New Insights on the Risk for Cardiovascular Disease in African Americans: The Role of Added Sugars

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ABSTRACT

African Americans are at increased risk for cardiovascular and metabolic diseases, including obesity, high BP, diabetes, CKD, myocardial infarction, and stroke. Here we summarize the current risks and provide an overview of the underlying risk factors that may account for these associations. By reviewing the relationship between cardiovascular and renal diseases and the African-American population during the early 20th century, the historic and recent associations of African heritage with cardiovascular disease, and modern population genetics, it is possible to assemble strong hypotheses for the primary underlying mechanisms driving the increased frequency of disease in African Americans. Our studies suggest that underlying genetic mechanisms may be responsible for the increased frequency of high BP and kidney disease in African Americans, with particular emphasis on the role of \( \text{APOL1} \) polymorphisms in causing kidney disease. In contrast, the Western diet, particularly the relatively high intake of fructose-containing sugars and sweetened beverages, appears to be the dominant force driving the increased risk of diabetes, obesity, and downstream complications. Given that intake of added sugars is a remediable risk factor, we recommend clinical trials to examine the reduction of sweetened beverages as a primary means for reducing cardiovascular risk in African Americans.


African Americans carry significantly higher risk for cardiovascular disease than non-Hispanic whites in the United States today, and this is associated with higher rates of obesity (1.5-fold), diabetes (1.7-fold), hypertension (1.4-fold), and ESRD (4-fold) (Table 1). However, this level of ethnic disparity has not always been present. For example, in the 1920s diabetes was much less common in African Americans than in whites. Understanding the evolution of disease provides major insights into etiology. Here we review current and past risks for cardiovascular disease in African Americans in order to tease out genetic and environmental risk factors that may help explain the higher risk in this ethnic group today.

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African Americans represent a minority population in the United States (44 million individuals or 14% of the population) that experiences an inordinately high rate of cardiovascular disease compared with the majority non-Hispanic white population (hereafter termed “whites”). African Americans have a higher prevalence of hypertension that is less well controlled than do whites, leading to higher rates of stroke and congestive heart failure. African Americans also have a higher risk (1.7-fold) for CKD and demonstrate a higher risk for progression of CKD even when BP is equivalently controlled. Indeed, ESRD is 4-fold more common in African Americans than whites. Thus, there is disproportionate morbidity and mortality in African Americans because of their predisposition to hypertension and kidney disease.

African Americans also have higher rates of obesity and diabetes than non-Hispanic whites. Obesity rates are higher in African Americans compared with whites, especially in African-American women, and the differences in obesity manifest in childhood. More than 50% of adult African-American women are obese (defined as a body mass index > 30 kg/m\(^2\)). The increase in obesity in African Americans is associated with increased frequency of insulin resistance, as well as a 50% higher frequency of diabetes. Despite the higher rates of
diabetes, African Americans have a lower frequency of metabolic syndrome and significantly less nonalcoholic fatty liver disease, in part because of less hypertriglyceridemia and higher levels of HDL cholesterol. Both the relatively benign fatty liver (hepatic steatosis) and its more dangerous sequelae (nonalcoholic steatohepatitis and cirrhosis) are significantly lower in the African-American population.

The increase in frequency of stroke and heart failure in African Americans is easily explained as these outcomes are primarily driven by BP and its underlying lesion (arteriosclerosis). However, it is well known that the risk for coronary artery disease (CAD) and its underlying lesion (atherosclerosis) is more complex and is driven by lipid levels, smoking, and other risk factors. Interestingly, fewer African Americans smoke cigarettes compared with whites (5.0% versus 10.2%). African Americans also have lower frequency of coronary artery calcification than whites, which may have a genetic basis. Nevertheless, African Americans have a greater incidence of CAD and a higher risk of early death from CAD.

A variety of mechanisms have been identified that might account for the higher risk for metabolic, cardiovascular and renal diseases in the African-American population (Table 2). One important factor, which is sadly not uncommon in minority populations, is having lower levels of education, higher rates of poverty, higher uninsured rates, and less access to health care. Another important factor is diet. For example, much emphasis has been placed on the relatively higher sodium, and lower potassium, content in the diet as it relates to risk for hypertension. While not all studies have confirmed that African Americans ingest a higher salt diet, intakes of >10 g/d are not uncommon. African Americans also consume diets higher in sugar (discussed in more detail later). Other differences in vascular physiology and pathology that may provide insights into the increased cardiovascular risk in this group have also been reported (Table 2). The higher frequency of preterm births and lower birth weights in African Americans also raises the possibility for epigenetic mechanisms (“fetal programming”) driving cardiovascular risk. However, one of the favored epigenetic mechanisms for hypertension, which is a congenital reduction in nephrin number, does not appear to correlate with hypertension in the African-American population despite lower birth weights being commonly observed. Vitamin D levels are also lower in African Americans compared with whites, and low vitamin D levels may be associated with increased risk for hypertension and cardiovascular disease. However, a recent study suggests that the lower vitamin D levels in African Americans may be due to lower vitamin D–binding protein levels (due to genetic polymorphisms), and measurements of bioactive vitamin D levels may be similar between ethnic groups. In addition, search for genetic differences has been largely unrewarding except for the remarkable discovery of the role of APOLI gene polymorphisms as risk factors for kidney disease in African Americans (discussed later). Thus, we would argue that new approaches are necessary to understand the driving mechanisms that are causing the increased cardiovascular and renal morbidity and mortality in this group. One approach might be to review the history of African Americans as it relates to their heritage.

**Table 1.** Current cardiovascular risks of African Americans

<table>
<thead>
<tr>
<th>Variable</th>
<th>African American</th>
<th>White</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (%)</td>
<td>37 (m), 53 (f)</td>
<td>33 (m), 32 (f)</td>
<td>1.1 (m), 1.7 (f)</td>
</tr>
<tr>
<td>Childhood obesity (%)</td>
<td>21 (m), 23 (f)</td>
<td>16 (m), 13 (f)</td>
<td>1.3 (m), 1.8 (f)</td>
</tr>
<tr>
<td>Fatty liver (MRI) (%)</td>
<td>24</td>
<td>33</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes prevalence (%)</td>
<td>11.3</td>
<td>6.8</td>
<td>1.66</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>41.3</td>
<td>28.6</td>
<td>1.44</td>
</tr>
<tr>
<td>ESRD (%)</td>
<td>0.1</td>
<td>0.024</td>
<td>4.17</td>
</tr>
<tr>
<td>Deaths from CAD/stroke rate (%)</td>
<td>141.3</td>
<td>117.7</td>
<td>1.20</td>
</tr>
</tbody>
</table>

m, male; f, female; MRI, magnetic resonance imaging; CAD, coronary artery disease.

The “cradle of humanity” where modern humans (*Homo sapiens*) originated some 200,000 years ago is thought to be near the Angolan-Namibian coast in West Africa. Early humans were hunter-gatherers who could not store foods as easily as later groups with agricultural economies, and hence were at greater risk during periods of famine. Indeed, extensive megadroughts occurred between 135 and 75,000 years ago, keeping the human population relatively small. Around 63,000–73,000 years ago, a large volcanic eruption in modern day Indonesia (Toba) caused major climatic changes worldwide, causing a prolonged volcanic winter with a severe drought in Africa that may have lasted 5–7 years. The human population, which has been calculated to be as low as 13,000–14,000 individuals at that time, was placed under extreme survival pressure. It was around that time that a small group (estimated to have included between 600 and 1500 women), known as the L3 clade (based on mitochondrial genome), left Africa from present-day Ethiopia, either by crossing in rafts at the horn of Africa to Arabia across the “Gate of Tears” (Bab-el Mandeb), or by passing across the Sinai Peninsula into Asia. This wayward group of adventurers met up and intermingled (to a minor degree) with other *Homo* species, including Neanderthals (in Europe) and Denisovans (in Siberia and southeast Asia), resulting in the non-African racial groups today.

As mentioned, the Founder L3 clade group was small, so despite minor intermingling with other *Homo* species, genetic diversity was relatively limited compared with the vast genetic diversity that remained in Africa. At least 14
major genetic cluster groups in Africa have been identified that correlate roughly with the different languages spoken (linguistic groups). One of the largest is the Niger-Congo language group (Niger-Kordofanian), which is centered in West Central and Central (sub-Saharan) Africa, and which includes the Bantu-speaking peoples. It was primarily individuals from this genetic group that were captured and enslaved in one of the darkest periods of human history. Between 1525 and 1866 approximately 12.5 million Africans were taken by ship across the Middle Passage to the Americas where they arrived in the Americas. Early studies of African Americans in the United States also showed a higher frequency of hypertension compared with whites. For example, in one study of 14,000 factory workers in New Orleans from the 1920s, high BP and kidney disease were more common in African Americans than in whites. Similarly, studies of an Afro-Caribbean population found higher BP compared with the indigenous Native Indian populations or local white settlers. Early studies also suggested that kidney disease was also more common in African Americans.

While the underlying cause for the increased risk for hypertension remains elusive, recent studies have provided insights into why African Americans are at increased risk for ESRD. Specifically, Niger-Congo Africans living in West Africa show a higher frequency of the G1 APOL1 gene polymorphism that appears to have developed as a means to reduce the risk for infection from African sleeping sickness. This infection, which can lead to meningoencephalitis and death, is caused by a trypanosome (Trypanosoma brucei) that is spread by the tsetse fly (Glossina species). The trypanosome can be killed in the host blood by certain APOL1 isoforms, which are taken up and form pores in the trypanosome. The G1 APOL1 polymorphism risk allele protects against one of the main Trypanosoma species (T. brucei rhodesiense) and is present in approximately 40% of the Yoruba population in Nigeria (part of the Niger-Congo group). However, if someone is homozygous for G1, or carries one G1 polymorphism with another (G2) polymorphism, or two G2 polymorphisms, then he or she is at marked risk for developing kidney disease and of progressing to ESRD. Approximately 22% of African Americans carry the G1 allele and reported unusually high frequencies of hypertension, many of whom went on to develop kidney disease. Renal biopsy studies confirmed that the primary lesion was of severe arteriolosclerosis with secondary glomerulosclerosis, lesions that can occur with severe primary hypertension.

### Table 2. Risk factors for cardiovascular disease in African Americans

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>African American (%)</th>
<th>White (%)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not finish high school</td>
<td>16.1</td>
<td>7.3</td>
<td>2.21</td>
</tr>
<tr>
<td>Income below poverty level</td>
<td>16.4</td>
<td>12.4</td>
<td>1.32</td>
</tr>
<tr>
<td>Unemployment</td>
<td>16.5</td>
<td>8.3</td>
<td>1.99</td>
</tr>
<tr>
<td>No health insurance</td>
<td>26.2</td>
<td>16.1</td>
<td>1.63</td>
</tr>
<tr>
<td>Life Expectancy</td>
<td>74 yr</td>
<td>78.5 yr</td>
<td>0.94</td>
</tr>
<tr>
<td>Congenital/epigenetic/genetic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm births</td>
<td>17.1</td>
<td>10.8</td>
<td>1.58</td>
</tr>
<tr>
<td>Lower birth weight (&lt;=2500 g)</td>
<td>13.1</td>
<td>4.8</td>
<td>2.73</td>
</tr>
<tr>
<td>Very low birth weight (&lt;1500 g)</td>
<td>2.9</td>
<td>0.8</td>
<td>3.62</td>
</tr>
</tbody>
</table>

Environmental risk factors include the following: sugar intake greater, lower-potassium diet, and higher salt intake in African Americans; physiologic and pathologic risk factors: sympathetic nervous system hyperactivity—increased BP to sympathetic stimulation (cold pressor test, from infused norepinephrine on high-salt diet, greater BP response to exercise, altered renal autoregulation; increased GFR response to high-salt diet, lower renal blood flow, salt sensitivity frequent, even in normotensive persons, with larger glomeruli.

### A GENETIC BASIS FOR HYPERTENSION AND KIDNEY DISEASE: ROLE OF APOL1

Given that the primary genetic background in African Americans is of the Congo-Niger linguistic group, one might expect to see similar increased risks for cardiovascular and renal disease if genes are important in the underlying cardiovascular risk. The invention of the BP cuff by Riva-Ricci in the late 1890s led to the rapid introduction of BP measurement in routine medical practice, especially when it became apparent that people with high BP demonstrated increased risk for stroke and heart disease. By the early 20th century, epidemiologic studies showed that hypertension was present in 5%–10% of the United States and European population, whereas it was distinctly uncommon among other populations (including Chinese, Indian, Mideast, Native American, Alaskan, and other populations) (reviewed by Johnson et al.). Several studies performed in Africa also suggested that hypertension was rare in African populations, although in some cases this was thought to relate to poor nutrition and sarcopenia. However, it is striking that early studies in Bantu-speaking groups


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13% carry the dreaded combination,79,81,82 Indeed, of African Americans with CKD, those bearing two risk alleles had a 31% chance for progression to ESRD versus 13% of those having zero or one risk allele.81 Persons carrying the APOL1 risk alleles also show a higher risk for cardiovascular disease (myocardial infarction and stroke).83

The mechanism by which the APOL1 polymorphism causes ESRD remains unclear; it may relate to effects on the podocyte and/or blood vessels. There is some evidence that APOL-1 is deposited in the afferent arteriole and periglomerular vasculature when renal biopsies are performed.84 Previous studies by Herrera’s group had shown that disease of the periglomerular vasculature can alter renal autoregulation,85 thus potentially explaining some of the renal physiologic and pathologic characteristics observed in African Americans.

While the APOL1 genetic polymorphism provides some insights into the increased risk for kidney disease and, to a lesser extent, BP in African Americans, it can only partially explain the increased cardiovascular risk in these patients. Other genetic mechanisms may also play a role, such as genetic polymorphisms in TGF-β86,87 or differential expression of the renin-angiotensin system.88 However, genetics alone are unlikely to explain much of the risk for cardiovascular disease among African Americans.89 In the next section we discuss another mechanism that may be the principal driver for the increased cardiovascular and renal risk.

THE RISE IN INTAKE OF ADDED SUGARS AND THEIR EFFECT ON AFRICAN AMERICANS

In the early 20th century, diabetes and obesity were uncommon in both the United States and Europe. Indeed, the prevalence of diabetes was only 2–3 cases per 100,000 people, and obesity in adults was in the range of 3%–5%.90,91 A striking aspect of that period was that diabetes was less common in African Americans than in whites. One of the better studies that investigated this relationship was by Haven Emerson, who was the New York City Health Commissioner. In 1924 he reported an alarming finding: a nearly 10-fold increase in diabetes over a 40-year period in New York City. The highest rates were among the sedentary, the wealthy, and those over age 45 years, with twice the rates among whites (especially of the Jewish faith92) compared with African Americans.4 However, one of the major risk factors was an occupation in the food industry, and there was an especially strong relationship with sugar intake. During this same period there were numerous reports of the introduction of sugar into various cultures associated with the emergence of diabetes,93–102 and these reports continued over the subsequent decades.103,104 This led investigators such as Frederick Banting to propose sugar intake as a cause of diabetes.105 However, investigators such as Joslin92,106 made the case that the cause of diabetes was more likely from overnutrition as opposed to the presence of a specific food in the diet, and this latter hypothesis was held for decades.

Sugar consists of a disaccharide containing fructose and glucose, and along with high fructose corn syrup (HFCS), are major sources of dietary fructose. In this regard, there is now incontrovertible evidence that fructose is special among nutrients in its ability to induce metabolic syndrome and diabetes.107 While it provides a caloric source, the primary risk from fructose relates to its unique metabolism that results in transient ATP depletion, resulting in the stimulation of the enzyme AMP deaminase and the generation of uric acid.108–112 Stimulation of this pathway results in inhibition of AMP kinase while at the same time inducing mitochondrial oxidative stress and intracellular uric acid generation, resulting in both fat accumulation (from stimulation of fat synthesis and blockade of fatty acid oxidation) and increased gluconeogenesis.109–112 The ability of fructose to cause obesity is not simply from its caloric value but rather from its capacity to induce leptin resistance (thereby blocking satiety responses) while at the same time reducing ATP production by blocking fat oxidation.109,113–115 Laboratory animals fed fructose develop features of metabolic syndrome and, if prone, will even develop diabetes.116,117 Features of metabolic syndrome can be induced even with caloric restriction provided the sugar (or fructose) content is high,116 demonstrating that it is not overnutrition but rather the presence of fructose that is responsible for the development of metabolic syndrome. Indeed, if fructose metabolism is blocked, the ability of sugar or fructose to induce metabolic syndrome is largely prevented. Even the ability of non–fructose-containing carbohydrates to cause fatty liver and hyperinsulinemia can be prevented by blocking fructose metabolism, as some of the carbohydrates are converted to fructose in the liver after ingestion.118

Studies in humans have also shown the remarkable ability of fructose to induce features of metabolic syndrome.119–121 While some clinical studies have argued that fructose is not special in its ability to induce metabolic syndrome,122–124 these latter studies inevitably are short term or have defects in experimental design (discussed by Johnson et al107). Indeed, recent studies suggest that humans may be more sensitive to the effects of fructose than most mammals because uric acid mediates some of the metabolic features.109–111 Humans have higher uric acid levels than most mammals as a result of a mutation in uricase,125 an enzyme that degrades uric acid. When uricase is inhibited in rats, even small concentrations of fructose-containing sugars can induce features of metabolic syndrome.126 Indeed, the loss of uricase in humans has been postulated to have provided a survival advantage to our hominoid ancestors by amplifying the effects of fructose from ripe fruits to stimulate fat storage during a prolonged period of seasonal famine that occurred in the mid-Miocene.127,128 Consistent with this hypothesis, the ancestral uricase was recently resurrected and found to partially block fructose-induced fat accumulation in cultured liver (HepG2) cells.129
There has also been a dramatic rise in intake of added sugars containing fructose over the last century, which has correlated tightly with the rise in obesity and diabetes (Figure 1). Indeed, the introduction of HFCS in the 1970s is associated with an overall 30% further increase in fructose intake, with an inflection in the rise of obesity and diabetes. One of the consequences of the studies on fructose metabolism is the recognition that it is not the caloric content that matters as much as whether ATP depletion occurs, the latter being primarily governed by the concentration of fructose that hits the liver.

This provides strong reasoning why soft drinks and sugary beverages may be so tightly associated with the development of obesity, metabolic syndrome, diabetes, and cardiovascular disease, as sugary beverages are often highly concentrated in fructose and are frequently ingested rapidly.

It is thus striking that the epidemiologic reversal, in which diabetes switched from being less common in African Americans to being more common, coincides with an epidemiologic reversal in sugar intake. In the 1920s, sugar was relatively expensive. During that period diabetes was more common in the northern, more wealthy states and was notably lower in the poorer, southern states. However, as sugar became progressively less expensive, it became affordable even for individuals with minimal income. Today, African Americans consume significantly more added sugars (including both sugar and HFCS) than whites (Table 3). Furthermore, African Americans in poverty ingest more soft drinks and candy than whites living under similar economic conditions. Currently 1 in 6 African Americans is ingesting more than 25% of their total calories as added sugars compared with 1 in 11 whites. The ingestion of two or more soft drinks or fruit juices has been reported to increase the risk of diabetes in African-American women by 1.24- and 1.31-fold, respectively. Not surprisingly, the rise in sugar and HFCS intake has been associated with the switch from diabetes being less common in African Americans to being more common. This switch occurred in the early 1970s in African American men and even earlier for African-American women. Similarly, diabetes was extremely rare in Africa in the early 20th century, but there has been a progressive rise in diabetes, hypertension, and obesity in urban communities in Africa as Western diet and culture take hold.

LIMITATIONS AND CAVEATS

We recognize that we have focused on primarily one environmental factor (sugar intake) and that other risk factors are almost certainly involved. However, there has not been enough emphasis on the important role of sugar intake on diabetes and cardiovascular disease. During the last century, soft drink intake has increased exponentially in the United States, from a mean of eleven 12-ounce drinks per year in 1909, to 105 drinks per year in 1950, to 242 drinks per year in 1970, to 410 drinks per year in 1980. Sugar intake accounted for more than half of all carbohydrate intake in 1980. Between 1970 and 2000, the intake of sweetened beverages in the United States further increased from 3.2% to 9% of total energy intake. African Americans are particularly at risk; as noted in Table 3, the mean intake of added sugars is around 17.5% of total calories in African Americans, and 17% are ingesting 25% of their diet as sugar. A study by Yang et al. shows that intake of more than 15% diet as added sugar increases the risk for cardiovascular disease.

Table 3. Dietary intake of sugar in African Americans versus whites

<table>
<thead>
<tr>
<th>Variable</th>
<th>Added Sugar Intake: Total Calories (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>15.7</td>
</tr>
<tr>
<td>White*</td>
<td>15.7</td>
</tr>
<tr>
<td>African American*</td>
<td>17.9</td>
</tr>
</tbody>
</table>

Data obtained from reference 23.

*In 2010, 70.8% of whites and 81.9% of African Americans were ingesting >10% calories as added sugars, and 9.1% and 16.9% were ingesting >25% of calories as added sugars, respectively. The World Health Organization recommends <10% intake, and the American Heart Association recommends 5% for women and 7.5% for men.
disease (equivalent to one 20-ounce Mountain Dew soda for a 2000-calorie drink). A recent study reported that approximately 9%–10% of energy intake in African American children and adults is from sugary beverages alone. When one considers that the American Heart Association recommends a limit of 6 and 9 teaspoons of added sugar daily for women and men (corresponding to 3%–7.5% of total energy intake for a 2000-calorie diet), respectively, it should be apparent that reduction in sugar intake should be a key recommendation to reduce cardiovascular disease. Indeed, studies have demonstrated the beneficial effect of lowering sugar intake on obesity and hypertension.

While African Americans today have higher rates of obesity, insulin resistance, and diabetes, a curious finding is that they tend to have lower rates of fatty liver and hyperlipidemia. Walker et al. reported that African Americans tend to absorb fructose less well than whites, suggesting they may, to a certain extent, be protected from the effects of sugar and HFCS. However, studies in laboratory animals have shown that fructose malabsorption often subsides with continued fructose exposure because of an upregulation of fructose transporters that occurs in the intestines. One potential reason may relate to uric acid, which tends to be lower in young African Americans than whites, likely due in part to a higher frequency of a polymorphism in urate transport (SLC2A9) that decreases uric acid levels. Over time, however, continued high exposure to fructose is known to increase both fructose absorption and uric acid levels. Interestingly, compared with whites, African Americans have a greater risk for developing hyperuricemia later in life.

**CONCLUSIONS**

In conclusion, African Americans are at high risk for cardiovascular and renal diseases. To date, the evidence suggests that a genetic basis for the higher risk for hypertension and kidney disease is likely. Recent studies indicate that polymorphisms in the APOLI gene may explain much of the increased risk for kidney disease in this population. In contrast, the higher risk for diabetes and obesity appears to have developed over the last century. While many mechanisms are probably involved, excessive intake of added sugars containing fructose appears to be a major risk factor and is particularly important because it is potentially remediable. We suggest clinical trials focusing on reducing intake of sugary beverages in this population.

**ACKNOWLEDGMENTS**

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**DISCLOSURES**

R.J.J. and M.A.L. are listed as inventors for several patent applications related to blocking fructose metabolism in metabolic and renal diseases (University of Colorado) and are also founders of Colorado Research Partners, LLC. R.J.J. has written two books on fructose for lay audiences (The Sugar Fix, Rodale, 2008 and The Fat Switch, mercola.com, 2012) and is on the scientific board of Amary and XORT Therapeutics.


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