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

Karim R. Saab,* Jessica Kendrick,* Joseph M. Yracheta,† Miguel A. Lanaspa,*‡ Maisha Pollard,§ and Richard J. Johnson*‡

*Renal Division, Department of Medicine, University of Colorado Anschutz Medical Center, Aurora, Colorado; †Department of Pharmaceutics, University of Washington, School of Pharmacy, Seattle, Washington; ‡Colorado Research Partners LLC, Aurora, Colorado; and §Fields Foundation, Aurora, Colorado

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 *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.

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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).[1–3] 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.[4] 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.

CARDIOVASCULAR RISK FOR AFRICAN AMERICANS, 2014

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[5–7] that is less well controlled[7] than do whites, leading to higher rates of stroke[8] and congestive heart failure.[9,10] African Americans also have a higher risk (1.7-fold) for CKD[6,11–14] and demonstrate a higher risk for progression of CKD even when BP is equivalently controlled.[15] Indeed, ESRD is 4-fold more common in African Americans than whites.[3] 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.[1] More than 50% of adult African-American women are obese (defined as a body mass index$>$30 kg/m^2).[1] The increase in obesity in African Americans is associated with increased frequency of insulin resistance, as well as a 50% higher frequency of diabetes.[1] Despite the higher rates of

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Correspondence: Dr. Richard J. Johnson, University of Colorado Aschutz Medical Campus, 12700 East 19th Avenue, Room 7015, Aurora, CO 80045. Email Richard.johnson@ucdenver.edu

Table 1. Current cardiovascular risks of African Americans[1]

Variable	African American	White	Ratio
Obesity (%)	37 (m), 53 (f)	33 (m), 32 (f)	1.1 (m), 1.7 (f)
Childhood obesity (%)	21 (m), 23 (f)	16 (m), 13 (f)	1.3 (m), 1.8 (f)
Fatty liver (MRI) (%)[2]	24	33	0.73
Diabetesprevalence (%)	11.3	6.8	1.66
Hypertension (%)	41.3	28.6	1.44
ESRD (%)[3]	0.1	0.024	4.17
Deaths from CAD/stroke rate (%)	141.3	117.7	1.20

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

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.[2,16–18] 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.[17]

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 (arteriolosclerosis). 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%).[1] African Americans also have lower frequency of coronary artery calcification than whites, which may have a genetic basis.[19,20] Nevertheless, African Americans have a greater incidence of CAD and a higher risk of early death from CAD.[21]

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).[1,22–37] 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.[1,38] 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.[39] 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[40] 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 nephron number, does not appear to correlate with hypertension in the African-American population despite lower birth weights being commonly observed.[41] Vitamin D levels are also lower in African Americans compared with whites,[42] 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.[43] In addition, search for genetic differences has been largely unrewarding except for the remarkable discovery of the role of *APOL1* 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.

EVOLUTIONARY ORIGINS AND COMPARATIVE STUDIES

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.[44,45] 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.[46,47] 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.[48,49] 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.[50] 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.[51–54] This wayward group of adventurers met up and intermingled (to a minor degree) with other *Homo* species, including Neanderthals (in Europe)[55] and Denisovans (in Siberia and southeast Asia),[56–58] 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.[59] At least 14

Table 2. Risk factors for cardiovascular disease in African Americans[1]

Risk Factor	African American (%)	White (%)	Ratio
Demographic			
Did not finish high school	16.1	7.3	2.21
Income below poverty level	16.4	12.4	1.32
Unemployment	16.5	8.3	1.99
No health insurance	26.2	16.1	1.63
Life Expectancy	74 yr	78.5 yr	0.94
Congenital/epigenetic/genetic			
Preterm births	17.1	10.8	1.58
Lower birth weight (<2500 g)[40]	13.1	4.8	2.73
Very low birth weight (<1500 g)[40]	2.9	0.8	3.62

Environmental risk factors include the following: sugar intake greater,[22,23] lower-potassium diet,[24] and higher salt intake[25] in African Americans; physiologic and pathologic risk factors: sympathetic nervous system hyperactivity—increased BP to sympathetic stimulation (cold pressor test,[26] from infused norepinephrine on high-salt diet,[27] greater BP response to exercise[28]); altered renal autoregulation: increased GFR response to high-salt diet,[29,30] lower renal blood flow,[31] salt sensitivity frequent[30,32,33]; renal vascular disease prominent: extensive glomerulosclerosis and vascular sclerosis,[34,35] even in normotensive persons,[36] with larger glomeruli.[37]

major genetic cluster groups in Africa have been identified that correlate roughly with the different languages spoken (linguistic groups).[44] 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.[60] Between 1525 and 1866 approximately 12.5 million Africans were taken by ship across the "Middle Passage" to the Americas where they were sold as slaves to work in the plantations and mines.[61] Often humans were chained naked in cargo holds for the 2-month journey across the sea and kept in unsanitary conditions that predisposed to infection, pestilence, and starvation. Ship records show that approximately 12% of Africans died before arriving in the Americas.[61]

Today the heritage of the African American reflects this history as well as the mixing with other ethnic-racial groups. Studies show that 70%–77% of the genes in African Americans are derived from West African populations (especially the Niger-Congo group), with 13%–18% of the genes originating from European groups and the remaining from other African groups.[44,60] As such, African Americans today represent a mix of genetic backgrounds of relatively high diversity.

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,[62] especially when it became apparent that people with high BP demonstrated increased risk for stroke and heart disease.[63] 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.*[64]). 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.[65–67] However, it is striking that early studies in Bantu-speaking groups reported unusually high frequencies of hypertension, many of whom went on to develop kidney disease.[68,69] Renal biopsy studies confirmed that the primary lesion was of severe arteriolosclerosis with secondary glomerulosclerosis, lesions that can occur with severe primary hypertension.[70]

Early studies of African Americans in the United States also showed a higher frequency of hypertension compared with whites.[71–74] 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.[71] Similarly, studies of an Afro-Caribbean population found higher BP compared with the indigenous Native Indian populations or local white settlers.[75,76] Early studies also suggested that kidney disease was also more common in African Americans.[71]

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.[77] The G1 *APOL1* polymorphism risk allele protects against one of the main *Trypanosoma* species (*T. brucei rhodesiense*)[78] and is present in approximately 40% of the Yoruba population in Nigeria (part of the Niger-Congo group).[79] 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.[80,81] Approximately 22% of African Americans carry the G1 allele and

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 preglomerular vasculature when renal biopsies are performed.[84] Previous studies by Herrera's group had shown that disease of the preglomerular 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-β[86,87] 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 faith[92]) 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 Joslin[92,106] 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 al.*[107]). 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).[130,131] 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.[132–134] 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.[108,118,135] 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,[132,136–149] 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.[150] 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).[22,23,151–153] Furthermore, African Americans in poverty ingest more soft drinks and candy than whites living under similar economic conditions.[151] Currently 1 in 6 African Americans is ingesting more than 25% of their total calories as added sugars compared with 1 in 11 whites.[23,154] 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.[145] Increased intake of added sugars also increases the risk for cardiovascular-associated mortality.[23] 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.[155] Similarly, diabetes was extremely rare in Africa in the early 20th century,[150] but there has been a progressive rise in diabetes, hypertension, and obesity in urban communities in Africa as Western diet and culture take hold.[150,156–158]

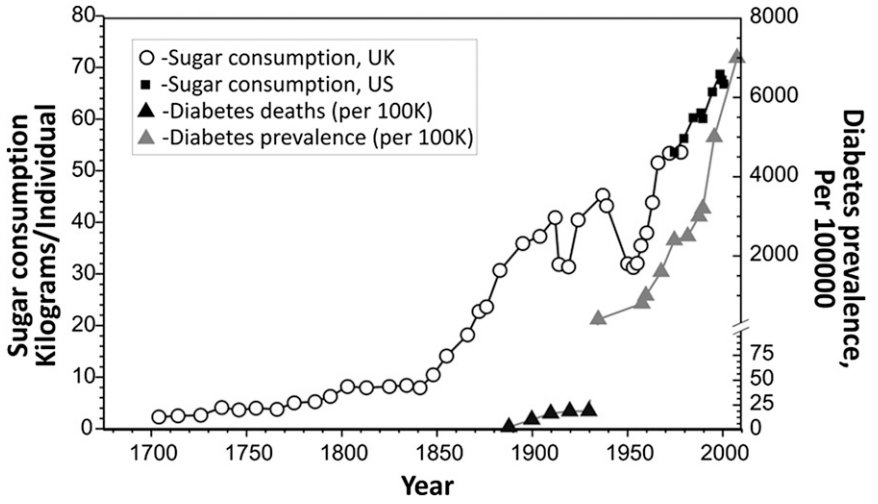

Figure 1. Rise in sugar intake correlates with rise in diabetes in the general population. Reproduced from reference 130 at the permission of the Endocrine Society.

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.[159] Sugar intake accounted for more than half of all carbohydrate intake in 1980.[159] Between 1970 and 2000, the intake of sweetened beverages in the United States further increased from 3.2% to 9% of total energy intake.[160] 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.[23] A study by Yang *et al.* shows that intake of more than 15% diet as added sugar increases the risk for cardiovascular

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

Variable	Added Sugar Intake: Total Calories (%)		
	1988–1994	1999–2004	2005–2010
All	15.7	16.8	14.9
White[a]	15.7	16.6	14.6
African American[a]	17.9	19.8	17.5

Data obtained from reference 23.

[a]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.[23] The World Health Organization recommends <10% intake,[153] and the American Heart Association recommends 5% for women and 7.5% for men.[162]

disease (equivalent to one 20-ounce Mountain Dew soda for a 2000-calorie drink).[23,154] A recent study reported that approximately 9%–10% of energy intake in African American children and adults is from sugary beverages alone.[161] 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 5%–7.5% of total energy intake for a 2000-calorie diet),[162] 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.[163–167]

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,[168] 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.[116,169] One potential reason may relate to uric acid, which tends to be lower in young African Americans than whites,[170] likely due in part to a higher frequency of a polymorphism in urate transport (*SLC2A9*) that decreases uric acid levels.[171,172] Over time, however, continued high exposure to fructose is known to increase both fructose absorption and uric acid levels.[173] Interestingly, compared with whites, African Americans have a greater risk for developing hyperuricemia later in life.[174]

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 *APOL1* 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.

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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 Amway and XORT Therapeutics.

REFERENCES

1. Frieden TR; Centers for Disease Control and Prevention (CDC): Foreword. *MMWR Surveill Summ* 62[Suppl 3]: 1–2, 2013
2. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH: Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. *Hepatology* 40: 1387–1395, 2004
3. Collins AJ, Foley RN, Herzog C, Chavers B, Gilbertson D, Ishani A, Kasiske B, Liu J, Mau LW, McBean M, Murray A, St Peter W, Guo H, Li Q, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agodoa L: United States Renal Data System 2008 Annual Data Report. *Am J Kidney Dis* 53[Suppl]: S1–S374, 2009
4. Emerson H, Larimore LD: Diabetes mellitus: A contribution to its epidemiology based chiefly on mortality statistics. *Arch Intern Med* 34: 585–630, 1924
5. Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P: The burden of adult hypertension in the United States 1999 to 2000: A rising tide. *Hypertension* 44: 398–404, 2004
6. National Health Survey: Blood pressure levels of persons 6-74 years of age United States, 1971-1974. *Vital and Health Statistics Series 11*. 1974. Available at: http://www.cdc.gov/nchs/data/series/sr_11/sr11_203.pdf. Accessed July 20, 2014
7. Hajjar I, Kotchen TA: Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. *JAMA* 290: 199–206, 2003
8. Hicks LS, Fairchild DG, Horng MS, Orav EJ, Bates DW, Ayanian JZ: Determinants of JNC VI guideline adherence, intensity of drug therapy, and blood pressure control by race and ethnicity. *Hypertension* 44: 429–434, 2004
9. Yancy CW: Heart failure in African Americans: A cardiovascular engima. *J Card Fail* 6: 183–186, 2000
10. Mensah GA, Mokdad AH, Ford ES, Greenlund KJ, Croft JB: State of disparities in cardiovascular health in the United States. *Circulation* 111: 1233–1241, 2005
11. Easterling RE: Racial factors in the incidence and causation of end-stage renal disease (ESRD). *Trans Am Soc Artif Intern Organs* 23: 28–33, 1977
12. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 41: 1–12, 2003
13. Tarver-Carr ME, Powe NR, Eberhardt MS, LaVeist TA, Kington RS, Coresh J, Brancati FL: Excess risk of chronic kidney disease among African-American versus white subjects in the United States: A population-based study of potential explanatory factors. *J Am Soc Nephrol* 13: 2363–2370, 2002
14. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of chronic kidney disease in the United States. *JAMA* 298: 2038–2047, 2007
15. Hebert LA, Kusek JW, Greene T, Agodoa LY, Jones CA, Levey AS, Breyer JA, Faubert P, Rolin HA, Wang SR; Modification of Diet in Renal Disease Study Group: Effects of blood pressure control on progressive renal disease in blacks and whites. *Hypertension* 30: 428–435, 1997
16. Gaillard T, Schuster D, Osei K: Metabolic syndrome in Black people of the African diaspora: The paradox of current classification, definition and criteria. *Ethnicity Dis* 19: S2-1–7, 2009
17. Kallwitz ER, Guzman G, TenCate V, Vitello J, Layden-Almer J, Berkes J, Patel R, Layden

TJ, Cotler SJ: The histologic spectrum of liver disease in African-American, non-Hispanic white, and Hispanic obesity surgery patients. *Am J Gastroenterol* 104: 64–69, 2009
18. Metcalf PA, Sharrett AR, Folsom AR, Duncan BB, Patsch W, Hutchinson RG, Szklo M, Davis CE, Tyroler HA: African American-white differences in lipids, lipoproteins, and apolipoproteins, by educational attainment, among middle-aged adults: The Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 148: 750–760, 1998
19. Divers J, Palmer ND, Lu L, Register TC, Carr JJ, Hicks PJ, Hightower RC, Smith SC, Xu J, Cox AJ, Hruska KA, Bowden DW, Lewis CE, Heiss G, Province MA, Borecki IB, Kerr KF, Chen YD, Palmas W, Rotter JI, Wassel CL, Bertoni AG, Herrington DM, Wagenknecht LE, Langefeld CD, Freedman BI: Admixture mapping of coronary artery calcified plaque in African Americans with type 2 diabetes mellitus. *Circ Cardiovasc Genet* 6: 97–105, 2013
20. Wassel CL, Pankow JS, Peralta CA, Choudhry S, Seldin MF, Arnett DK: Genetic ancestry is associated with subclinical cardiovascular disease in African-Americans and Hispanics from the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Genet* 2: 629–636, 2009
21. Ferdinand KC: Coronary artery disease in minority racial and ethnic groups in the United States. *Am J Cardiol* 97[2A]: 12A–19A, 2006
22. Kerr GR, Amante P, Decker M, Callen PW: Supermarket sales of high-sugar products in predominantly Black, Hispanic, and white census tracts of Houston, Texas. *Am J Clin Nutr* 37: 622–631, 1983
23. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB: Added sugar intake and cardiovascular diseases mortality among US adults. *JAMA Intern Med* 174: 516–524, 2014
24. Tobian L: Hypothesis: Low dietary K may lead to renal failure in blacks with hypertension and severe intimal thickening. *Am J Med Sci* 295: 384–388, 1988
25. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Urinary and serum electrolytes in untreated black and white hypertensives. *J Chronic Dis* 40: 839–847, 1987
26. Knox SS, Hausdorff J, Markovitz JH; Coronary Artery Risk Development in Young Adults Study: Reactivity as a predictor of subsequent blood pressure: Racial differences in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Hypertension* 40: 914–919, 2002
27. Dimsdale JE, Graham RM, Ziegler MG, Zusman RM, Berry CC: Age, race, diagnosis, and sodium effects on the pressor response to infused norepinephrine. *Hypertension* 10: 564–569, 1987
28. Ekelund LG, Suchindran CM, Karon JM, McMahon RP, Tyroler HA: Black-white differences in exercise blood pressure. The Lipid Research Clinics Program Prevalence Study. *Circulation* 81: 1568–1574, 1990
29. Parmer RJ, Stone RA, Cervenka JH: Renal hemodynamics in essential hypertension. Racial differences in response to changes in dietary sodium. *Hypertension* 24: 752–757, 1994
30. Campese VM, Parise M, Karubian F, Bigazzi R: Abnormal renal hemodynamics in black salt-sensitive patients with hypertension. *Hypertension* 18: 805–812, 1991
31. Levy SB, Talner LB, Coel MN, Holle R, Stone RA: Renal vasculature in essential hypertension: racial differences. *Ann Intern Med* 88: 12–16, 1978
32. Luft FC, Miller JZ, Grim CE, Fineberg NS, Christian JC, Daugherty SA, Weinberger MH: Salt sensitivity and resistance of blood pressure. Age and race as factors in physiological responses. *Hypertension* 17 [Suppl]: I102–I108, 1991
33. Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS: Definitions and characteristics of sodium sensitivity and blood pressure resistance. *Hypertension* 8: II127–II134, 1986
34. Marcantoni C, Ma LJ, Federspiel C, Fogo AB: Hypertensive nephrosclerosis in African Americans versus Caucasians. *Kidney Int* 62: 172–180, 2002
35. Fogo A, Breyer JA, Smith MC, Cleveland WH, Agodoa L, Kirk KA, Glassock R; AASK Pilot Study Investigators: Accuracy of the diagnosis of hypertensive nephrosclerosis in African Americans: A report from the African American Study of Kidney Disease (AASK) Trial. *Kidney Int* 51: 244–252, 1997
36. Tracy RE, Bhandaru SY, Oalmann MC, Guzman MA, Newmann WP 3rd: Blood pressure and nephrosclerosis in black and white men and women aged 25 to 54. *Mod Pathol* 4: 602–609, 1991
37. Abdi R, Slakey D, Kittur D, Racusen LC: Heterogeneity of glomerular size in normal donor kidneys: Impact of race. *Am J Kidney Dis* 32: 43–46, 1998
38. Perneger TV, Whelton PK, Klag MJ: Race and end-stage renal disease. Socioeconomic status and access to health care as mediating factors. *Arch Intern Med* 155: 1201–1208, 1995
39. Tayo BO, Luke A, McKenzie CA, Kramer H, Cao G, Durazo-Arvizu R, Forrester T, Adeyemo AA, Cooper RS: Patterns of sodium and potassium excretion and blood pressure in the African Diaspora. *J Hum Hypertens* 26: 315–324, 2012
40. Fang J, Madhavan S, Alderman MH: Low birth weight: Race and maternal nativity—impact of community income. *Pediatrics* 103: E5, 1999
41. Hughson MD, Gobe GC, Hoy WE, Manning RD Jr, Douglas-Denton R, Bertram JF: Associations of glomerular number and birth weight with clinicopathological features of African Americans and whites. *Am J Kidney Dis* 52: 18–28, 2008
42. Melamed ML, Michos ED, Post W, Astor B: 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 168: 1629–1637, 2008
43. Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, Tamez H, Zhang D, Bhan I, Karumanchi SA, Powe NR, Thadhani R: Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med* 369: 1991–2000, 2013
44. Tishkoff SA, Reed FA, Friedlaender FR, Ehret C, Ranciaro A, Froment A, Hirbo JB, Awomoyi AA, Bodo JM, Doumbo O, Ibrahim M, Juma AT, Kotze MJ, Lema G, Moore JH, Mortensen H, Nyambo TB, Omar SA, Powell K, Pretorius GS, Smith MW, Thera MA, Wambebe C, Weber JL, Williams SM: The genetic structure and history of Africans and African Americans. *Science* 324: 1035–1044, 2009
45. Vigilant L, Stoneking M, Harpending H, Hawkes K, Wilson AC: African populations and the evolution of human mitochondrial DNA. *Science* 253: 1503–1507, 1991
46. Cohen AS, Stone JR, Beuning KR, Park LE, Reinthal PN, Dettman D, Scholz CA, Johnson TC, King JW, Talbot MR, Brown ET, Ivory SJ: Ecological consequences of early Late Pleistocene megadroughts in tropical Africa. *Proc Natl Acad Sci U S A* 104: 16422–16427, 2007
47. Scholz CA, Johnson TC, Cohen AS, King JW, Peck JA, Overpeck JT, Talbot MR, Brown ET, Kalindekafe L, Amoako PY, Lyons RP, Shanahan TM, Castañeda IS, Heil CW, Forman SL, McHargue LR, Beuning KR, Gomez J, Pierson J: East African megadroughts between 135 and 75 thousand years ago and bearing on early-modern human origins. *Proc Natl Acad Sci U S A* 104: 16416–16421, 2007
48. Ambrose SH: Late Pleistocene human population bottlenecks, volcanic winter, and differentiation of modern humans. *J Hum Evol* 34: 623–651, 1998
49. Williams MAJ, Ambrose SH, van Der Kaars S, Ruehlemann C, Chattopadhyaya U, Pal J, Chauhan PR: Environmental impact of the 73 ka Toba super-eruption in South Asia. *Palaeogeogr Palaeoclimatol Palaeoecol* 284: 295–314, 2009
50. Laval G, Patin E, Barreiro LB, Quintana-Murci L: Formulating a historical and demographic model of recent human evolution based on resequencing data from noncoding regions. *PLoS ONE* 5: e10284, 2010
51. Watson E, Forster P, Richards M, Bandelt HJ: Mitochondrial footprints of human expansions in Africa. *Am J Hum Genet* 61: 691–704, 1997

52. Reed FA, Tishkoff SA: African human diversity, origins and migrations. *Curr Opin Genet Dev* 16: 597–605, 2006
53. Forster P, Matsumura S: Evolution. Did early humans go north or south? *Science* 308: 965–966, 2005
54. Quintana-Murci L, Semino O, Bandelt HJ, Passarino G, McElreavey K, Santachiara-Benerecetti AS: Genetic evidence of an early exit of Homo sapiens sapiens from Africa through eastern Africa. *Nat Genet* 23: 437–441, 1999
55. Green RE, Krause J, Briggs AW, Maricic T, Stenzel U, Kircher M, Patterson N, Li H, Zhai W, Fritz MH, Hansen NF, Durand EY, Malaspinas AS, Jensen JD, Marques-Bonet T, Alkan C, Prüfer K, Meyer M, Burbano HA, Good JM, Schultz R, Aximu-Petri A, Butthof A, Höber B, Höffner B, Siegemund M, Weihmann A, Nusbaum C, Lander ES, Russ C, Novod N, Affourtit J, Egholm M, Verna C, Rudan P, Brajkovic D, Kucan Z, Gusic I, Doronichev VB, Golovanova LV, Lalueza-Fox C, de la Rasilla M, Fortea J, Rosas A, Schmitz RW, Johnson PL, Eichler EE, Falush D, Birney E, Mullikin JC, Slatkin M, Nielsen R, Kelso J, Lachmann M, Reich D, Pääbo S: A draft sequence of the Neandertal genome. *Science* 328: 710–722, 2010
56. Reich D, Green RE, Kircher M, Krause J, Patterson N, Durand EY, Viola B, Briggs AW, Stenzel U, Johnson PL, Maricic T, Good JM, Marques-Bonet T, Alkan C, Fu Q, Mallick S, Li H, Meyer M, Eichler EE, Stoneking M, Richards M, Talamo S, Shunkov MV, Derevianko AP, Hublin JJ, Kelso J, Slatkin M, Pääbo S: Genetic history of an archaic hominin group from Denisova Cave in Siberia. *Nature* 468: 1053–1060, 2010
57. Reich D, Patterson N, Kircher M, Delfin F, Nandineni MR, Pugach I, Ko AM, Ko YC, Jinam TA, Phipps ME, Saitou N, Wollstein A, Kayser M, Pääbo S, Stoneking M: Denisova admixture and the first modern human dispersals into Southeast Asia and Oceania. *Am J Hum Genet* 89: 516–528, 2011
58. Meyer M, Kircher M, Gansauge MT, Li H, Racimo F, Mallick S, Schraiber JG, Jay F, Prüfer K, de Filippo C, Sudmant PH, Alkan C, Fu Q, Do R, Rohland N, Tandon A, Siebauer M, Green RE, Bryc K, Briggs AW, Stenzel U, Dabney J, Shendure J, Kitzman J, Hammer MF, Shunkov MV, Derevianko AP, Patterson N, Andrés AM, Eichler EE, Slatkin M, Reich D, Kelso J, Pääbo S: A high-coverage genome sequence from an archaic Denisovan individual. *Science* 338: 222–226, 2012
59. Campbell MC, Tishkoff SA: African genetic diversity: Implications for human demographic history, modern human origins, and complex disease mapping. *Annu Rev Genomics Hum Genet* 9: 403–433, 2008
60. Zakharia F, Basu A, Absher D, Assimes TL, Go AS, Hlatky MA, Iribarren C, Knowles JW, Li J, Narasimhan B, Sidney S, Southwick A, Myers RM, Quertermous T, Risch N, Tang H: Characterizing the admixed African ancestry of African Americans. *Genome Biol* 10: R141, 2009
61. Eltis D, Richardson D: Transatlantic Slave Trade Data Base. 2014. Available at: http://www.slavevoyages.org/tast/index.faces
62. Faught FA: *Blood Pressure Primer*, The Sphygmomanometer and its Practical Application, Philadelphia, G.P. Pilling and Son, 1914, pp 130
63. Medico-Actuarial Mortality Investigation. Association of Life Insurance Medical Directors and the Actuarial Society of America, 1, 1912
64. Johnson RJ, Titte S, Cade JR, Rideout BA, Oliver WJ: Uric acid, evolution and primitive cultures. *Semin Nephrol* 25: 3–8, 2005
65. Donnison C: Blood pressure in the African native; its bearing upon the aetiology of hyperpiesia and arteriosclerosis. *Lancet* 1: 6–7, 1929
66. Kaminer B, Lutz WP: Blood pressure in Bushmen of the Kalahari Desert. *Circulation* 22: 289–295, 1960
67. Williams A: The blood pressure of Africans. *E African Med J* 18: 109–117, 1941
68. Ordman B: A review of the incidence of hypertension in the non-European races; survey of blood pressures in the South African Bantu. *Clin Proc* 7: 183–210, 1948
69. Becker BJP: Cardio-vascular disease in the Bantu and coloured races of South Africa; atheromatosis. *S Afr J Med Sci* 11**:** 97–105, 1946
70. Isaacson C, Kincaid-Smith P: Study of the kidney in the Bantu with hypertension. *Br Heart J* 24: 372–374, 1962
71. Adams J: Some racial differences in blood pressure and morbidity in a group of white and colored workers. *Am J Med Sci* 184: 342–350, 1930
72. Allen FP: Cardiovascular impairment among one thousand negro factory workers. *Am J Public Health Nations Health* 22: 579–586, 1932
73. Flaxman N: Heart disease in the Middle West. *Am J Med Sci* 188: 639, 1934
74. Schultze VE, Schwab EH: Arteriolar hypertension in American Negroes. *Am Heart J* 11**:** 66–74, 1936
75. Kean BH: Blood pressure studies on West Indians and Panamanians living on the isthmus of Panama. *Arch Intern Med* 68: 466–475, 1941
76. Saunders GM, Bancroft H: Blood pressure studies on negro and white men and women living in the Virgin Islands of the United States. *Am Heart J* 23: 410–421, 1942
77. Pays E, Vanhollebeke B, Vanhamme L, Paturiaux-Hanocq F, Nolan DP, Pérez-Morga D: The trypanolytic factor of human serum. *Nat Rev Microbiol* 4: 477–486, 2006
78. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, Bowden DW, Langefeld CD, Oleksyk TK, Uscinski Knob AL, Bernhardy AJ, Hicks PJ, Nelson GW, Vanhollebeke B, Winkler CA, Kopp JB, Pays E, Pollak MR: Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 329: 841–845, 2010
79. Ko WY, Rajan P, Gomez F, Scheinfeldt L, An P, Winkler CA, Froment A, Nyambo TB, Omar SA, Wambebe C, Ranciaro A, Hirbo JB, Tishkoff SA: Identifying Darwinian selection acting on different human APOL1 variants among diverse African populations. *Am J Hum Genet* 93: 54–66, 2013
80. Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, Feldman HI, Parekh RS, Kusek JW, Greene TH, Fink JC, Anderson AH, Choi MJ, Wright JT Jr, Lash JP, Freedman BI, Ojo A, Winkler CA, Raj DS, Kopp JB, He J, Jensvold NG, Tao K, Lipkowitz MS, Appel LJ; AASK Study InvestigatorsCRIC Study Investigators: APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 369: 2183–2196, 2013
81. Foster MC, Coresh J, Fornage M, Astor BC, Grams M, Franceschini N, Boerwinkle E, Parekh RS, Kao WH: APOL1 variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol* 24: 1484–1491, 2013
82. Lipkowitz MS, Freedman BI, Langefeld CD, Comeau ME, Bowden DW, Kao WH, Astor BC, Bottinger EP, Iyengar SK, Klotman PE, Freedman RG, Zhang W, Parekh RS, Choi MJ, Nelson GW, Winkler CA, Kopp JB; SK Investigators: Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. *Kidney Int* 83: 114–120, 2013
83. Ito K, Bick AG, Flannick J, Friedman DJ, Genovese G, Parfenov M, Depalma SR, Gupta N, Gabriel S, Taylor HA Jr, Fox E, Newton-Cheh CH, Kathiresan S, Hirschhorn J, Altshuler D, Pollak M, Wilson JG, Seidman JG, Seidman C: Increased burden of cardiovascular disease in carriers of APOL1 Genetic Variants. *Circ Res* 114: 845–850, 2014
84. Madhavan SM, O'Toole JF, Konieczkowski M, Ganesan S, Bruggeman LA, Sedor JR: APOL1 localization in normal kidney and nondiabetic kidney disease. *J Am Soc Nephrol* 22: 2119–2128, 2011
85. Sánchez-Lozada LG, Tapia E, Johnson RJ, Rodríguez-Iturbe B, Herrera-Acosta J: Glomerular hemodynamic changes associated with arteriolar lesions and tubulointerstitial inflammation. *Kidney Int Suppl* 86, Suppl (Suppl): S9–S14, 2003
86. Suthanthiran M, Khanna A, Cukran D, Adhikarla R, Sharma VK, Singh T, August P: Transforming growth factor-beta 1 hyperexpression in African American end-stage renal disease patients. *Kidney Int* 53: 639–644, 1998

87. Suthanthiran M, Li B, Song JO, Ding R, Sharma VK, Schwartz JE, August P: Transforming growth factor-beta 1 hyperexpression in African-American hypertensives: A novel mediator of hypertension and/or target organ damage. *Proc Natl Acad Sci U S A* 97: 3479–3484, 2000
88. Duru K, Farrow S, Wang JM, Lockette W, Kurtz T: Frequency of a deletion polymorphism in the gene for angiotensin converting enzyme is increased in African-Americans with hypertension. *Am J Hypertens* 7: 759–762, 1994
89. McCormack S, Grant SF: Genetics of obesity and type 2 diabetes in African Americans. *J Obes* 2013: 396416, 2013
90. Osler W: *The Principles and Practice of Medicine*, New York, D. Appleton and Co., 1893
91. Helmchen LA, Henderson RM: Changes in the distribution of body mass index of white US men, 1890-2000. *Ann Hum Biol* 31: 174–181, 2004
92. Joslin EP, Dublin LI, Marks HH: Studies in diabetes mellitus. III. Interpretation of the variations in diabetes incidence. *Am J Med Sci* 189: 163–191, 1935
93. Bose CL: Discussion on diabetes in the tropics. III. *BMJ* 19: 1054–1056, 1907
94. Bose RK: Discussion on diabetes in the tropics. II. *BMJ* 19: 1053–1054, 1907
95. Cantle J: Discussion on diabetes in the tropics. [Discussion] *BMJ* 19: 1063, 1907
96. Chakravarti S: Discussion on diabetes in the tropics. IV. *BMJ* 19: 1056–1057, 1907
97. Charles R: Diabetes in the tropics. *BMJ* 19: 1051–1064, 1907
98. Charles R: Discussion on diabetes in the tropics. I. *BMJ* 19: 1051–1053, 1907
99. Fernando HM: Discussion on diabetes in the tropics. [Discussion] *BMJ* 19: 1060, 1907
100. Mallick IM: Discussion on diabetes in the tropics. [Discussion] *BMJ* 19: 1061–1062, 1907
101. Sandwith PM: Discussion on diabetes in the tropics. VI. *BMJ* 19: 1059–1060, 1907
102. Ziemann H: Discussion on diabetes in the tropics. [Discussion] *BMJ* 19: 1061, 1907
103. Cohen AM, Bavly S, Poznanski R: Change of diet of Yemenite Jews in relation to diabetes and ischaemic heart-disease. *Lancet* 2: 1399–1401, 1961
104. Campbell GD: Diabetes in Asians and Africans in and around Durban. *S Afr Med J* 37: 1195–1208, 1963
105. Banting F: The history of insulin. *Edin Med J* 36: 1–18, 1929.
106. Joslin EP, Dublin LI, Marks HH: Studies in diabetes mellitus. II. Its incidence and the factors underlying its variations. *Am J Med Sci* 187: 433–457, 1934
107. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, Shafiu M, Sundaram S, Le M, Ishimoto T, Sautin YY, Lanaspa MA: Sugar, uric acid, and the etiology of diabetes and obesity. *Diabetes* 62: 3307–3315, 2013
108. Ishimoto T, Lanaspa MA, Le MT, Garcia GE, Diggle CP, Maclean PS, Jackman MR, Asipu A, Roncal-Jimenez CA, Kosugi T, Rivard CJ, Maruyama S, Rodriguez-Iturbe B, Sánchez-Lozada LG, Bonthron DT, Sautin YY, Johnson RJ: Opposing effects of fructokinase C and A isoforms on fructose-induced metabolic syndrome in mice. *Proc Natl Acad Sci U S A* 109: 4320–4325, 2012
109. Lanaspa MA, Cicerchi C, Garcia G, Li N, Roncal-Jimenez CA, Rivard CJ, Hunter B, Andrés-Hernando A, Ishimoto T, Sánchez-Lozada LG, Thomas J, Hodges RS, Mant CT, Johnson RJ: Counteracting roles of AMP deaminase and AMP kinase in the development of fatty liver. *PLoS ONE* 7: e48801, 2012
110. Lanaspa MA, Sanchez-Lozada LG, Choi YJ, Cicerchi C, Kanbay M, Roncal-Jimenez CA, Ishimoto T, Li N, Marek G, Duranay M, Schreiner G, Rodriguez-Iturbe B, Nakagawa T, Kang DH, Sautin YY, Johnson RJ: Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. *J Biol Chem* 287: 40732–40744, 2012
111. Lanaspa MA, Sanchez-Lozada LG, Cicerchi C, Li N, Roncal-Jimenez CA, Ishimoto T, Le M, Garcia GE, Thomas JB, Rivard CJ, Andres-Hernando A, Hunter B, Schreiner G, Rodriguez-Iturbe B, Sautin YY, Johnson RJ: Uric acid stimulates fructokinase and accelerates fructose metabolism in the development of fatty liver. *PLoS ONE* 7: e47948, 2012
112. Cicerchi C, Li N, Kratzer J, Garcia G, Roncal Jimenez CA, Tanabe K, Hunter B, Rivard CJ, Sautin YY, Gaucher E, Johnson RJ, Lanaspa MA: Uric acid-dependent inhibition of AMP Kinase induces hepatic glucose production in diabetes and starvation: Evolutionary Implications of the Uricase loss in hominids [published online ahead of print April 22, 2014]. *FASEB J* doi: 10.1096/fj.13-243634
113. Shapiro A, Mu W, Roncal C, Cheng KY, Johnson RJ, Scarpace PJ: Fructose-induced leptin resistance exacerbates weight gain in response to subsequent high-fat feeding. *Am J Physiol Regul Integr Comp Physiol* 295: R1370–R1375, 2008
114. Shapiro A, Tümer N, Gao Y, Cheng KY, Scarpace PJ: Prevention and reversal of diet-induced leptin resistance with a sugar-free diet despite high fat content. *Br J Nutr* 106: 390–397, 2011
115. Cox CL, Stanhope KL, Schwarz JM, Graham JL, Hatcher B, Griffen SC, Bremer AA, Berglund L, McGahan JP, Havel PJ, Keim NL: Consumption of fructose-sweetened beverages for 10 weeks reduces net fat oxidation and energy expenditure in overweight/obese men and women. *Eur J Clin Nutr* 66: 201–208, 2012
116. Roncal-Jimenez CA, Lanaspa MA, Rivard CJ, Nakagawa T, Sanchez-Lozada LG, Jalal D, Andres-Hernando A, Tanabe K, Madero M, Li N, Cicerchi C, Mc Fann K, Sautin YY, Johnson RJ: Sucrose induces fatty liver and pancreatic inflammation in male breeder rats independent of excess energy intake. *Metabolism* 60: 1259–1270, 2011
117. Cummings BP, Stanhope KL, Graham JL, Evans JL, Baskin DG, Griffen SC, Havel PJ: Dietary fructose accelerates the development of diabetes in UCD-T2DM rats: Amelioration by the antioxidant, alpha-lipoic acid. *Am J Physiol Regul Integr Comp Physiol* 298: R1343–R1350, 2010
118. Lanaspa MA, Ishimoto T, Li N, Cicerchi C, Orlicky DJ, Ruzycki P, Rivard C, Inaba S, Roncal-Jimenez CA, Bales ES, Diggle CP, Asipu A, Petrash JM, Kosugi T, Maruyama S, Sanchez-Lozada LG, McManaman JL, Bonthron DT, Sautin YY, Johnson RJ: Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome. *Nat Commun* 4: 2434, 2013
119. Stanhope KL, Bremer AA, Medici V, Nakajima K, Ito Y, Nakano T, Chen G, Fong TH, Lee V, Menorca RI, Keim NL, Havel PJ: Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women. *J Clin Endocrinol Metab* 96: E1596–E1605, 2011
120. Stanhope KL, Griffen SC, Keim NL, Ai M, Otokozawa S, Nakajima K, Schaefer E, Havel PJ: Consumption of fructose-, but not glucose-sweetened beverages produces an atherogenic lipid profile in overweight/obese men and women. *Diabetes* 56[Suppl 1]: A16, 2007
121. Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Ai M, Otokozawa S, Nakajima K, Nakano T, Beysen C, Hellerstein MK, Berglund L, Havel PJ: Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest* 119: 1322–1334, 2009
122. Ha V, Sievenpiper JL, de Souza RJ, Chiavaroli L, Wang DD, Cozma AI, Mirrahimi A, Yu ME, Carleton AJ, Dibuono M, Jenkins AL, Leiter LA, Wolever TM, Beyene J, Kendall CW, Jenkins DJ: Effect of fructose on blood pressure: A systematic review and meta-analysis of controlled feeding trials. *Hypertension* 59: 787–795, 2012
123. Sievenpiper JL, de Souza RJ, Mirrahimi A, Yu ME, Carleton AJ, Beyene J, Chiavaroli L, Di Buono M, Jenkins AL, Leiter LA, Wolever TM, Kendall CW, Jenkins DJ: Effect of fructose on body weight in controlled feeding trials: A systematic review and meta-analysis. *Ann Intern Med* 156: 291–304, 2012

124. Melanson KJ, Zukley L, Lowndes J, Nguyen V, Angelopoulos TJ, Rippe JM: Effects of high-fructose corn syrup and sucrose consumption on circulating glucose, insulin, leptin, and ghrelin and on appetite in normal-weight women. *Nutrition* 23: 103–112, 2007
125. Oda M, Satta Y, Takenaka O, Takahata N: Loss of urate oxidase activity in hominoids and its evolutionary implications. *Mol Biol Evol* 19: 640–653, 2002
126. Tapia E, Cristóbal M, García-Arroyo FE, Soto V, Monroy-Sánchez F, Pacheco U, Lanaspa MA, Roncal-Jiménez CA, Cruz-Robles D, Ishimoto T, Madero M, Johnson RJ, Sánchez-Lozada LG: Synergistic effect of uricase blockade plus physiological amounts of fructose-glucose on glomerular hypertension and oxidative stress in rats. *Am J Physiol Renal Physiol* 304: F727–F736, 2013
127. Johnson RJ, Andrews P: Fructose, uricase, and the back-to-Africa hypothesis. *Evol Anthropol* 19: 250–257, 2010
128. Johnson RJ, Andrews P: Thrifty genes and the greatest pandemic in history: A possible Miocene connection with the epidemics of obesity and diabetes. *Sci Am* 2014, in press
129. Kratzer JT, Lanaspa MA, Murphy MN, Cicerchi C, Gravese CL, Tipton PA, Ortlund EA, Johnson RJ, Gaucher EA: Evolutionary history and metabolic insights of ancient mammalian uricases. *Proc Natl Acad Sci U S A* 111: 3763–3768, 2014
130. Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG, Feig DI, Shafiu M, Segal M, Glassock RJ, Shimada M, Roncal C, Nakagawa T: Hypothesis: Could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev* 30: 96–116, 2009
131. Johnson RJ, Segal MS, Sautin Y, Nakagawa T, Feig DI, Kang DH, Gersch MS, Benner S, Sánchez-Lozada LG: Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. *Am J Clin Nutr* 86: 899–906, 2007
132. Bray GA, Nielsen SJ, Popkin BM: Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* 79: 537–543, 2004
133. Tappy L, Lê KA: Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev* 90: 23–46, 2010
134. Havel PJ: Dietary fructose: Implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. *Nutr Rev* 63: 133–157, 2005
135. Ishimoto T, Lanaspa MA, Rivard CJ, Roncal-Jimenez CA, Orlicky DJ, Cicerchi C, McMahan RH, Abdelmalek MF, Rosen HR, Jackman MR, MacLean PS, Diggle CP, Asipu A, Inaba S, Kosugi T, Sato W, Maruyama S, Sánchez-Lozada LG, Sautin YY, Hill JO, Bonthron DT, Johnson RJ: High-fat and high-sucrose (western) diet induces steatohepatitis that is dependent on fructokinase. *Hepatology* 58: 1632–1643, 2013
136. Hu FB, Malik VS: Sugar-sweetened beverages and risk of obesity and type 2 diabetes: Epidemiologic evidence. *Physiol Behav* 100: 47–54, 2010
137. Malik VS, Pan A, Willett WC, Hu FB: Sugar-sweetened beverages and weight gain in children and adults: A systematic review and meta-analysis. *Am J Clin Nutr* 98: 1084–1102, 2013
138. Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB: Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: A meta-analysis. *Diabetes Care* 33: 2477–2483, 2010
139. Malik VS, Willett WC, Hu FB: Sugar-sweetened beverages and BMI in children and adolescents: Reanalyses of a meta-analysis. *Am J Clin Nutr* 89: 438–439, author reply 439–440, 2009
140. Denova-Gutiérrez E, Jiménez-Aguilar A, Halley-Castillo E, Huitrón-Bravo G, Talavera JO, Pineda-Pérez D, Díaz-Montiel JC, Salmerón J: Association between sweetened beverage consumption and body mass index, proportion of body fat and body fat distribution in Mexican adolescents. *Ann Nutr Metab* 53: 245–251, 2008
141. Denova-Gutiérrez E, Talavera JO, Huitrón-Bravo G, Méndez-Hernández P, Salmerón J: Sweetened beverage consumption and increased risk of metabolic syndrome in Mexican adults. *Public Health Nutr* 13: 835–842, 2010
142. Ludwig DS, Peterson KE, Gortmaker SL: Relation between consumption of sugar-sweetened drinks and childhood obesity: A prospective, observational analysis. *Lancet* 357: 505–508, 2001
143. Maersk M, Belza A, Stødkilde-Jørgensen H, Ringgaard S, Chabanova E, Thomsen H, Pedersen SB, Astrup A, Richelsen B: Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: A 6-mo randomized intervention study. *Am J Clin Nutr* 95: 283–289, 2012
144. Montonen J, Järvinen R, Knekt P, Heliövaara M, Reunanen A: Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. *J Nutr* 137: 1447–1454, 2007
145. Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L: Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. *Arch Intern Med* 168: 1487–1492, 2008
146. Paynter NP, Yeh HC, Voutilainen S, Schmidt MI, Heiss G, Folsom AR, Brancati FL, Kao WH: Coffee and sweetened beverage consumption and the risk of type 2 diabetes mellitus: the atherosclerosis risk in communities study. *Am J Epidemiol* 164: 1075–1084, 2006
147. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB: Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA* 292: 927–934, 2004
148. Mills CA: Diabetes mellitus: Sugar consumption in its etiology. *Arch Intern Med* 46: 582–584, 1930
149. Vartanian LR, Schwartz MB, Brownell KD: Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health* 97: 667–675, 2007
150. Mills CA: Diabetes mellitus: Is climate a responsible factor in the etiology? *Arch Intern Med* 30: 569–581, 1930
151. Dresser C: Food consumption profiles of white and black persons aged 1-74 years: United States 1971-1974. Vital and Health Statistics Series 11. Hyattsville, MD, National Center for Health Statistics, 1979
152. Thompson FE, McNeel TS, Dowling EC, Midthune D, Morrissette M, Zeruto CA: Interrelationships of added sugars intake, socioeconomic status, and race/ethnicity in adults in the United States: National Health Interview Survey, 2005. *J Am Diet Assoc* 109: 1376–1383, 2009
153. World Health Organization: *Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation*, Geneva, Switzerland, World Health Organization, 2003
154. Schmidt LA: New unsweetened truths about sugar. *JAMA Intern Med* 174: 525–526, 2014
155. Gavin JR 3rd: Diabetes in minorities: Reflections on the medical dilemma and the healthcare crisis. *Trans Am Clin Climatol Assoc*, 107: 213–223; discussion 223-215, 1996
156. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J: Global burden of hypertension: Analysis of worldwide data. *Lancet* 365: 217–223, 2005
157. Cappuccio FP, Micah FB, Emmett L, Kerry SM, Antwi S, Martin-Peprah R, Phillips RO, Plange-Rhule J, Eastwood JB: Prevalence, detection, management, and control of hypertension in Ashanti, West Africa. *Hypertension* 43: 1017–1022, 2004
158. Mtabaji JP, Moriguchi Y, Nara Y, Mizushima S, Mano M, Yamori Y: Ethnic differences in salt sensitivity: Genetic or environmental factors? *Clin Exp Pharmacol Physiol Suppl* 20: 65–67, 1992
159. Anderson TA: Recent trends in carbohydrate consumption. *Annu Rev Nutr* 2: 113–132, 1982
160. Nielsen SJ, Popkin BM: Changes in beverage intake between 1977 and 2001. *Am J Prev Med* 27: 205–210, 2004
161. Miller PE, McKinnon RA, Krebs-Smith SM, Subar AF, Chriqui J, Kahle L, Reedy J: Sugar-sweetened beverage consumption in the U.S.: Novel assessment methodology. *Am J Prev Med* 45: 416–421, 2013

162. Johnson RK, Appel LJ, Brands M, Howard BV, Lefevre M, Lustig RH, Sacks F, Steffen LM, Wylie-Rosett J; American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention: Dietary sugars intake and cardiovascular health: A scientific statement from the American Heart Association. *Circulation* 120: 1011–1020, 2009
163. Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK, Ludwig DS: A randomized trial of sugar-sweetened beverages and adolescent body weight. *N Engl J Med* 367: 1407–1416, 2012
164. de Ruyter JC, Olthof MR, Seidell JC, Katan MB: A trial of sugar-free or sugar-sweetened beverages and body weight in children. *N Engl J Med* 367: 1397–1406, 2012
165. Te Morenga L, Mallard S, Mann J: Dietary sugars and body weight: Systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* 346: e7492, 2013
166. Hu FB: Resolved: There is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. *Obes Rev* 14: 606–619, 2013
167. Chen L, Caballero B, Mitchell DC, Loria C, Lin PH, Champagne CM, Elmer PJ, Ard JD, Batch BC, Anderson CA, Appel LJ: Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: A prospective study among United States adults. *Circulation* 121: 2398–2406, 2010
168. Walker RW, Lê KA, Davis J, Alderete TL, Cherry R, Lebel S, Goran MI: High rates of fructose malabsorption are associated with reduced liver fat in obese African Americans. *J Am Coll Nutr* 31: 369–374, 2012
169. Burant CF, Saxena M: Rapid reversible substrate regulation of fructose transporter expression in rat small intestine and kidney. *Am J Physiol* 267: G71–G79, 1994
170. Gaffo AL, Jacobs DR Jr, Lewis CE, Mikuls TR, Saag KG: Association between being African-American, serum urate levels and the risk of developing hyperuricemia: Findings from the Coronary Artery Risk Development in Young Adults cohort. *Arthritis Res Ther* 14: R4, 2012
171. Dehghan A, Köttgen A, Yang Q, Hwang SJ, Kao WL, Rivadeneira F, Boerwinkle E, Levy D, Hofman A, Astor BC, Benjamin EJ, van Duijn CM, Witteman JC, Coresh J, Fox CS: Association of three genetic loci with uric acid concentration and risk of gout: A genome-wide association study. *Lancet* 372: 1953–1961, 2008
172. Merriman TR: Population heterogeneity in the genetic control of serum urate. *Semin Nephrol* 31: 420–425, 2011
173. Choi JW, Ford ES, Gao X, Choi HK: Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: The Third National Health and Nutrition Examination Survey. *Arthritis Rheum* 59: 109–116, 2008
174. McAdams-DeMarco MA, Law A, Maynard JW, Coresh J, Baer AN: Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. *BMC Musculoskelet Disord* 14: 347, 2013