Interethnic Differences in Serum Lipids and Implications for Cardiometabolic Disease Risk in African Ancestry Populations

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ABSTRACT

African Americans generally have a healthier lipid profile (lower triglycerides and higher high-density lipoprotein cholesterol concentration) compared with those of other ethnicities. Paradoxically, African Americans do not experience a decreased risk of the cardiometabolic diseases that serum lipids are expected to predict. This review explores this mismatch between biomarker and disease among African ancestry individuals by investigating the presence of interethnic differences in the biological relationships underlying the serum lipids—disease association. This review also discusses the physiologic and genomic factors underlying these interethnic differences. Additionally, because of the importance of serum lipids in assessing disease risk, interethnic differences in serum lipids have implications for identifying African ancestry individuals at risk of cardiometabolic disease. Where possible, data from Africa is included, to further elucidate these ancestral differences in the context of a different environmental background.

African Americans (AA) are generally found to have a healthier lipid profile (lower triglycerides [TG] and higher high-density lipoprotein cholesterol concentration [HDLC]) with a less atherogenic distribution of lipoprotein particles [1-3] compared with those of other ethnicities. Based on the more favorable lipid profile among African ancestry individuals and the established role of serum lipids as a biomarker predictive of cardiometabolic disease, one could reasonably anticipate a reduced burden of these diseases among AA. Epidemiological data, however, do not support this expectation (Table 1) [4]. In fact, AA have a markedly higher prevalence of cardiovascular disease than European ancestry (EA) individuals, driven primarily by a higher prevalence of hypertension. The prevalence of type 2 diabetes (T2D) in AA is more than twice the prevalence in EA individuals. This mismatch between biomarker and disease among AA suggests that ancestry may add further complexity to the underlying relationships that serum lipids are expected to capture. We will try to answer why a favorable lipid profile does not translate into reduced cardiometabolic risk for African ancestry individuals. To address this key question, we will investigate the assumptions necessary to go from biomarker to disease and assess how interethnic differences could affect these assumptions. Moreover, we will discuss the physiologic and genomic factors underlying these interethnic differences. Finally, we will investigate the impact that this mismatch may have on identifying African ancestry individuals at risk of cardiometabolic disease. Much of the evidence relevant to this "metabolic paradox" involves comparisons of AA and EA, yet observations in West Africans may also be of considerable importance. Whereas admixed AA have a large proportion of shared ancestry with West Africans (~80%), the environmental context is dramatically different across populations, which may prove to be very informative for understanding the relative contributions of inherited and environmental influences on these complex traits. West African individuals are generally leaner and more physically active than their AA counterparts, yet with increasing urbanization and Westernization, they are also experiencing dramatic increases in cardiometabolic disease. In fact, it is anticipated that Africa will experience some of the most dramatic increases in T2D worldwide [5]. Complex disease research in Africa is experiencing notable advances, spurred, in part, by efforts such as the Human Health and Heredity in Africa initiative (H3Africa [6,7]), more data from Africa is available, with much more anticipated in the short term as major research projects release results. Thus, in this review, we will address these questions, drawing in data from Africa where available.

INTERETHNIC DIFFERENCES IN SERUM LIPIDS

Ethnic differences in serum lipids have been widely reported. The most consistently observed difference in the concentration of serum lipids is lower TG among African ancestry individuals. This difference can be seen among ethnicities in the United States in the NHANES (National Health and Nutrition Examination Survey) dataset, which was designed to be representative of the US population: mean TG was 113, 143, and 158 mg/dl in AA, European Americans, and Mexican Americans, respectively [8]. Differences in TG are also observed in children; for example, TG was 15.7 mg/dl lower among AA compared with

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TABLE 1. U.S. prevalence of cardiometabolic diseases and predictors of risk

	African American		European American	
	Men	Women	Men	Women
Cardiovascular disease	44.8	47.3	37.4	33.8
Coronary heart disease	7.9	7.6	8.5	5.8
Myocardial infarction	4.3	2.2	4.3	2.1
Stroke	4.5	4.4	2.4	3.3
Hypertension	43.0	45.7	33.9	31.3
Diagnosed diabetes mellitus	14.3	14.7	6.8	6.5
Undiagnosed diabetes mellitus	4.8	4.0	3.9	1.9
Heart failure	4.5	3.8	2.7	1.8
Metabolic syndrome	25.3	38.8	37.2	31.5
Low HDL	16.6	6.6	29.5	10.1
Overweight and obesity	70.8	77.7	72.3	59.3

Non-Hispanic white and black individuals ≥20 years. Data from AHA Report on Heart Disease and Stroke Statistics [4]. All data given as percentages.
HDL, high-density lipoprotein.

non-AA children (predominantly EA) [9]. The prevalence of high TG (>150 mg/dl) among NHANES AA children and adolescents was less than one-half that of EA [10]. Data from West Africa agree with these findings, with mean TG values that are generally even lower than what is observed among admixed AA. For illustration, mean TG values from population-based studies of adults without lipid-altering diseases are presented by ethnicity (Figure 1) [8,11-28].

Among US populations, AA are also generally found to have HDLC concentrations about 4 to 5 mg/dl higher than those of other ethnic groups [8], differences that are also apparent in studies of children and adolescents [1,9,10,29,30]. However, this difference in distribution is not what is observed among Africans, where the HDLC concentration is more similar to [31,32] or lower [33,34] than what is observed in EA individuals. It is unclear what leads to this discrepancy between African ancestry individuals in different locations, but it seems reasonable that HDLC is under the influence of an environmental factor that differs between the United States and Africa. Some environmental factors—malnutrition and urbanization—are worth investigating further in order to understand these low HDLC concentrations among Africans. Researchers have found the low HDLC co-occurs with micronutrient deficiencies, as well as with low body weight [35]. Studies of the Capetown, South Africa, in 1990 and in 2008/2009 showed marked increases in the prevalence of low HDLC, from 37.3% to 55.1% among men and 30.0% to 67.7% among women. Peer et al. [36] highlight increasing adiposity and urbanization as likely contributors. In contrast, higher HDLC values were observed among members of the Gbagi tribe in Abuja, Nigeria, who were living in an urban compared with a rural environment, despite higher body mass index (BMI) and waist circumference among the urban dwellers [11]. Further work is necessary to disentangle the components of "urbanization" that are most relevant for cardiometabolic disease risk. An intriguing study of 1,266 diabetic individuals in the Congo suggests a different association between HDLC and cardiometabolic disease in this environment: among individuals with low HDLC, the rate of fatal cardiovascular events was 13.5%, but among those with high HDLC, the rate was 20%. Additionally, the mean change in blood glucose after a meal was similar in the high and low categories (131.2 and 137.0 mg/dl, respectively) and was much lower in those with intermediate HDLC levels (87 mg/dl). Importantly, HDLC also had a U-shaped relationship with risk of atherosclerotic complications [37]. Further investigations into this relationship in other African populations are needed.

PHYSIOLOGY UNDERLYING INTERETHNIC DIFFERENCES IN SERUM LIPIDS

Serum lipids are strongly correlated with fat distribution, particularly an individual's visceral adipose tissue. Visceral adipose tissue is known to be a uniquely pathogenic fat depot in terms of cardiometabolic risk. Visceral adipose tissue is more strongly associated with development of key perturbations for cardiometabolic risk, including impaired glucose tolerance, blood pressure, and dyslipidemia, than are other anthropometric measures (including BMI, waist circumference, waist-hip ratio, leg fat percentage, trunk fat percentage) [38] or subcutaneous adipose tissue [39,40]. Visceral adipose tissue is known to correlate strongly with serum lipids, with increased visceral adipose tissue contributing to increased liver fat content, which, in turn, leads to greater production of very low-density lipoprotein and higher circulating TG [41]. In fact, in a study of 723 AA and EA men and women, visceral adipose tissue explained over 24% of the variation in fasting TG and 31%

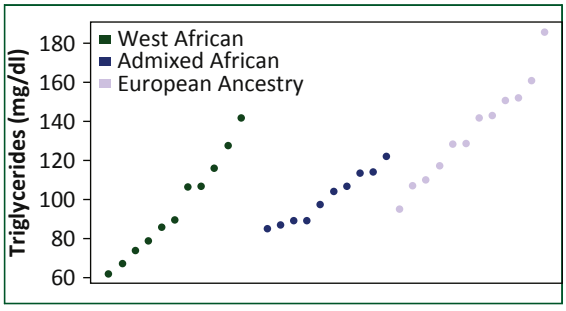

FIGURE 1. Distribution of triglycerides by ancestry. Reported triglyceride values in studies of West Africans [11-20], African Americans [8,14,17,21-23,25-28], and those of European ancestry [8,21-25,27]. Limited to those without disease (type 2 diabetes, hypertension, human immunodeficiency virus, or liver disease). Weighted means were used to combine by sex and alcohol drinking status (if reported). Due to amount of available data, European ancestry studies were limited to the United States and the United Kingdom.

of the ratio of total cholesterol to HDLC [42]. Liver fat has been argued to be a more relevant (yet strongly correlated) depot and was shown to be a better predictor of concentration of very low-density lipoprotein than was visceral adipose tissue [1].

African ancestry individuals are less prone to deposit fat in the depots associated with increased cardiometabolic risk. Visceral adipose tissue is markedly lower among AA compared with EA individuals [43,44]. For example, in a comparison of EA from the Framingham Heart Study and AA from Jackson Heart Study, the mean visceral adipose tissue among AA women was one-half that of EA women (774.5 vs. 1536.7 cm^3), with an even greater difference among men (840.6 vs. 2455.8 cm^3), despite a higher BMI in AA [45]. At similar height and proportions of body fat, trunk fat, and leg fat, obese AA women had lower visceral adipose tissue and TG than their EA counterparts [38]. Similar results were observed for African Caribbean individuals compared with those of European and South Asian ancestry [46]. AA also have less fat in the peritoneal cavity and less liver fat compared with individuals of EA and Hispanic ancestry after adjusting for age and total body fat [47]. Likewise, a lower prevalence of fatty liver was observed among AA compared with other ethnicities in the MESA (Multi-Ethnic Study of Atherosclerosis), even after adjusting for relevant risk factors [48]. In contrast, AA generally deposit fat more readily in less metabolically active regions, such as the subcutaneous tissue and in the lower extremities [47].

Underlying interethnic differences in visceral adipose tissue are further complicated by ethnic variability in the ability to approximate this parameter with a common measurement, waist circumference. Despite the fact that waist circumference captures both subcutaneous and visceral adipose tissue, it has been shown to be a good predictor of visceral adipose tissue among both EA and AA [49]. As might be expected given interethnic (and sex) differences in subcutaneous and visceral adipose tissue deposition, significant sex-ethnicity interactions were observed in this relationship [49]. Increasing waist circumference was associated with larger increases in visceral adipose tissue in women of European ancestry compared with those of African ancestry. The association between waist circumference and visceral adipose tissue was the same, however, among AA, West Africans, black South Africans, and African immigrants in the United States [50].

Given the central role of visceral adipose tissue in the distribution of serum lipids, and the interethnic differences in how overall adiposity reflects visceral adipose tissue, the relationship between body fatness and serum lipids is weaker in AA than in other ethnicities [9,10,51]. This difference has also been observed in African ancestry versus EA adolescents in South Africa, an environment in which the EA individuals were heavier than the African ancestry individuals, the reverse of what is observed in the United States [52]. There is some evidence of sexual dimorphism in the association between visceral adipose tissue and serum lipids: associations were weaker among AA women from the Jackson Heart Study compared with EA women from the Framingham Heart Study, but AA men had a stronger association between visceral adipose tissue and serum lipids than did EA men [45]. Similarly, among Tanzanian men, BMI was significantly correlated with both TG and HDLC, whereas it was not associated with serum lipids among women [53]. These findings are likely to reflect both ethnic and sex differences in fat distribution.

The fact that African ancestry individuals have lower fat deposition in the regions associated with higher cardiometabolic risk is undoubtedly an important factor underlying the observed interethnic differences in serum lipids. However, it is important to note that AA still had significantly lower TG than either Hispanic or European ancestry individuals even after adjustment for liver fat content [47]. The observed interethnic differences in serum lipids may also be influenced by interethnic differences in the activity of lipoprotein lipase (LPL), acute insulin response, and apolipoprotein CIII (ApoCIII) concentration.

LPL is the enzyme primarily responsible for the hydrolysis of TG. AA have significantly greater LPL activity than do EA [42]. LPL activity explained 23.2% of the variability in HDLC, whereas the addition of sex, fat mass, visceral adipose tissue, and age only accounted for an additional 10.3%. After adjusting for this set of variables, no significant effect of ethnicity remained. In contrast, whereas LPL activity was also a significant predictor of TG, it explained less of the variability in TG (4.8%), with visceral adipose tissue being the strongest predictor (24.2%) and ethnicity remaining significant [42]. Thus, these predictors do not completely explain the differences in TG due to ethnicity.

Ethnic differences in insulin response may underlie some of the observed differences in LPL activity. Insulin stimulates LPL, and a significantly higher acute insulin response to glucose challenge has been observed in AA compared with EA individuals, even after adjustment for obesity, body fat distribution, and behavioral factors [54]. A nearly 2.5× higher acute insulin response was seen among AA compared with age- and BMI-matched EA women [55], with similar results observed in children [56,57]. This increased insulin response is associated with greater clearance of free fatty acids, which may contribute to lower constitutive TG levels. There is also some evidence of higher *LPL* messenger ribonucleic acid expression in subcutaneous compared with visceral adipose tissue [58,59], and differences in distribution of body fat has also been proposed as contributing to higher LPL activity among African ancestry individuals [34].

ApoCIII is an apolipoprotein on the surface of very low-density lipoprotein particles that inhibits LPL and hepatic lipase. AA have lower ApoCIII than do EA, and interethnic differences in TG were no longer statistically significant after adjusting for ApoCIII levels [60]. Similarly, in an analysis of AA and EA women of similar age and BMI, in multivariate models, visceral adipose tissue and ApoCIII

were statistically significant predictors of TG concentration, and, after adjusting for these parameters, ethnicity was no longer associated with TG [61].

Based on these findings, it seems reasonable to assume that interethnic differences in visceral adipose tissue, LPL activity, acute insulin response, and ApoCIII concentration relatedly or independently explain the interethnic differences observed in serum lipids. However, considering the confluence of interethnic differences in all of these parameters of significance to cardiometabolic health, how well do serum lipids serve as biomarkers for insulin resistance and cardiovascular risk?

SERUM LIPIDS AND INSULIN RESISTANCE AMONG AFRICAN ANCESTRY INDIVIDUALS

Insulin resistance is associated with dyslipidemia, one of the significant reasons that serum lipids are included as markers of cardiometabolic risk, yet there is evidence of interethnic differences in the association between serum lipids and insulin resistance, as has been previously reviewed [62-65]. As mentioned above, insulin stimulates LPL activity, and insulin resistance is thought to depress LPL activity [66,67], one of the mechanisms through which insulin resistance is thought to lead to increased TG. A key study of AA confirmed the strong inverse association between LPL activity and TG concentration (adjusted $R^2 = 54\%$; $p < 0.001$), yet showed no difference in LPL activity across tertiles of insulin resistance. Thus, insulin resistance did not diminish LPL activity among AA, one explanation for apparent protection from the elevated TG that is associated with insulin resistance [68]. In agreement with these data, after adjusting for visceral adipose tissue, insulin resistance was not associated with TG concentration among AA women [61]. Likewise, in a separate study, neither HDLC nor TG correlated with insulin sensitivity among AA women, though both were strongly associated among EA women [69]. Similar findings were observed in South Africa among individuals of African and European descent [33]. There was no significant association between lipid profiles and impaired glucose regulation among East African young people [70]. The ratio of TG to HDLC is being considered as a less invasive predictor of insulin resistance and has been shown to be useful in other ethnic groups [71,72]. However, the predictive value of this ratio is less clear among those of African ancestry. The ratio was found not to be associated with insulin resistance among AA women [73,74]. The ratio was predictive of fasting blood glucose among Ghanaian women, though the optimal threshold was considerably lower than had been found among other ethnic groups [75]. The interethnic differences in fat deposition, serum lipids, and insulin resistance are well described in a study of 2,170 African, European, and Hispanic Americans [47]. AA had the lowest level of intraperitoneal fat, liver fat, and TG, but a similar prevalence of insulin resistance as Hispanic ancestry individuals, who had the highest level of intraperitoneal fat, liver fat, and TG. Even after adjustment for intraperitoneal fat, AA still had the highest insulin resistance and the lowest TG of the 3 groups. Guerrero et al. [47] concluded that the metabolic response to obesity and insulin resistance differs in AA compared with the other ethnicities. In contrast to other ethnicities, insulin resistance among AA occurred with relatively lower TG, higher HDLC, lower visceral adiposity, and lower levels of liver TG [47]. Thus, serum lipids do not reflect insulin resistance in the same way among AA and other ethnic groups.

SERUM LIPIDS, OBESITY, AND CARDIOVASCULAR DISEASE RISK

There is also some evidence of a different association between serum lipids and cardiovascular disease among African ancestry individuals. The INTERHEART Africa project was an extension of the original INTERHEART study, a global study of risk factors for acute myocardial infarction, that added 9 sub-Saharan African countries to the initial 52 included countries. The ratio of apolipoprotein B (associated predominantly with low-density lipoprotein particles) to apolipoprotein A-1 (associated with HDL particles) had a much lower odds ratio among black Africans than among Europeans/other Africans (3.43 vs. 6.88) [76]. Similarly, the Framingham Heart Study equations, designed on the basis of the association of risk factors (including serum lipids) with cardiovascular outcomes in a prospective study of EA were not highly predictive of cardiovascular disease mortality in AA [77]. The Dallas Heart Study reports interethnic differences in the association between HDLC and coronary heart disease: whereas there was an inverse association among EA, HDLC and coronary heart disease were not associated among AA [78]. In a study of individuals in the United Kingdom, African Caribbeans had a 35% lower risk of coronary heart disease and 50% higher risk of stroke than EA individuals, even after adjusting for traditional risk factors, including BMI and serum lipids [21].

Similarly, there is also evidence of a different association between obesity and cardiometabolic disease by ethnicity. At every category of BMI, AA participants in the Jackson Heart Study had higher prevalence of T2D and hypertension than EA in the Framingham Heart Study, despite lower prevalence of high TG and similar prevalence of low HDLC. Significant ethnicity-BMI interactions were observed in the association between BMI and each of these outcomes, indicating that across obesity categories, BMI was more strongly associated with negative metabolic consequences in EA compared with AA [79]. Similar observations have been made in other studies [38,80-82]. In the INTERHEART Africa project, the association between acute myocardial infarction as predicted by abdominal obesity and acute myocardial infarction was dramatically lower among

black Africans compared to Europeans/other Africans (2.01 vs. 5.53) [76].

THE METABOLIC SYNDROME

Given the known interrelatedness between risk factors and outcomes for cardiovascular disease and T2D, the metabolic syndrome (MetSyn) classification was designed to capture the impact of several cardiometabolic risk factors (low TG, high HDLC, high fasting blood glucose, high abdominal obesity, and high blood pressure) in order to identify individuals at increased risk of disease for targeted interventions. Given the generally healthier lipid profile among African ancestry individuals and that the concentration of serum lipids are evaluated in 2 of the 5 included thresholds, one might expect a decreased prevalence of MetSyn among AA compared with EA. This has been observed, particularly among adolescents and children. Among NHANES adolescents, the prevalence of MetSyn among AA was less than one-half that among EA, and this primarily reflected much lower presence of high TG (12.9% in AA, 38.1% in EA, and 45.0% among Hispanic Americans) and low HDLC (19.0% of AA, 35.7% in EA, and 41.6% in Hispanic Americans) [83]. Among adults, however, the prevalence of MetSyn is not consistently lower among AA compared with other ethnic groups. Whereas the presence of dyslipidemia, especially high TG, is still generally lower among AA than EA, a higher prevalence of elevations in blood pressure and fasting blood glucose may offset the more favorable lipid profile. Among women, especially, higher waist circumference often drives a greater prevalence of MetSyn among AA, whereas the prevalence of MetSyn among AA men remains lower than [4,22] or equivalent to [23] what is observed among EA. Data on the prevalence and contributors to MetSyn among Africans adds further complexity to this picture. Whereas AA generally have high or comparable HDLC levels compared with those of EA, West Africans have a higher degree of low HDLC [84]. In contrast to studies in the United States, where the prevalence of low HDLC and high TG are similar [23], in studies in Africa, these MetSyn components are often highly discordant. Among Nigerian T2D individuals, 61.8% had low HDLC, whereas only 10% had low TG [85]. Among Ghanaian hypertension patients with MetSyn, 96% had low HDLC, but only 32% had high TG [86]. In a Ugandan rural general population, 71.3% had low HDLC, but only 5% had high TG [87]. As seen among AA, higher abdominal obesity fuels higher MetSyn rates among women compared with men [53,85].

Whereas the evidence clearly indicates that interethnic differences in the distribution of serum lipids reduce the number of African ancestry individuals that are classified as having MetSyn, it is a separate question whether that classification is underidentifying individuals that are at risk. Whereas the mismatch in the prevalence of MetSyn compared with cardiovascular disease and T2D in African ancestry individuals certainly supports the underidentification of this rubric, there is further evidence that is relevant.

MetSyn has been associated with greater vascular dysfunction in both AA and EA [23]. However, in individuals without MetSyn, AA had worse vascular function than EA did [23,88], suggesting that at-risk AA individuals are not being sufficiently captured by the MetSyn criteria. Impaired endothelium-dependent dilation, a key early event in the development of atherosclerosis [89], and the metabolic determinants of endothelium-dependent vasodilation differed by ethnicity: systolic blood pressure was a more significant predictor among in AA, whereas insulin resistance was a more significant predictor among EA [88]. Increased weighting of hypertension in AA eliminated ethnic differences in some vascular measures, but it did not eliminate the worse microvascular endothelial function observed in AA compared with EA subjects without MetSyn, suggesting that factors other than blood pressure are contributing to the increased microvascular dysfunction seen in AA [23]. The prevalence of peripheral artery disease, which usually reflects underlying atherosclerosis in peripheral arteries, is also informative. Among individuals from the NHANES dataset with peripheral artery disease, the proportion of individuals who were classified as having MetSyn was much smaller among AA (24.5%) than EA (41.5%) and Hispanic (38.9%). Conversely, the prevalence of peripheral artery disease among those with MetSyn was significantly higher in AA (12.0%) than EA (7.2%) and Hispanic (4.6%) individuals [90]. Individuals with peripheral artery disease are often asymptomatic, but at high risk of cardiovascular disease events, but these data indicate that AA with this disease are less likely to be identified by MetSyn, and, when they are, more subclinical disease may be present [90].

GENOMIC INFLUENCES ON INTERETHNIC DIFFERENCES IN SERUM LIPIDS

Given the consistently lower TG distribution across African ancestry populations despite divergent environmental backgrounds, it seems clear that genetic factors contribute to these interethnic differences. The less consistent differences with HDLC, particularly the generally higher HDLC among AA than other ethnicities in the United States compared with the generally lower HDLC among African ancestry populations in Africa, support an important role for an environmental factor(s) that differs in the United States and Africa. AA are an admixed population, with chromosomes that are a mosaic of segments that are inherited from 2 main parental populations, West African and European. In an individual, ancestry at a particular locus can be estimated based on allele frequencies in the parental populations giving a probability that the person has 0, 1, or 2 African alleles at that site. By averaging these values across the genome, an individual's genome-wide average ancestry can be estimated. With considerable variability, AA have approximately 80% African

ancestry. Simple association tests show that a 10% increase in African ancestry correlates with a 1% decrease in TG and a 0.7 mg/dl increase in HDLC, after adjustment for covariates [91]. Similar results have also been found in other studies [92,93].

Admixture mapping is a process that takes advantage of interethnic differences in phenotypes to isolate regions of the genome where local ancestry in admixed individuals is associated with a trait: if European ancestry is higher in a particular region among AA with low HDLC, then variants in that region may be associated with HDLC. For HDLC, admixture mapping and subsequent follow-up pointed to the influence of *LPL* for HDLC concentration [28], as had been previously reported [93]. For TG, 3 independent signals were discovered, 1 in an intergenic region, 1 in *NRXN3*, and 1 in *TTC7B* [28]. Interestingly, the associated single-nucleotide polymorphism in *NRXN3* had previously been associated with obesity, BMI, and waist circumference in a genome-wide association study [94-96]. A previous admixture study had also identified *GCKR* as potentially contributing to interethnic differences in TG [93]; this locus is an established lipids locus [24].

Lipoprotein lipase is a central enzyme in the concentration of serum lipids. Variants in this gene, particularly missense variant rs328, are well established as contributing to serum lipid concentrations. rs328 is associated with increased LPL activity, which increases lipolysis, decreasing TG and increasing HDLC concentrations. This variant is less prevalent among African ancestry than EA individuals (minor allele frequency among 1,000 genomes: African: 0.05 vs. EA: 0.12 [97]). Interestingly, ethnic differences at this locus have been observed. A study of AA from the Howard University Family Study found that associations between rs328 and serum lipids differed depending on the ancestry of the individual at that locus (the local ancestry). Among AA with EA at this locus, the variant was associated with a more favorable lipid profile than among those with only African ancestry at this locus. For TG, the association among AA with only European local ancestry matched what had previously been reported for EA. For HDLC, however, the association among AA with only European local ancestry was much higher than what had been previously reported for EA (15 vs. ~5 mg/dl). For both TG and HDLC, the associations among individuals with only African local ancestry matched associations found among West Africans at that locus (Figure 2) [98-103]. In agreement with these data, a study of AA in the Jackson Heart Study also showed a larger effect size for rs328 in the presence of European local ancestry [93]. Deo et al. [93] propose that these results suggest that a causal variant for this effect is not rs328, but a variant that is tightly linked with rs328 on a European ancestry background, but not on an African background. In a large meta-analysis of >100,000 EA individuals, *LPL* variant rs12678919 (in tight linkage disequilibrium with rs328) was strongly associated with a favorable lipid profile (higher HDLC and lower TG). This association was replicated in a follow-up sample of AA. There was no statistically significant heterogeneity for AA

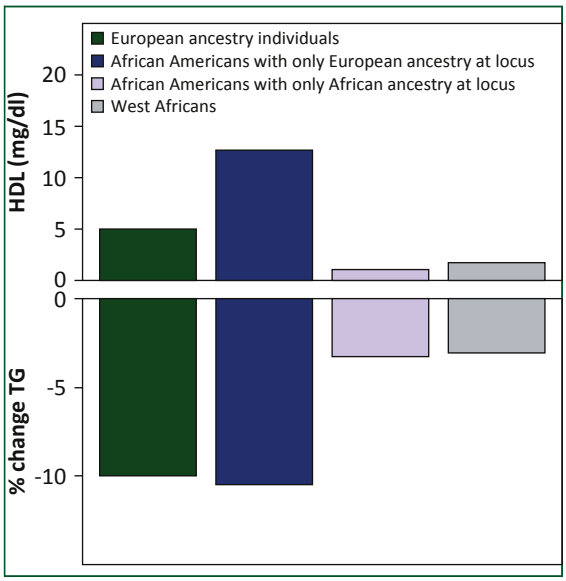

FIGURE 2. Interethnic differences in the association between *LPL* variant rs328 and serum lipids. Reported data on associations for rs328 for individuals of European (high-density lipoprotein [HDL] [98-101] and triglycerides [TG] [102]) and African ancestry individuals [97].

compared with EA; however, the association in AA was much less statistically significant than in the comparably sized EA replication analysis ($p = 5 \times 10^{-3}$ vs. 1×10^{-11} for n = 8,061 and 7,063) [24].

A study of black and white South African women showed interethnic differences in the associations among 3 established lipids genes, *LPL*, *LIPC* (hepatic lipase), and *CETP* (cholesterylester transfer protein). In contrast to the direction of the ancestry differences at *LPL* reported here, the associations for *LPL* were significant in black South African women, but not among their white counterparts, despite a larger sample size and a higher prevalence of the variant. Similar interethnic differences were observed for *LIPC* and *CETP* [34]. In contrast, associations in these genes in EA and AA have been observed to be broadly similar [24,92,104,105]. Both *LPL* and *CETP* have been implicated in genome-wide studies of MetSyn in EA [106,107], AA [108], and, recently, in Africans [109].

Beyond these notable variants, generally similar results have been seen for genome-wide association studies of lipids across ethnicities [24,92,104]; however, the relatively limited degree of replication of EA-discovered loci among AA has been noted [8,104]. For instance, a large meta-analysis of >100,000 EA identified 95 lipids loci and attempted replication of these in 8,071 AA; only 30% of the single-nucleotide polymorphisms tested for each trait were generalizable to AA (directionally consistent and $p < 0.05$) (Table S12 of [24]). Failure to replicate findings among African ancestry individuals could represent the following: relatively smaller sample sizes among African

ancestry studies; interethnic differences in linkage disequilibrium such that variants tagging a causal locus among EA may not tag the locus among AA; interethnic differences in allele frequencies; or difference across populations in the relative importance of a particular locus as a result of different selection pressures. Larger genome-wide studies of African ancestry individuals are needed. Additionally, careful consideration of linkage disequilibrium structure differences across ancestries can yield new insights in previously identified regions [104,110].

FUTURE DIRECTIONS: IMPROVING THE IDENTIFICATION OF AT-RISK INDIVIDUALS

In the context of interethnic differences in the prevalence of risk factors and in the association between risk factors and disease, ancestry-agnostic thresholds seem inadequate. Yet identifying individuals of African ancestry at higher risk of cardiometabolic disease is an urgent public health need both in the United States, where the disproportionate burden of disease is borne by AA, and in Africa, where urbanization and Westernization are contributing to some of the fastest anticipated increases in cardiometabolic diseases in the world. What can be done to improve identification of these at-risk individuals for more aggressive treatment?

It has been proposed that the MetSyn could be altered to improve risk identification among African ancestry individuals. Some have suggested that establishing ethnic-specific thresholds for serum lipids should be adopted to reflect the lower values at which serum lipids may associate with insulin resistance [111,112]. It has also been suggested to alter the obesity threshold values: lowering the threshold values for African ancestry men, whereas threshold values remain high for women [113,114]. Weighting hypertension more heavily in the classification of MetSyn among AA has been shown to better distinguish between AA with and without microvascular dysfunction, although this improvement does not eliminate interethnic differences in endothelial dysfunction [23]. Another approach that has been proposed is creating a continuous MetSyn severity score that allows for different loadings for each component across ethnicity and sex groups. For instance, analyses of NHANES data resulted in equations that down-weighted TG in AA compared with EA. Importantly, this method also provides a useful tool for follow-up of an individual's risk over time [115].

Beyond the MetSyn classification, it is worth considering other risk factors that may result in an improved identification of at-risk African ancestry individuals. One such possible biomarker is lipoprotein(a), which has been associated with increased cardiovascular disease outcomes [116-118]. Lipoprotein(a) is typically much higher in AA than EA; for instance, median lipoprotein(a)was 4.3 mg/dl in EA and 12.8 mg/dl in the AA of Atherosclerosis Risk in Communities study [118]. Lipoprotein(a) has been associated with similar increased cardiovascular disease risk in both EA and AA [118]. Additionally, a measure informative for chronic kidney disease has been proposed to improve identification of cardiometabolic risk among African ancestry populations [63].

SUMMARY

Overall, the presence of important interethnic differences in the distribution of serum lipids, along with a range of other factors that are relevant for cardiometabolic risk motivate the need to conduct more research in African ancestry populations. Studies that investigate the association between serum lipids and risk of disease among African ancestry populations, especially in a range of environmental contexts, are urgently needed. Additionally, studies evaluating known and novel biomarkers that may more effectively identify cardiometabolic risk among African ancestry populations could be of enormous public health significance given the large and growing burden of disease among these individuals.

REFERENCES

1. D'Adamo E, Northrup V, Weiss R, et al. Ethnic differences in lipoprotein subclasses in obese adolescents: importance of liver and intraabdominal fat accretion. Am J Clin Nutr 2010;92:500–8.
2. Johnson JL, Slentz CA, Duscha BD, et al. Gender and racial differences in lipoprotein subclass distributions: the STRRIDE study. Atherosclerosis 2004;176:371–7.
3. Miljkovic-Gacic I, Bunker CH, Ferrell RE, et al. Lipoprotein subclass and particle size differences in Afro-Caribbeans, African Americans, and white Americans: associations with hepatic lipase gene variation. Metabolism 2006;55:96–102.
4. Roger VL, Go AS, Lloyd-Jones DM, et al., for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125:e2–220.
5. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–53.
6. Ramsay M, Growing genomic research on the African continent: the H3Africa Consortium. S Afr Med J 2015;105:1016–7.
7. H3Africa. Welcome. Available at: www.h3africa.org. Accessed February 10, 2017.
8. Chang MH, Ned RM, Hong Y, et al. Racial/ethnic variation in the association of lipid-related genetic variants with blood lipids in the US adult population. Circ Cardiovasc Genet 2011;4:523–33.
9. Dai S, Fulton JE, Harrist RB, Grunbaum JA, Steffen LM, Labarthe DR. Blood lipids in children: age-related patterns and association with body-fat indices: Project HeartBeat! Am J Prev Med 2009;37(Suppl 1): S56–64.
10. Lamb MM, Ogden CL, Carroll MD, Lacher DA, Flegal KM. Association of body fat percentage with lipid concentrations in children and adolescents: United States, 1999—2004. Am J Clin Nutr 2011;94: 877–83.
11. Adediran O, Akintunde AA, Edo AE, Opadijo OG, Araoye AM. Impact of urbanization and gender on frequency of metabolic syndrome among native Abuja settlers in Nigeria. J Cardiovasc Dis Res 2012;3: 191–6.
12. Sossa C, Delisle H, Agueh V, Makoutodé M, Fayomi B. Insulin resistance status and four-year changes in other cardiometabolic risk factors in West-African adults: the Benin study. Eur J Prev Cardiol 2013;20:1042–50.
13. Thiombiano LP, Mbaye A, Sarr SA, et al. Prévalence de la dyslipidémie dans la population rurale de Guéoul (Sénégal). Ann Cardiol Angéiol 2016;65:77–80.

14. Bentley AR, Doumatey AP, Chen G, et al. Variation in APOL1 contributes to ancestry-level differences in HDLc-kidney function association. Int J Nephrol 2012;2012:748984.
15. Fontbonne A, Cournil A, Cames C, et al. Anthropometric characteristics and cardiometabolic risk factors in a sample of urban-dwelling adults in Senegal. Diabetes Metab 2011;37:52–8.
16. Ahaneku GI, Ahaneku JE, Osuji CU, Oguejiofor CO, Opara PC. Lipid patterns, alcohol intake and BMI of adult Nigerians in a sub-urban slum in Enugu, Nigeria. Pan Afr Med J 2014;18:37.
17. Clark DO, Gao S, Lane KA, et al. Obesity and 10-year mortality in very old African Americans and Yoruba-Nigerians: exploring the obesity paradox. J Gerontol A Biol Sci Med Sci 2014;69:1162–9.
18. Arthur F, Adu-Frimpong M, Osei-Yeboah J, Mensah FO, Owusu L. The prevalence of metabolic syndrome and its predominant components among pre- and postmenopausal Ghanaian women. BMC Res Notes 2013;6:446.
19. Sabir AA, Isezuo SA, Ohwovoriole AE, et al. Rural-urban differences in plasma lipid levels and prevalence of dyslipidemia in Hausa-Fulani of north-western Nigeria. Ethn Dis 2013;23:374–8.
20. Adedoyin RA, Afolabi A, Adegoke OO, Akintomide AO, Awotidebe TO. Relationship between socioeconomic status and metabolic syndrome among Nigerian adults. Diabetes Metab Syndr 2013;7:91–4.
21. Tillin T, Hughes AD, Mayet J, et al. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited)—a prospective population-based study. J Am Coll Cardiol 2013;61:1777–86.
22. Vishnu A, Gurka MJ, DeBoer MD. The severity of the metabolic syndrome increases over time within individuals, independent of baseline metabolic syndrome status and medication use: the Atherosclerosis Risk in Communities Study. Atherosclerosis 2015;243:278–85.
23. Shen J, Poole JC, Topel ML, et al. Subclinical vascular dysfunction associated with metabolic syndrome in African Americans and whites. J Clin Endocrinol Metab 2015;100:4231–9.
24. Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature 2010;466:707–13.
25. Guan W, Cao J, Steffen BT, et al. Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol 2015;35:996–1001.
26. Willer CJ, Schmidt EM, Sengupta S, et al., for the Global Lipids Genetics Consortium. Discovery and refinement of loci associated with lipid levels. Nat Genet 2013;45:1274–83.
27. Beydoun MA, Kuczmarski MTF, Wang Y, Mason MA, Evans MK, Zonderman AB. Receiver-operating characteristics of adiposity for metabolic syndrome: the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. Public Health Nutr 2011;14:77–92.
28. Shetty PB, Tang H, Feng T, et al., for the CARe Consortium. Variants for HDL-C, LDL-C, and triglycerides identified from admixture mapping and fine-mapping analysis in African American families. Circ Cardiovasc Genet 2015;8:106–13.
29. Centers for Disease Control and Prevention. Prevalence of abnormal lipid levels among youths—United States, 1999—2006. MMWR Morb Mortal Wkly Rep 2010;59:29–33.
30. Giannini C, Santoro N, Caprio S, et al. The triglyceride-to-HDL cholesterol ratio: association with insulin resistance in obese youths of different ethnic backgrounds. Diabetes Care 2011;34:1869–74.
31. Punyadeera C, van der Merwe MT, Crowther NJ, Toman M, Schlaphoff GP, Gray IP. Ethnic differences in lipid metabolism in two groups of obese South African women. J Lipid Res 2001;42:760–7.
32. Sliwa K, Lyons JG, Carrington MJ, Lecour S, Maraid AD, Raal FJ, Stewart S. Different lipid profiles according to ethnicity in the Heart of Soweto study cohort of de novo presentations of heart disease. Cardiovasc J Afr 2012;23:389–95.
33. Goedecke JH, Utzschneider K, Faulenbach MV, et al. Ethnic differences in serum lipoproteins and their determinants in South African women. Metabolism 2010;59:1341–50.
34. Ellman N, Keswell D, Collins M, Tootla M, Goedecke JH. Ethnic differences in the association between lipid metabolism genes and lipid levels in black and white South African women. Atherosclerosis 2015;240:311–7.
35. Delisle H, Ntandou G, Sodjinou R, Couillard C, Després JP. At-risk serum cholesterol profile at both ends of the nutrition spectrum in West African adults? The Benin study. Nutrients 2013;5:1366–83.
36. Peer N, Steyn K, Lombard C, Gaziano T, Levitt N. Alarming rise in prevalence of atherogenic dyslipidaemia in the black population of Cape Town: the Cardiovascular Risk in Black South Africans (CRIBSA) study. Eur J Prev Cardiol 2014;21:1549–56.
37. Longo-Mbenza B, Kasiam Lasi On'kin JB, Nge Okwe A, Kangola Kabangu N. The metabolic syndrome in a Congolese population and its implications for metabolic syndrome definitions. Diabetes Metab Syndr 2011;5:17–24.
38. Bi X, Seabolt L, Shibao C, et al. DXA-measured visceral adipose tissue predicts impaired glucose tolerance and metabolic syndrome in obese Caucasian and African-American women. Eur J Clin Nutr 2015;69:329–36.
39. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 2007;116:39–48.
40. Liu J, Fox CS, Hickson DA, et al. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: the Jackson Heart Study. J Clin Endocrinol Metab 2010;95:5419–26.
41. Adiels M, Olofsson SO, Taskinen MR, Borén J. Overproduction of very low—density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. Arterioscler Thromb and Vasc Biol 2008;28:1225–36.
42. Despres JP, Couillard C, Gagnon J, et al. Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study. Arterioscler Thromb Vasc Biol 2000;20:1932–8.
43. Katzmarzyk PT, Bray GA, Greenway FL, et al. Racial differences in abdominal depot-specific adiposity in white and African American adults. Am J Clin Nutr 2010;91:7–15.
44. Conway JM, Yanovski SZ, Avila NA, Hubbard VS. Visceral adipose tissue differences in black and white women. Am J Clin Nutr 1995;61:765–71.
45. Liu J, Coady S, Carr JJ, Hoffmann U, Taylor HA, Fox CS. Differential associations of abdominal visceral, subcutaneous adipose tissue with cardiometabolic risk factors between African and European Americans. Obesity (Silver Spring) 2014;22:811–8.
46. Eastwood SV, Tillin T, Dehbi HM, et al. Ethnic differences in associations between fat deposition and incident diabetes and underlying mechanisms: the SABRE study. Obesity (Silver Spring) 2015;23:699–706.
47. Guerrero R, Vega GL, Grundy SM, Browning JD. Ethnic differences in hepatic steatosis: an insulin resistance paradox? Hepatology 2009;49:791–801.
48. Tota-Maharaj R, Blaha MJ, Zeb I, et al. Ethnic and sex differences in fatty liver on cardiac computed tomography: the Multi-Ethnic Study of Atherosclerosis. Mayo Clin Proc 2014;89:493–503.
49. Hill JO, Sidney S, Lewis CE, Tolan K, Scherzinger AL, Stamm ER. Racial differences in amounts of visceral adipose tissue in young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Am J Clin Nutr 1999;69:381–7.
50. Sumner AE, Micklesfield LK, Ricks M, et al. Waist circumference, BMI, and visceral adipose tissue in white women and women of African descent. Obesity (Silver Spring) 2011;19:671–4.
51. Hosain GM, Rahman M, Williams KJ, Berenson AB. Racial differences in the association between body fat distribution and lipid profiles among reproductive-aged women. Diabetes Metab 2010;36:278–85.

52. Mamabolo RL, Sparks M, Moss SJ, Monyeki MA. The association between dyslipidemia and anthropometric indicators in black and white adolescents residing in Tlokwe Municipality, North-West Province, South Africa: the PAHL study. Afr Health Sci 2014;14: 929–38.
53. Njelekela MA, Mpembeni R, Muhihi A, et al. Gender-related differences in the prevalence of cardiovascular disease risk factors and their correlates in urban Tanzania. BMC Cardiovasc Disord 2009;9:30.
54. Haffner SM, Ralph DA, Saad MF, et al. Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. Diabetes 1996;45:742–8.
55. Chow CC, Periwal V, Csako G, et al. Higher acute insulin response to glucose may determine greater free fatty acid clearance in African-American women. J Clin Endocrinol Metab 2011;96: 2456–63.
56. Gower BA, Herd SL, Goran MI. Anti-lipolytic effects of insulin in African American and white prepubertal boys. Obes Res 2001;9: 224–8.
57. Hasson RE, Adam TC, Davis JN, et al. Ethnic differences in insulin action in obese African-American and Latino adolescents. J Clin Endocrinol Metab 2010;95:4048–51.
58. Drolet R, Richard C, Sniderman AD, et al. Hypertrophy and hyperplasia of abdominal adipose tissues in women. Int J Obes (Lond) 2007;32:283–91.
59. Fried SK, Russell CD, Grauso NL, Brolin RE. Lipoprotein lipase regulation by insulin and glucocorticoid in subcutaneous and omental adipose tissues of obese women and men. J Clin Invest 1993;92:2191–8.
60. Florez H, Mendez A, Casanova-Romero P, et al. Increased apolipoprotein C-III levels associated with insulin resistance contribute to dyslipidemia in normoglycemic and diabetic subjects from a triethnic population. Atherosclerosis 2006;188:134–41.
61. Sumner AE, Furtado JD, Courville AB, et al. ApoC-III and visceral adipose tissue contribute to paradoxically normal triglyceride levels in insulin-resistant African-American women. Nutr Metab (Lond) 2013;10:73.
62. Sumner AE. Ethnic differences in triglyceride levels and high-density lipoprotein lead to underdiagnosis of the metabolic syndrome in black children and adults. J Pediatr 2009;155. S7.e7—e11.
63. Gaillard T, Schuster D, Osei K. Metabolic syndrome in black people of the African diaspora: the paradox of current classification, definition and criteria. Ethn Dis 2009;19(Suppl 2). S2-1—7.
64. Dagogo-Jack I, Dagogo-Jack S. Dissociation between cardiovascular risk markers and clinical outcomes in African Americans: need for greater mechanistic insight. Curr Cardiovasc Risk Rep 2011;5:200–6.
65. Osei K. Metabolic syndrome in blacks: are the criteria right? Curr Diab Rep 2010;10:199–208.
66. Maheux P, Azhar S, Kern PA, Chen YD, Reuven GM. Relationship between insulin-mediated glucose disposal and regulation of plasma and adipose tissue lipoprotein lipase. Diabetologia 1997;40: 850–8.
67. Knudsen P, Eriksson J, Lahdenperä S, et al., for the Botnia Study Group. Changes of lipolytic enzymes cluster with insulin resistance syndrome. Diabetologia 1995;38:344–50.
68. Sumner AE, Vega GL, Genovese DJ, Finley KB, Bergman RN, Boston RC. Normal triglyceride levels despite insulin resistance in African Americans: role of lipoprotein lipase. Metabolism 2005;54: 902–9.
69. Gower BA, Ard JD, Hunter GR, Fernandez J, Ovalle F. Elements of the metabolic syndrome: association with insulin sensitivity and effects of ethnicity. Metab Syndr Relat Disord 2007;5:77–86.
70. Oya J, Vistisen D, Christensen DL, et al. Geographic differences in the associations between impaired glucose regulation and cardiovascular risk factors among young adults. Diabet Med 2015;32: 497–504.
71. Salazar MR, Carbajal HA, Espeche WG, et al. Relation among the plasma triglyceride/high-density lipoprotein cholesterol concentration ratio, insulin resistance, and associated cardiometabolic risk factors in men and women. Am J Cardiol 2012;109: 1749–53.
72. Li HY, Chen BD, Ma YT, et al. Optimal cutoff of the triglyceride to high-density lipoprotein cholesterol ratio to detect cardiovascular risk factors among Han adults in Xinjiang. J Health Popul Nutr 2016; 35:30.
73. Maturu A, DeWitt P, Kern PA, Rasouli N. The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio as a predictor of β-cell function in African American women. Metabolism 2015;64: 561–5.
74. Sumner AE, Harman JL, Buxbaum SG, et al. The triglyceride/high-density lipoprotein cholesterol ratio fails to predict insulin resistance in African-American women: an analysis of Jackson Heart Study. Metab Syndr Relat Disord 2010;8:511–4.
75. Arthur FK, Adu-Frimpong M, Osei-Yeboah J, Mensah FO, Owusu L. Prediction of metabolic syndrome among postmenopausal Ghanaian women using obesity and atherogenic markers. Lipids Health Dis 2012;11:101.
76. Steyn K, Sliwa K, Hawken S, et al., for the INTERHEART Investigators in Africa. Risk factors associated with myocardial infarction in Africa: the INTERHEART Africa study. Circulation 2005;112:3554–61.
77. Grundy SM, D'Agostino RB Sr, Mosca L, et al. Cardiovascular risk assessment based on US cohort studies: findings from a National Heart, Lung, and Blood Institute workshop. Circulation 2001;104: 491–6.
78. Chandra A, Neeland IJ, Das SR, et al. Relation of black race between high density lipoprotein cholesterol content, high density lipoprotein particles and coronary events (from the Dallas Heart Study). Am J Cardiol 2015;115:890–4.
79. Taylor HA Jr, Coady SA, Levy D, et al. Relationships of BMI to cardiovascular risk factors differ by ethnicity. Obesity (Silver Spring) 2010;18:1638–45.
80. Brandon LJ, Proctor L, Cole CL. Influence of obesity assessments on cardiometabolic risks in African and European American women. Ethn Dis 2014;24:475–80.
81. Dowling HJ, Pi-Sunyer FX. Race-dependent health risks of upper body obesity. Diabetes 1993;42:537–43.
82. Howard BV, Criqui MH, Curb JD, et al. Risk factor clustering in the insulin resistance syndrome and its relationship to cardiovascular disease in postmenopausal white, black, Hispanic, and Asian/Pacific Islander women. Metabolism 2003;52:362–71.
83. Miller JM, Kaylor MB, Johannsson M, Bay C, Churilla JR. Prevalence of metabolic syndrome and individual criterion in US adolescents: 2001—2010 National Health and Nutrition Examination Survey. Metab Syndr Relat Disord 2014;12:527–32.
84. Sumner AE, Zhou J, Doumatey A, et al. Low HDL-cholesterol with normal triglyceride levels is the most common lipid pattern in West Africans and African Americans with metabolic syndrome: implications for cardiovascular disease prevention. CVD Prev Control 2010; 5:75–80.
85. Ezenwaka C, Okoye O, Esonwune C, et al. High prevalence of abdominal obesity increases the risk of the metabolic syndrome in Nigerian type 2 diabetes patients: using the International Diabetes Federation worldwide definition. Metab Syndr Relat Disord 2014; 12:277–82.
86. Bello-Rodriguez BM, Sanchez-Cruz G, Delgado-Bustillo F, Asiama G. The relationship between metabolic syndrome and target organ damage in Ghanaian with stage-2 hypertension. Ghana Med J 2013; 47:189–96.
87. Asiki G, Murphy GA, Baisley K, et al. Prevalence of dyslipidaemia and associated risk factors in a rural population in South-Western Uganda: a community based survey. PLoS One 2015;10:e0126166.
88. Lteif AA, Han K, Mather KJ. Obesity, insulin resistance, and the metabolic syndrome: determinants of endothelial dysfunction in whites and blacks. Circulation 2005;112:32–8.
89. Vanhoutte PM, Shimokawa H, Feletou M, Tang EH. Endothelial dysfunction and vascular disease—a 30th anniversary update. Acta Physiol (Oxf) 2017;219:22–96.

90. Sumner AD, Khalil YK, Reed JF 3rd. The relationship of peripheral arterial disease and metabolic syndrome prevalence in asymptomatic US adults 40 years and older: results from the National Health and Nutrition Examination Survey (1999—2004). J Clin Hypertens (Greenwich) 2012;14:144–8.
91. Bentley AR, Rotimi CN. Interethnic variation in lipid profiles: implications for underidentification of African-Americans at risk for metabolic disorders. Exp Rev Endocrinol Metab 2012;7:659–67.
92. Coram MA, Duan Q, Hoffmann TJ, et al. Genome-wide characterization of shared and distinct genetic components that influence blood lipid levels in ethnically diverse human populations. Am J Hum Genet 2013;92:904–16.
93. Deo RC, Reich D, Tandon A, et al. Genetic differences between the determinants of lipid profile phenotypes in African and European Americans: the Jackson Heart Study. PLoS Genet 2009;5:e1000342.
94. Wang K, Li WD, Zhang CK, et al. A genome-wide association study on obesity and obesity-related traits. PLoS One 2011;6:e18939.
95. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 2010;42:937–48.
96. Heard-Costa NL, Zillikens MC, Monda KL, et al. *NRXN3* is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. PLoS Genet 2009;5:e1000539.
97. Auton A, Brooks LD, Durbin RM, et al., for the 1,000 Genomes Project Consortium. A global reference for human genetic variation. Nature 2015;526:68–74.
98. Kathiresan S, Melander O, Anevski D, et al. Polymorphisms associated with cholesterol and risk of cardiovascular events. N Engl J Med 2008;358:1240–9.
99. Legry V, Bokor S, Beghin L, et al., for the HELENA Study Group. Associations between common genetic polymorphisms in the liver X receptor alpha and its target genes with the serum HDL-cholesterol concentration in adolescents of the HELENA Study. Atherosclerosis 2011;216:166–9.
100. Lu Y, Dollé ME, Imholz S, et al. Multiple genetic variants along candidate pathways influence plasma high-density lipoprotein cholesterol concentrations. J Lipid Res 2008;49:2582–9.
101. Nettleton JA, Steffen LM, Ballantyne CM, Boerwinkle E, Folsom AR. Associations between HDL-cholesterol and polymorphisms in hepatic lipase and lipoprotein lipase genes are modified by dietary fat intake in African American and White adults. Atherosclerosis 2007;194:e131–40.
102. Sagoo GS, Tatt I, Salanti G, et al. Seven lipoprotein lipase gene polymorphisms, lipid fractions, and coronary disease: a HuGE association review and meta-analysis. Am J Epidemiol 2008;168:1233–46.
103. Bentley AR, Chen G, Shriner D, et al. Gene-based sequencing identifies lipid-influencing variants with ethnicity-specific effects in African Americans. PLoS Genet 2014;10:e1004190.
104. Adeyemo A, Bentley AR, Meilleur KG, et al. Transferability and fine mapping of genome-wide associated loci for lipids in African Americans. BMC Med Genet 2012;13:88.
105. Pirim D, Wang X, Niemsiri V, et al. Resequencing of the CETP gene in American whites and African blacks: association of rare and common variants with HDL-cholesterol levels. Metabolism 2016;65:36–47.
106. Kristiansson K, Perola M, Tikkanen E, et al. Genome-wide screen for metabolic syndrome susceptibility loci reveals strong lipid gene contribution but no evidence for common genetic basis for clustering of metabolic syndrome traits. Circ Cardiovasc Genet 2012;5:242–9.
107. Kraja AT, Vaidya D, Pankow JS, et al. A bivariate genome-wide approach to metabolic syndrome: STAMPEED Consortium. Diabetes 2011;60:1329–39.
108. Carty CL, Bhattacharjee S, Haessler J, et al. Analysis of Metabolic Syndrome Components in >15,000 African Americans identifies pleiotropic variants: results from the Population Architecture Using Genomics and Epidemiology study. Circ Cardiovasc Genet 2014;7:505–13.
109. Tekola-Ayele F, Doumatey AP, Shriner D, et al. Genome-wide association study identifies African-ancestry specific variants for metabolic syndrome. Mol Genet Metab 2015;116:305–13.
110. Lanktree MB, Elbers CC, Li Y, et al. Genetic meta-analysis of 15,901 African Americans identifies variation in EXOC3L1 is associated with HDL concentration. J Lipid Res 2015;56:1781–6.
111. Li C, Ford ES, Meng YX, Mokdad AH, Reaven GM. Does the association of the triglyceride to high-density lipoprotein cholesterol ratio with fasting serum insulin differ by race/ethnicity? Cardiovasc Diabetol 2008;7:4.
112. Stein E, Kushner H, Gidding S, Falkner B. Plasma lipid concentrations in nondiabetic African American adults: associations with insulin resistance and the metabolic syndrome. Metabolism 2007;56:954–60.
113. Kruger HS, Schutte AE, Walsh CM, Kruger A, Rennie KL. Body mass index cut-points to identify cardiometabolic risk in black South Africans. Eur J Nutr 2015;56:192–202.
114. El Mabchour A, Delisle H, Vilgrain C, Larco P, Sodjinou R, Batal M. Specific cut-off points for waist circumference and waist-to-height ratio as predictors of cardiometabolic risk in black subjects: a cross-sectional study in Benin and Haiti. Diabetes Metab Syndr Obes 2015;8:513–23.
115. Gurka MJ, Lilly CL, Oliver MN, DeBoer MD. An examination of sex and racial/ethnic differences in the metabolic syndrome among adults: a confirmatory factor analysis and a resulting continuous severity score. Metabolism 2014;63:218–25.
116. Ergou S, Kaptoge S, Perry PL, et al., for the Emerging Risk Factors Collaboration. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009;302:412–23.
117. Kamstrup PR, Tybjærg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009;301:2331–9.
118. Virani SS, Brautbar A, Davis BC, et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2012;125:241–9.