 2004).
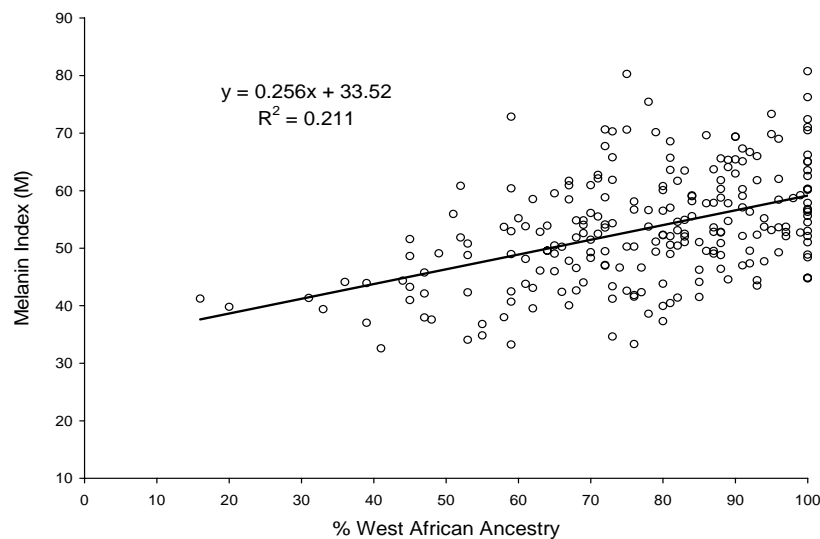
Figure 4
Relationship between skin color (M index) and west African genetic ancestry (%)
in African Americans from Washington, DC.

Skin color is a complex trait that is influenced by the interactions of multiple genes (McEvoy, Beleza, and Shriver, 2006; Sturm, Box, and Ramsay, 1998). The correlation between race (based on skin color) and disease is largely due to the interaction of the phenotype (skin color) with society (racism).

Researchers have examined both genetic and environmental explanations in an attempt to understand the complex relationship between skin color and disease (Davis, 2005; Dressler, Balieiro, and Dos Santos, 1999; Frisancho et al., 1999; Gomez, 2006; Gravlee and Dressler, 2005; Gravlee, Dressler, and Bernard, 2005; James 1999; Mosley et al., 2000). It is clear that cultural elements cannot be overlooked or separated from genetic and environmental explanations, although these factors are very difficult to measure or quantify. A study conducted on hypertension and skin color in Puerto Rico by Gravlee et al. (2005) attempted to develop such a tool using skin reflectance spectrophotometry and psychosocial instruments (Gravlee and Dressler, 2005; Gravlee, Dressler, and Bernard, 2005). Importantly, he disclaims

that the local cultural model for skin color in Puerto Rico varies from the North American model of race. However, in an effort to isolate the cultural and biological dimensions of skin color and to measure self-perceived color and skin pigmentation, they create a metage called color incongruity (Gravlee and Dressler, 2005; Gravlee, Dressler, and Bernard, 2005). The team posits that the inconsistency between self-perception and pigmentation may prove a useful indicator of exposure to social stressors related to blood pressure (Gravlee and Dressler, 2005; Gravlee, Dressler, and Bernard, 2005).

The work conducted by Gravlee and many others acknowledges the impact of skin color variation, visibility and meaning in society on health outcomes nationally and internationally. The research completed thus far argues that it may yet be possible to illuminate the effects race has on health. Another dimension to this relationship is the confounding factors of poverty and racism. A clear example is the role economic and cultural elements play in cardiovascular disease among African Americans. Some believe that there is an

underlying behavioral determinant influencing the disparity between Whites and Blacks in CVD trends other than differences in SES (James 1999). In fact, high risk behaviors such as smoking and lack of physical activity may have been identified. James (1999) postulates that poorly understood social-cultural contributors are the reason for the appearance of such high risk behaviors in the Black community. These culpable social-cultural contributors are likely psychological stress from poverty and racism (James, 1999).

James' conclusions are interesting since biology (meaning race) is viewed in the biomedical field to be the leading factor involved in the poor health of African Americans. Is race as important to the average person? For many people it is, but it has nothing to do with innate risk factors, but socio-political "real life" issues structured within the framework of skin color. Issues such as access to and quality of health care, and socioeconomic factors ranging from dietary knowledge and assistance, education, employment, access to healthy living and working environments, exposure to lead and other toxins, are the everyday challenges. These challenges are associated in one way or another with "racism" that contributes to the poor health of communities of color.

Davis et al. (2005) recently examined the relationship between the prevalence of hypertension and self-perceived stress from racial discrimination in an African American cohort from Atlanta, Georgia. Stress levels were found to be a significant predictor of hypertension. Approximately 74% of their study population reported a high rate of exposure to racial discrimination (Davis, 2005). The study by Davis et al. (2005) demonstrates a connection between race and disease. Skin color which in the U.S. is a proxy for race has meaning and significance in society which interacts with the social environment to create a physiological response to discrimination called stress. Stress in turn contributes to disease and/or in behaviors that indirectly influence disease (i.e., smoking, drinking, overeating and a lack of physical activity). This is a different type of social determinant on health since the relationship

between racism and health is mediated through skin color.

Concluding Remarks on Race and Health Disparities
Several models have been used to explain health disparities, these include racial-genetic, health-behavior, socioeconomic status, psychosocial stress, and structural construct (Dressler, Oths, and Gravlee, 2005). The racial genetic model accounts for health disparities by focusing on the distribution of genetic variants in different racial groups. The health-behavior model approaches the dilemma from the perspective of individual behaviors related to health that are unequally distributed between ethnic/racial groups. The socioeconomic status model attributes health disparities to the distribution of certain ethnic /racial groups in the lower tiers of socioeconomic status. The psychosocial stress model explains health disparities as they relate to the stress induced from experiences of racism and discrimination. The structural-constructivist model looks at dual roles of group perceptions from external sources and group perceptions of the environment.

An interesting version of psychological and socioeconomic models of health disparities is the model introduced by Camara Jones, "Impact of Racism on Health" (Jones, 2001). In this model, the racial climate consists of three levels of racism which impact health outcomes. The levels of interaction are personally mediated, internalized, and institutionalized racism. Personally mediated racism in the form of discrimination can lead to stress and differential treatment. Internalized racism includes the manifestation of behaviors that come about as a result of the stigmatized races accepting limitations placed on their full humanity. The third level is institutional racism which addresses how structural factors impact access to services including healthcare (Jones, 2001).

All of these models represent potentially valid pathways to explain the health disparities but they should not be thought of as mutually exclusive. The health status of African Americans varies across the country and thus is linked to the history of those communities. The

history of racism, marginalization, segregation, in the deep south is quite different than in the pacific northwest.

It is clear that genetic differences exist between human populations. These genetic differences are loosely correlated with socially defined race which is largely based on skin color. Examples from African and Hispanic Americans reveal the high biological diversity within the two groups due to diverse social and genetic histories that extend beyond skin color and language. It is unclear however, how much biology plays a role in health disparities.

The importance of genetic differences in contributing to 'racial' health disparities is yet to be understood. Biomedical studies that use race as a proxy for biology and culture will likely be unsuccessful because careful distinction must be made between race as a statistical risk factor (due to environment) and causal genetic variables. In a hierarchical society like the U.S. which stratifies race based on skin color; "social status indicators" and "biological or genetic traits" will be correlated (Kittles and Weiss, 2003). Thus, race cannot serve as a proxy for direct measurement of risk. A person's race is due to biological, cultural, and psychological factors. The present health disparities in the U.S. are the result of complex interactions among genetic variants, environmental (natural and social) factors, and health-related behaviors. Thus, the effects of biology cannot be completely separated from environmental and behavioral effects. If race is to be used as a proxy for genetic risk, it will only be effective to the extent that cultural, social, environmental and genetic risk factors are themselves correlated.

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