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ORIGINAL RESEARCH

Racial and Ethnic Differences in the Association Between Classical Cardiovascular Risk Factors and Common Carotid Intima-Media Thickness: An Individual Participant Data Meta-Analysis

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BACKGROUND: The major risk factors for atherosclerotic cardiovascular disease differ by race or ethnicity but have largely been defined using populations of European ancestry. Despite the rising prevalence of cardiovascular disease in Africa there are few related data from African populations. Therefore, we compared the association of established cardiovascular risk factors with carotid-intima media thickness (CIMT), a subclinical marker of atherosclerosis, between African, African American, Asian, European, and Hispanic populations.

METHODS AND RESULTS: Cross-sectional analyses of 34 025 men and women drawn from 15 cohorts in Africa, Asia, Europe, and North America were undertaken. Classical cardiovascular risk factors were assessed and CIMT measured using B-mode ultrasound. Ethnic differences in the association of established cardiovascular risk factors with CIMT were determined using a 2-stage individual participant data meta-analysis with beta coefficients expressed as a percentage using the White population as the reference group. CIMT adjusted for risk factors was the greatest among African American populations followed by Asian, European, and Hispanic populations with African populations having the lowest mean CIMT. In all racial or ethnic groups, men had higher CIMT levels compared with women. Age, sex, body mass index, and systolic blood pressure had a significant positive association with CIMT in all races and ethnicities at varying magnitudes. When compared with European populations, the association of age, sex, and systolic blood pressure with CIMT was weaker in all races and ethnicities. Smoking (beta coefficient, 0.39; 95% CI, 0.09–0.70), body mass index (beta coefficient, 0.05; 95% CI, 0.01–0.08) and glucose (beta coefficient, 0.13; 95% CI, 0.06–0.19) had the strongest positive association with CIMT in the Asian population when compared with all other racial and ethnic groups. High-density lipoprotein-cholesterol had significant protective effects in African American (beta coefficient, −0.31; 95% CI, −0.42 to −0.21) and African (beta coefficient, −0.26; 95% CI, −0.31 to −0.19) populations only.

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H3Africa AWI-Gen and USE-IMT collaborative study group members are listed in the Supplemental Material.

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CONCLUSIONS: The strength of association between established cardiovascular risk factors and CIMT differed across the racial or ethnic groups and may be due to lifestyle risk factors and genetics. These differences have implications for race- ethnicity-specific primary prevention strategies and also give insights into the differential contribution of risk factors to the pathogenesis of cardiovascular disease. The greatest burden of subclinical atherosclerosis in African American individuals warrants further investigations.

Key Words: atherosclerosis ■ cardiovascular disease risk ■ carotid intima-media thickness ■ ethnicity ■ individual participant data meta-analysis ■ race

CLINICAL PERSPECTIVE

What Is New?

- African American populations had the highest carotid intima-media thickness followed by Asian, European, and Hispanic groups, with African populations having the lowest.
- Age, sex, body mass index, and systolic blood pressure were associated with carotid intima-media thickness in all racial or ethnic groups to varying degrees whereas smoking, alcohol intake, exercise, glucose, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were each associated with carotid intima-media thickness in all racial or ethnic groups except Hispanics.

What Are the Clinical Implications?

- The differential association of these cardiovascular disease risk factors with carotid intima-media thickness in the various racial and ethnic groups suggests that a universally applicable intervention for atherosclerotic disease may be less optimal than programs tailored to each group.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities study
AWI-Gen	African-Wits-INDEPTH (International Network for the Demographic Evaluation of Populations and Their Health in Low- and Middle-Income Countries) Genomic Studies
H3Africa	Human Hereditary and Health Africa
KIHD	Kuopio Ischemic Heart Disease Risk Factor Study in Finland
MESA	Multi-Ethnic Study of Atherosclerosis
NBS	Nijmegen Biomedical Study
NOMAS	Northern Manhattan Study
USE-IMT	Use Intima-Media Thickness

Cardiovascular disease (CVD) is the primary cause of deaths globally.[1,2] Differences in the prevalence of the classical risk factors between racial or ethnic groups have been reported to account for the differences in CVD burden.[3] Previous studies examining racial and ethnic differences in CVD events have been largely conducted outside of the African region mostly in migrant populations residing in high-income countries.[4–6]

The INTERHEART and PURE (Prospective Urban Rural Epidemiology) studies[7,8] are the only studies that have included African participants residing in Africa. These studies demonstrated that the risk of myocardial infarction due to smoking, BMI, blood pressure, and lipids did not differ by geographical location or race or ethnicity. The INTERHEART study included 578 African participants drawn from Mozambique, Nigeria, South Africa, Sudan, and Uganda and the PURE study included study participants from Zimbabwe and South Africa. The paucity of data from African countries is problematic as the prevalence of CVDs has been reported to be increasing across the continent.[2,8] In terms of primary prevention it is important to identify risk factors and the strength of their association with cardiovascular events or measures of atherosclerosis and whether differences exist between racial or ethnic groups for these associations.

Carotid intima-media thickness (CIMT) is a proxy for subclinical atherosclerosis and is related to CVD risk.[9] With regard to African-ancestry participants, most studies on CIMT have been conducted in African American populations[4,6] with one in African populations residing in Africa.[10] The recent USE-IMT (Use Intima-Media Thickness) analyses of ethnic differences in the association between cardiovascular risk factors and CIMT used African American populations as a proxy for endemic African populations.[6]

The current study uses individual participant data meta-analyses (IPD-MA) using data from the USE-IMT project[11] combined with the large pan-African AWI-Gen (Africa-Wits-INDEPTH [International Network for the Demographic Evaluation of Populations and Their Health in Low- and Middle-Income Countries] Genomic) study,[12] a Human Hereditary and Health in Africa (H3Africa) Collaborative Center, to investigate

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the association of classical cardiovascular risk factors with CIMT with the inclusion of a large pan-African cohort. In this study we determined the differences in the association of classical cardiovascular risk factors with CIMT among African populations residing in Africa and African American, Asian, Hispanic, and European populations.

METHODS

Data for these analyses are made up of baseline data from the USE-IMT initiative and the H3Africa AWI-Gen studies. The AWI-Gen data can be accessed from the European Genome-phenome Archive (https://ega-archive.org/datasets/EGA00001002482). The phenotype data set accession IDs is EGAD00010001996. The procedure to obtain access to the USE-IMT data goes through contacting the principal investigator (M.L.B.). The principal investigator will then contact the principal investigators of the individual cohorts to ask for access through cohort-specific existing procedures.

Ethical Approval

The AWI-Gen study received ethics approval from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa (initial approval number: M121029 and renewed approval number: M170880) and cohort specific ethical approvals were also obtained. The USE-IMT study received ethics approval from the institutional review committee of the University Medical Centre Utrecht, Utrecht, the Netherlands. The individual US studies received ethical approval from their respective ethics committees or institutional review boards. All participants within each individual study provided informed consent before recruitment. Approval for use of the data included in these analyses was provided by the principal investigators of the H3Africa AWI-Gen and USE-IMT through a signed data transfer agreement.

Study Population

African participants were recruited for H3Africa AWI-Gen study, a population-based cross-sectional study investigating genomic and environmental risks factors for cardiometabolic diseases across 6 African sites including in Burkina Faso and Ghana (West Africa); Kenya (East Africa), and South Africa.[12] The 6 cohorts were drawn from 5 Health and Socio-Demographic Surveillance Sites of the International Network for Demographic Evaluation of Populations and Their Health and adults of the same age from Soweto, South Africa. We included all 6 cohorts from the AWI-Gen study composed of adults aged 40 to 60 years old. The USE-IMT project is an IPD-MA as described in detail elsewhere.[11] The USE-IMT comprised adult men and women recruited for 18 cohorts from various countries in Europe, Asia, and North America.

In order to adequately compare the USE-IMT cohorts with the AWI-Gen cohorts, we applied an age restriction. We excluded 9 cohorts (n=5930) from the 18 cohorts (n=41 612) contributing to USE-IMT based on participant's age <40 or >60 years. Further exclusions (n=1657) were based on missing data for biomarkers: glucose, low density lipoprotein cholesterol (LDL-C), triglycerides, and physical activity. The final data set included in this IPD-MA consisted of 34 025 adults aged 40 to 60 years drawn from 15 cohorts (9 from USE-IMT and 6 from AWI-Gen) in 11 countries.

The following cohorts contributed the recruited participants of European ancestry: FATE (Firefighters and Their Endothelium Study in Canada),[13] ARIC (Atherosclerosis Risk in Communities) study,[14] MESA (Multi-Ethnic Study of Atherosclerosis),[15] and NOMAS (Northern Manhattan Study),[16] all from the United States; KIHD (Kuopio Ischemic Heart Disease Risk Factor Study) in Finland,[17] Malmö Diet and Cancer Study in Sweden,[18] Tromsø Study in Norway,[19] and the NBS (Nijmegen Biomedical Study) in the Netherlands.[20] African American and Hispanic participants were recruited from the ARIC, MESA, and NOMAS studies in the United States and participants from the Asian racial group were recruited from the OSACA2 (Osaka Follow-up Study for Carotid Atherosclerosis) study in Japan[21] and migrant Asians (Chinese) from the NBS, ARIC, and MESA studies from the United States (Table S1). Analyses were limited to participants with data on CIMT and the following established cardiovascular risk factors: age, sex, smoking, alcohol, physical activity, body mass index, blood pressure, serum glucose, LDL-C, and HDL-C.

Race and ethnicity were self-identified by the participants of the various cohorts. Most cohorts adopted separate questions about ethnicity (Hispanic/Latino ethnicity) and race (White/Black) because these are distinct concepts.[22] In addition, some studies collected information on country of origin among all races and language spoken at home to help classify multiracial individuals who may only identify with a single group.[23] We used the sociocultural context of race and ethnicity variables to assign sufficient attribution to explanatory biological factors (and based on the literature), and reported on the relationships among prespecified racial or ethnic groups according to recent recommendations for use of race and ethnicity in research.[24] White racial group refers to participants of European ancestry and Black racial group refers to participants of African ancestry classified as African people residing in Africa and African American referring to African people in the diaspora.

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Data Harmonization

Several steps were taken to harmonize all extracted data for the current analyses. Data included were cross-sectional baseline data from the various cohorts thus offsetting differences in study designs. We obtained available crude individual level data (for each cohort) on interested common variables giving us the opportunity to standardize units of measurements of the variables. Weight was measured in kilograms in all cohorts and height was measured in centimeters in the USE-IMT and millimeters in the AWI-Gen study and was converted to meters. Subsequent body mass index (BMI) was calculated as weight divided by height in meters squared. We converted all serum biochemical marker data (glucose, LDL-C, and HDL-C) into mmol/L. Blood pressure was measured as systolic and diastolic pressures in mm Hg. In the study sites from Africa hypertension was defined as a reported history of hypertension and/or a blood pressure of ≥140/90 mm Hg and diabetes was defined as self-reported presence of diabetes and/or a fasting glucose of ≥7 mmol/L or random blood glucose of ≥11 mmol/L. The other sites did not have data on the history of self-reported hypertension or diabetes and therefore these conditions were diagnosed using the measured blood pressure and glucose levels. Data on therapies for hypertension or diabetes were not available to us. Alcohol intake in the USE-IMT was reported as the number of beverages consumed per week whereas in the AWI-Gen study it was reported as never consumed, current nonproblematic consumer, current problematic consumer, or former consumer.[12] We thus recoded the merged variable into 2 mutually exclusive variables as 0 "never consumed" and 1 "ever consumed" (ie, reporting consumption of at least 1 beverage per week or current nonproblematic consumer, current problematic consumer, or former consumer). Smoking was coded as 0, never smoked and 1, current or former smoker. Physical activity was measured differently within the various study cohorts. Some studies used questionnaires to assess leisure activity and moderate-to-vigorous physical activity in some detail, whereas others asked whether subjects engaged in any form of physical activity and the type and duration per day or week. Those who reported not engaging in any form of physical activity or lower than 150 minutes of moderate-to-vigorous physical activity per week were coded as 0 (no form of physical activity) and those who reported ≥150 minutes of moderate-to-vigorous physical activity per week or engaging in activities that require physical exertion (eg, walking, cycling) or some form of physical activity for at least 4 hours per week or several times per week were categorized as 1 (some form of physical activity).

Common CIMT

Images of CIMT obtained varied across cohorts and from 2 to 6. Some cohorts measured 1 angle and others multiple angles. The outcome variable, CIMT, was thus computed as an average of all available angles (from the number of angles, from the far wall, and from 1 or both sides of the neck) of the common CIMT measurements from each included cohort. All common CIMT values were used in the analysis, including values larger than 1.5 mm, which are suggestive of plaque. The same protocol was used for the 6 cohorts in the H3Africa AWI-Gen study limiting variability in measurements whereas different protocols were used by the various USE-IMT cohorts. As absolute differences in common CIMT levels between AWI-Gen and the USE-IMT cohorts could arise from differences in methodology employed in obtaining measurements, we harmonized the mean common CIMT by computing cohort-specific standard Z scores using the formula, $z=(x-\mu)/\sigma$, where x is the crude participant CIMT, μ is each population's mean CIMT, and σ is each population's SD.

Statistical Analysis

Participants were stratified by racial or ethnic background and by cohorts and their characteristics were summarized using counts and frequencies for categorical data and means±SD for normally distributed continuous data. We used mixed-effect multilevel linear regression analyses to compute and compare mean (with 95% CIs) CIMT between the different races or ethnicities while adjusting for the classical CVD risk factors. We further compared mean differences between African American, West, East, and South African people. We also conducted similar subgroup analyses for populations of Asian (Japanese versus Chinese American) and European ancestry with the European group split into European people in Europe and European people in North America. Adjustments were done in order to determine whether any variations in racial or ethnic differences were due to differential patterning of CVD risk factors by ethnicity. Because of significant sex×race or ethnicity interactions in the combined sample, we presented mean differences in CIMT for the combined sample and for women and men separately. To determine whether changes in ultrasound technology would affect CIMT measurement precision, we generated a variable (ultra-tech) in which studies conducted between 1980 and 1999 were coded as 0 and those that were conducted between 2000 and 2020 were coded as 1. These years were considered because ultrasound technology advanced considerably from early 2000s.[25] We initially carried out comparisons of CIMT levels between these groups

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using Student *t* test, and then adjusted for the classical cardiovascular risk factors in adjusted linear regressions analyses with a post prediction to compute the means for comparison.

To determine the association between the established cardiovascular risk factors and common CIMT *Z* score, we conducted a 1-staged IPD-MA using mixed-effect multilevel regression with a random-effects approach for each original cohort. We adjusted for all the established CVD risk factors separately for each racial or ethnic group. For the AWI-Gen cohorts, we also adjusted for HIV as its prevalence was high in East and South African cohorts and it is thought to contribute to the risk of CVD.[26] Data on HIV status was available only for the AWI-Gen cohorts. We further tested for the significance of an HIV×sex interaction. This is because the epidemiology of HIV in sub-Saharan Africa differs between women and men.[10] No significant sex×HIV interaction was observed. The following equation represents the mixed-effect models used in these analyses:

$$y = X\beta + Zu + \varepsilon,\ y \sim F$$

where y is the outcome variable, CIMT, X is the fixed-effect variables (classical cardiovascular risk factors) for which the β regression coefficients are to be estimated, and Z is the design matrix for the random-effects u, which is the various races or ethnicities (study cohorts and countries nested within). Finally, ε is the residual error between the expected and observed value. Also (Xβ+Zu) is the linear predictor and F is the distributional family, which is Gaussian. We opted for a mixed-effect multilevel analyses because of the possibility of clustering of participants from the various cohorts within each of the racial or ethnic groups.

We further conducted pooled analyses using a fixed-effect inverse-variance IPD-MA approach to determine ethnic differences in CVD risk factors associated with common CIMT *Z* score. This also enabled us to plot the estimates using forest plots. In this pooled analysis, HIV was not included in the model because only the AWI-Gen cohort had HIV data. The meta-analysis pooling of the main effects on mean CIMT of each risk factor enabled us to obtain the associations of each risk factor with CIMT across the racial or ethnic groups. The IPD was conducted for each established classical CVD risk factor and in each analysis adjustments were made for the other established classical CVD risk factors. We further conducted pooled analyses for men and women separately due to sex×race or ethnicity interactions. Because of similarities in the effect sizes of the risk factors with raw mean CIMT and CIMT *Z* scores, we reported the associated differences in CIMT in mm. The results are presented as forest plots with 95% CIs. To further quantify the differences in the magnitude of association of each risk factor with common CIMT according to race or ethnicity, we conducted a mixed-effect multilevel regression with a random-effects approach, as described previously, for each original cohort. We then extended this model by adding the interaction terms for race or ethnicity with each CVD risk factor. Beta coefficients (with 95% CIs) for each risk factor in each racial or ethnic group were obtained with populations of European ancestry as the reference group in all analyses. From the obtained effect measure (beta value) for each racial or ethnic group we converted the beta value to a percentage, again using the European racial group as a reference and for whom the beta coefficient was set at 100%. This enabled us to observe the difference in the magnitude of the association of the risk factors with CIMT for each ethnic group compared with the European racial group in percentage terms and for easy visualization or interpretation of the estimated magnitudes. To compare the differences in magnitude of association of each risk factor with CIMT within the individual racial or ethnic groups, we further computed and compared their standardized betas.

The established classical cardiovascular risk factors that were adjusted for in all the inferential analyses were age, sex, smoking, alcohol intake, BMI, systolic blood pressure (SBP), glucose, LDL-C, and HDL-C. We used LDL-C in preference to total cholesterol because of the universal use of LDL-C in treatment guidelines for CVD prevention.[27–29] We further analyzed whether LDL-C/HDL-C ratio was more important than LDL-C and HDL-C in predicting CIMT. We first included all 3 markers in the same model and checked for significant collinearity using the variance inflation factor. We then compared the variance (adjusted R^2) of the model that included both HDL-C and LDL-C with that of the model that included the ratio only. A 2-sided $P<0.05$ is considered statistically significant in all inferential analyses. All statistical analyses were conducted in STATA v14.2 (StataCorp LP, College Station, TX).

RESULTS

Basic Characteristics of Cohorts by Racial and Ethnic Groups

The study consisted of 15 cohorts drawn from Africa, Asia, Europe, and North America. Baseline characteristics of the included cohorts are presented in Table S1 and baseline characteristics of participants by race and ethnicity are presented in Table 1. A total of 34 025 individuals with a mean±SD age of 52±5 years and crude CIMT of 0.69±0.14 mm were studied. Hispanic individuals were older (54±5 years) than other ethnic groups with African individuals having the lowest mean age (50±6 years). An approximately equal number of

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Table 1. Baseline Characteristics of USE-IMT and AWI-Gen Collaborative Study Participants According to Racial and Ethnic Groups

Factors	Asian	African	African American	European	Hispanic	All
Combined population						
N	573	9428	4182	18 817	980	34 025
Age, y	53±5	50±6	52±5	53±5	54±5	52±5
Smoking, %	15.3	29.5	28.9	26.6	19.3	27.2
Alcohol, %	88.7	93.3	38.8	95.3	70.5	78.3
Physical activity, %	83.1	94.9	88.9	91.3	74.2	90.3
HIV+ART, %	…	12.2	…	…	…	…
BMI, kg/m^2	24.2±3.3	24.1±1.07	29.7±4.56	26.7±4.5	29.6±5.3	26.4±5.7
SBP, mm Hg	123±20	124±22	127±20	125±19	123±20	125±20
DBP, mm Hg	77±12	79±13	79±12	77±12	75±11	78±12
Glucose, mmol/L	5.52±1.73	5.06±1.62	6.21±2.88	5.37±1.47	5.4±2.1	5.39±1.8
HDL, mmol/L	1.33±0.72	1.18±0.41	1.40±0.44	1.35±0.41	1.21±0.33	1.30±0.43
LDL, mmol/L	3.03±0.75	2.30±0.99	3.41±1.08	3.80±1.12	3.2±0.86	3.28±0.14
Hypertension	34.5	27.5	28.1	26.6	21.7	27.1
Diabetes	9.9	6.5	15.5	5.3	9.9	7.0
Common CIMT in mm	0.72±0.22	0.64±0.12	0.70±0.15	0.69±0.15	0.68±0.12	0.68±0.14
Women						
N (%)	282 (49)	4745 (50)	2548 (61)	8947 (48)	534 (54)	17 055 (50)
Age, y	53±5	50±6	52±5	53±5	54±5	52±5
Smoking, %	6.2	3.9	24.8	26.2	16.7	19.1
Alcohol, %	87.9	29.8	93.0	94.0	64.0	75.0
Physical activity, %	81.9	91.4	94.7	91.7	71.8	91.2
HIV+ART, %	…	13.2	…	…	…	…
BMI, kg/m^2	23.7±3.3	25.5±6.9	30.8±6.4	26.1±5.1	30.3±5.9	26.7±6.0
SBP, mm Hg	121±22	122±23	127±21	123±20	122±20	123±21
DBP, mm Hg	77±11	78±13	77±11	74±12	73±11	76±12
Glucose, mmol/L	5.33±1.56	5.08±1.74	6.28±3.10	5.29±1.47	5.30±2.02	5.41±1.92
HDL, mmol/L	1.45±0.40	1.15±0.38	1.49±0.45	1.53±0.42	1.31±0.35	1.44±0.45
LDL, mmol/L	3.03±0.74	2.27±0.98	3.42±1.09	3.75±1.16	3.15±0.86	3.28±1.23
Hypertension	24.1	27.3	25.9	23.2	21.2	24.9
Diabetes	7.7	7.4	16.2	4.4	8.9	7.3
Common CIMT in mm	0.68±0.20	0.64±0.12	0.69±0.16	0.66±0.13	0.66±0.11	0.66±0.13
Men						
N (%)	291 (51)	4683 (50)	1634 (39)	9870 (52)	446 (46)	16 924 (50)
Age, y	53±5	50±6	52±5	53±5	53±5	52±5
Smoking, %	23.9	54.3	36.7	27.0	22.4	35.3
Alcohol, %	83.6	45.8	93.7	96.5	78.3	81.6
Physical activity, %	84.5	86.4	95.2	91.0	77.1	89.5
HIV+ART, %	…	11.0	…	…	…	…
BMI, kg/m^2	24.7±3.1	22.6±4.6	27.9±4.7	27.2±3.8	28.7±4.5	26.2±4.5
SBP, mm Hg	125±19	126±21	128±20	127±19	123±19	127±19
DBP, mm Hg	80±11	80±13	82±12	80±12	77±11	80±12
Glucose, mmol/L	5.70±1.86	5.03±1.50	6.11±2.50	5.43±1.47	5.62±2.17	5.43±1.69
HDL, mmol/L	1.23±0.33	1.21±0.44	1.27±0.41	1.20±0.33	1.09±0.28	1.23±0.37
LDL, mmol/L	3.13±0.75	2.34±0.99	3.41±1.07	3.86±1.08	3.15±0.86	3.40±1.20
Hypertension	40.0	27.8	31.3	29.6	22.4	29.4
Diabetes	11.1	5.3	14.5	5.6	10.0	6.7
Common CIMT in mm	0.76±0.23	0.64±0.12	0.73±0.15	0.72±0.15	0.69±0.13	0.71±0.15

Data presented as percentages (%) or mean±SD. ART indicates antiretroviral therapy; AWI-Gen, Africa-Wits-INDEPTH (International Network for the Demographic Evaluation of Populations and Their Health in Low- and Middle-Income Countries) Genomic Study; BMI, body mass index; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; and USE-IMT, Use Intima-Media Thickness.

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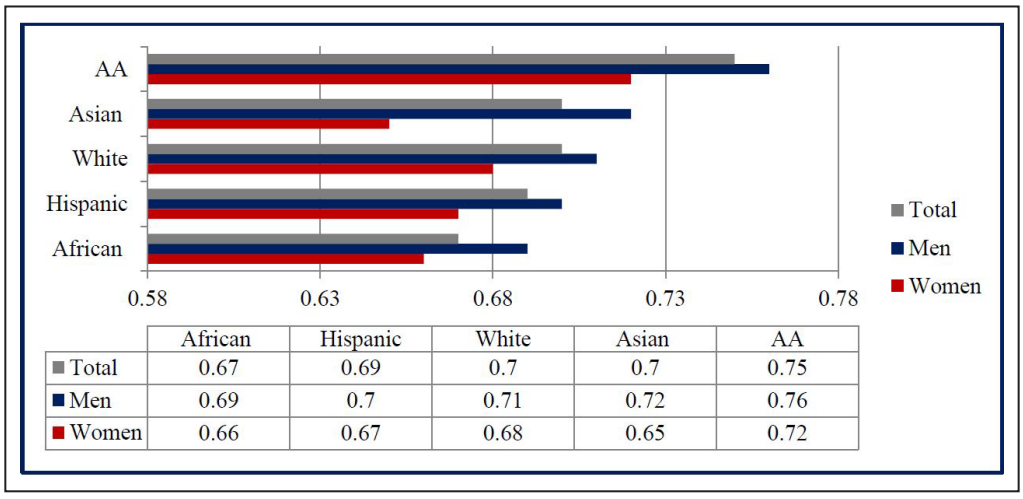
women and men were included in this meta-analysis. More men were smokers and current alcohol consumers than women across all ethnic groups. African (30%) and African American (29%) participants had the highest smoking rates with Asian participants (15%) having the lowest rates. African American and Hispanic participants had the highest mean BMI and African and Asian participants reported the lowest levels. African women had higher mean BMI than their male counterparts whereas the opposite was observed in all other racial and ethnic groups. African participants generally had lower levels of fasting glucose, HDL-C, and LDL-C compared with all other races and ethnicities. African American participants had the highest glucose and HDL levels whereas European participants had the highest LDL-C levels (Table 1). Asian participants reported the highest prevalence of hypertension with African American participants also reporting high levels of hypertension and the highest levels of diabetes in both women and men.

Mean CIMT Levels Across Racial and Ethnic Groups

The adjusted CIMT levels for each racial or ethnic group as total and men and women separately are presented in Figure 1. In the combined populations, age, sex, smoking, alcohol, physical activity, glucose, HDL-C, and LDL-C were adjusted sequentially (model 1, unadjusted; model 2, adjusted for age, sex, and sex×race or ethnicity interaction; and model 3, model 2 plus the classical cardiovascular risk factors) to see the differential effect of behavioral and metabolic risk factors on mean common CIMT levels across the races and ethnicities. The results of these sequential models are presented in Table S2 and show that these adjustments led to modest falls in CIMT levels in all racial or ethnic groups except for the African group where CIMT values rose slightly. The adjusted mean CIMT was highest among African American individuals followed by European individuals in Europe, Asian and Hispanic populations with African and European individuals in North America having the lowest mean CIMT. There was a significant sex and race or ethnicity interaction, P=0.001 (Table S3); hence we conducted separate analyses for women and men.

Men from all the ethnic groups had higher adjusted CIMT compared with women. African American women had the highest adjusted mean CIMT levels followed by African, European, and Hispanic women with Asian women recording the lowest adjusted CIMT levels. A similar trend was observed in men except that Asian men had the second highest CIMT level. We further performed a subgroup analysis among African-ancestry participants by comparing mean CIMT levels between African American participants and East (Kenya), West (Ghana and Burkina Faso), and South African participants. In these analyses we observed that African American individuals had the highest mean CIMT followed by West, South, and East African individuals (see Table 2). We also conducted subgroup analyses comparing



	African	Hispanic	White	Asian	AA
Total	0.67	0.69	0.7	0.7	0.75
Men	0.69	0.7	0.71	0.72	0.76
Women	0.66	0.67	0.68	0.65	0.72

Figure 1. Adjusted means of common CIMT in mm (with 95% CIs) across the racial and ethnic groups in the USE-IMT and AWI-Gen collaborative study's combined sample.
Values adjusted for age, sex (in the total sample), smoking, alcohol consumption, physical activity, systolic blood pressure, body mass index, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. AA indicates African American; AWI-Gen, Africa-Wits-INDEPTH (International Network for the Demographic Evaluation of Populations and Their Health in Low- and Middle-Income Countries) Genomic Study; CIMT, carotid intima-media thickness; USE-IMT, use intima-media thickness; and White, European racial group.

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Table 2. Adjusted Mean Levels of Carotid Intima-Media Thickness (With 95% CIs) in Participants With African Ancestry Including African American and East, West, and South African Participants

	African American (n=4182)	West African (N=4090)	East African (N=1940)	South African (N=3398)	$P_{interaction}$
Combined sample					
Model 1	0.78 (0.74–0.82)	0.68 (0.66–0.69)	0.59 (0.57–0.61)	0.62 (0.61–0.64)	…
Model 2	0.78 (0.74–0.81)	0.68 (0.66–0.69)	0.60 (0.58–0.62)	0.62 (0.61–0.63)	<0.001
Model 3	0.75 (0.72–0.77)	0.69 (0.67–0.70)	0.60 (0.57–0.62)	0.61 (0.59–0.62)	<0.001
Women					
Model 1	0.76 (0.72–0.81)	0.67 (0.65–0.69)	0.60 (0.56–0.63)	0.62 (0.60–0.65)	…
Model 2	0.75 (0.71–0.79)	0.67 (0.65–0.69)	0.61 (0.58–0.64)	0.62 (0.60–0.64)	…
Model 3	0.72 (0.68–0.75)	0.68 (0.66–0.70)	0.60 (0.58–0.63)	0.61 (0.59–0.62)	…
Men					
Model 1	0.79 (0.75–0.83)	0.69 (0.67–0.70)	0.58 (0.57–0.60)	0.62 (0.61–0.63)	…
Model 2	0.78 (0.75–0.82)	0.68 (0.67–0.69)	0.59 (0.57–0.61)	0.62 (0.61–0.63)	…
Model 3	0.76 (0.73–0.78)	0.69 (0.67–0.72)	0.59 (0.56–0.62)	0.61 (0.59–0.63)	…

Model 1 is crude unadjusted; model 2 is adjusted for age, sex, and sex×race or ethnicity interaction (sex-stratified analyses were adjusted for age only); and model 3 is model 2 with adjustment for smoking, alcohol, physical activity, systolic blood pressure, body mass index, glucose, high-density lipoprotein, and low-density lipoprotein. $P_{interaction}$, *P* value for ethnicity×sex multiplicative interaction term.

adjusted mean CIMT levels of Chinese American with Japanese subjects (these 2 populations constitute the "Asian" racial group in the present study) as well as European American subjects with European people resident in Europe (these 2 populations constitute the "European" racial group in the present study). In these analyses we observed that the CIMT–level of Japanese subjects (0.72 mm; 95% CI, 0.57–0.83) was not significantly different to that of Chinese Americans (0.73 mm; 95% CI, 0.67–0.79). In subgroup analyses, the mean CIMT for European subjects resident in Europe was higher (0.72 mm; 95% CI, 0.70–0.74) than European subjects from North American (0.66 mm; 95% CI, 0.63–0.69).

We further noticed ultrasound technology did not affect the mean CIMT levels. In a paired comparison there was no difference (*P*=0.105) in means between older (0.68; 95% CI, 0.68–0.70) and newer (0.67; 95% CI, 0.67–0.69) technologies. Further adjustments of the classical risk factors did not yield any difference in the computed mean values. Technology thus did not have an effect on the obtained mean CIMT measurements in this study.

Racial and Ethnic Differences in Association of CVD Risk Factors With Common CIMT

Results of the IPD-MAs to determine whether there were racial or ethnic differences in the association of classical CVD risk factors with CIMT are presented as forest plots for the combined sample (Figure 2), women (Figure 3), and men (Figure 4). The data are also presented for the combined sample in Table 3 in which the beta coefficients for the associations with CIMT are expressed as percentages using the European racial ethnic group as a reference with a set value of 100%. The measure of heterogeneity obtained from the IPD-MA is presented in Table S4. In the pooled IPD-MA for each risk factor with adjustment for other factors, we noticed that age, sex, BMI, and SBP were significantly associated with CIMT in all races or ethnicities and at varying magnitudes (Table 3). The beta values measuring association between age and CIMT were smaller in African subjects (88% that of the beta from the reference group), Hispanic subjects (63%) and Asian subjects (50%) but the same for African American subjects when compared with the European racial ethnic group.

For all racial and ethnic groups, SBP and men had lower beta coefficients compared with the European racial ethnic group. Smoking was significantly associated with CIMT in all groups except for the Hispanic population, being strongest in the Asian group where the beta value was 140% that of the beta from the reference group. Alcohol intake was inversely associated with common CIMT in all groups except Asian subjects but was significant only in African subjects (−0.09; 95% CI, −0.16 to −0.04) and African American subjects (−0.20; −0.38 to −0.03). Physical activity was inversely associated with CIMT in African and European subjects but positively associated with CIMT in Asian subjects. BMI was significantly associated with CIMT in all populations, being strongest in the Asian group (250% that of the beta from the reference group). The beta coefficients for the association between glucose and CIMT were highest in the Asian populations (650% that of the beta from the reference group) and were nonsignificant only

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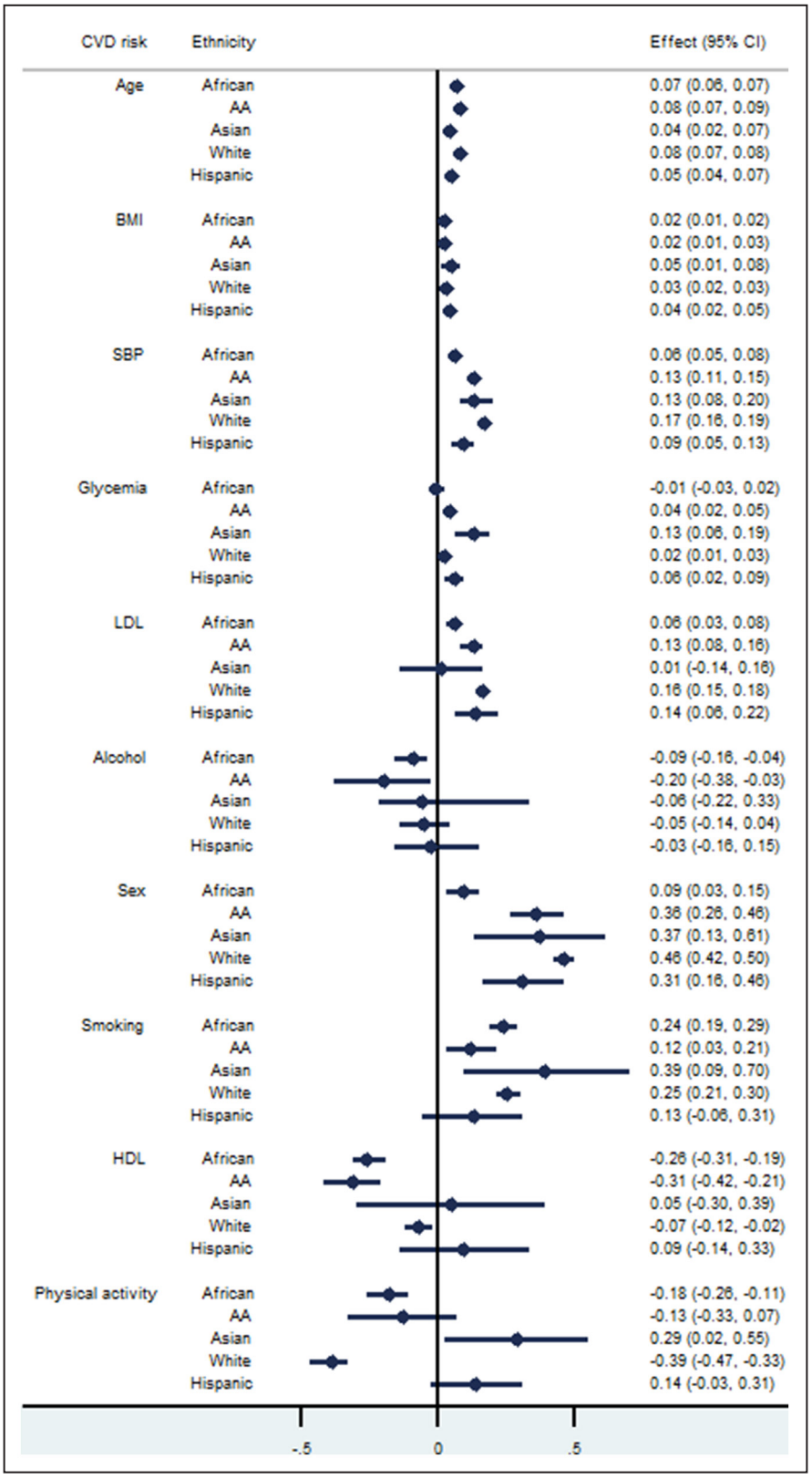

Figure 2. Forest plot of individual participant data meta-analyses showing associations of classical CVD risk factors with CIMT in the combined sample.
AA indicates African American; BMI, body mass index; CIMT, carotid intima-media thickness; CVD, cardiovascular diseases; HDL, high density lipoprotein; LDL, low density lipoprotein cholesterol; and SBP, systolic blood pressure.

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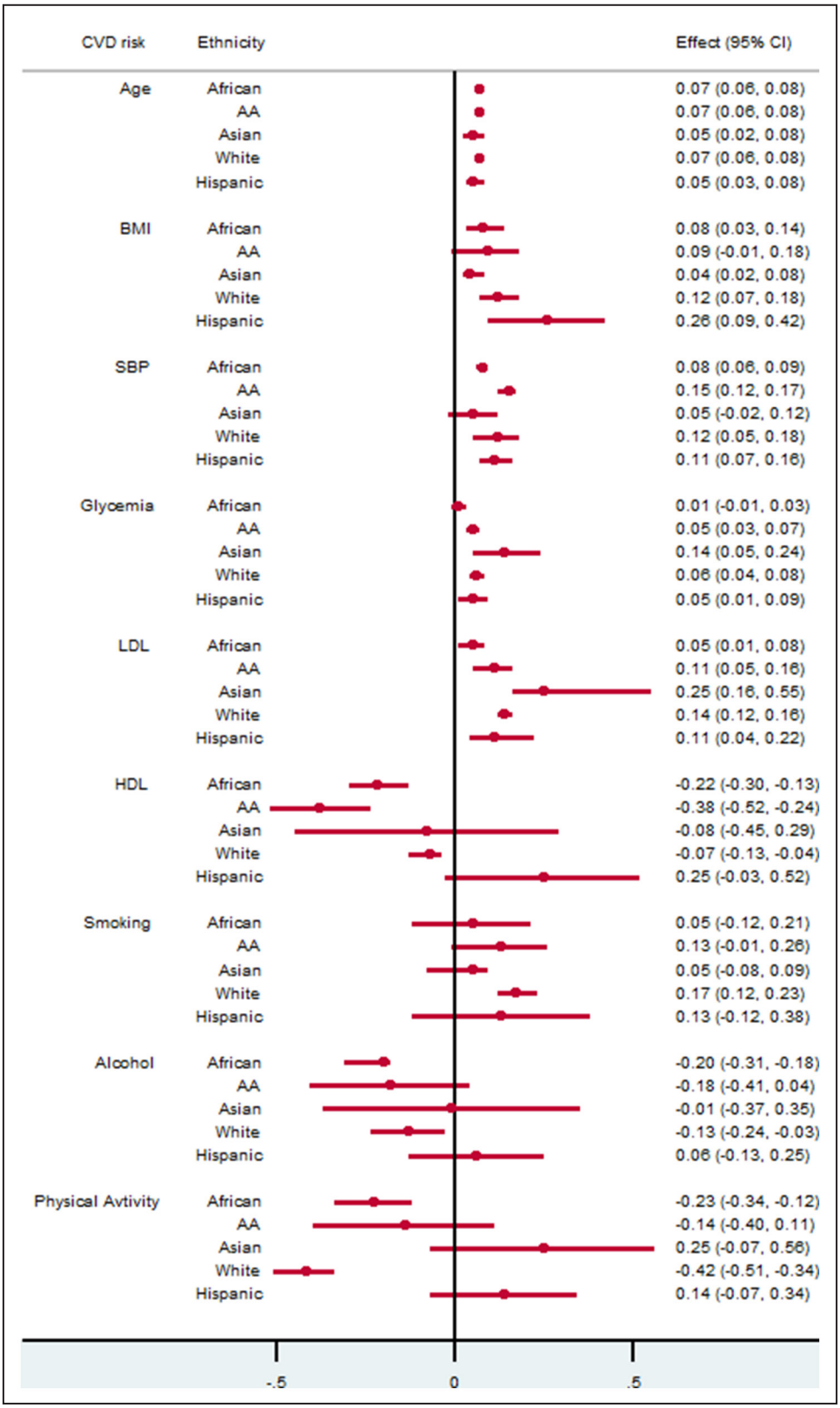

Figure 3. Forest plot of individual participant data meta-analyses showing associations of classical CVD risk factors with CIMT in women.
AA indicates African American; BMI, body mass index; CIMT, carotid intima-media thickness; CVD, cardiovascular diseases; HDL, high-density lipoprotein; LDL, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

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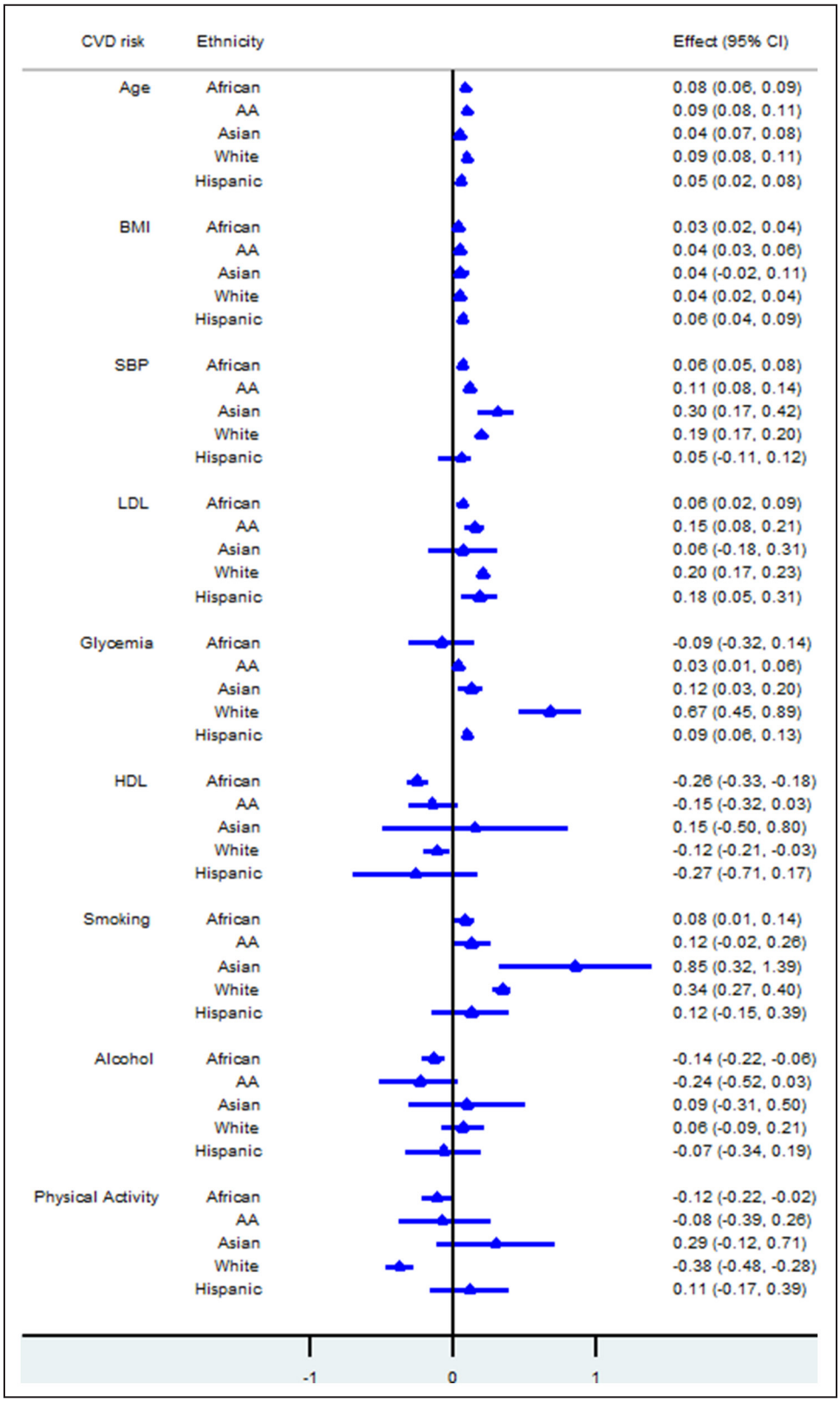

Figure 4. Forest plot of individual participant data meta-analyses showing associations of classical CVD risk factors with CIMT in men.

AA indicates African American; BMI, body mass index; CIMT, carotid intima-media thickness; CVD, cardiovascular diseases; HDL, high-density lipoprotein; LDL, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

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Table 3. Relations of the Established Cardiovascular Disease Risk Factors in Racial and Ethnic Groups for the Outcome Common CIMT

	European		Asian		African		African American		Hispanic	
	β (95% CIs)	Ref	β (95% CIs)	%	β (95% CIs)	%	β (95% CIs)	%	β (95% CIs)	%
Age, y	0.08 (0.07 to 0.09)	Ref	0.04 (0.03 to 0.09)	50	0.07 (0.06 to 0.07)	88	0.08 (0.07 to 0.09)	100	0.05 (0.04 to 0.08)	63
Men vs women	0.46 (0.42 to 0.50	Ref	0.37 (0.13 to 0.61)	80	0.09 (0.03 to 0.15)	20	0.36 (0.26 to 0.46)	78	0.31 (0.16 to 0.46)	67
Smoking	0.25 (0.21 to 0.30)	Ref	0.39 (0.09 to 0.70)	140	0.24 (0.19 to 0.29)	96	0.12 (0.03 to 0.21)	48	0.13 (−0.06 to 0.31)	52
Alcohol	−0.05 (−0.14 to 0.04)	Ref	0.06 (−0.22 to 0.33)	120	−0.09 (−0.16 to −0.04)	180	−0.20 (−0.38 to −0.03)	400	−0.03 (−0.16 to 0.15)	60
Physical activity	−0.39 (−0.47 to −0.33)	Ref	0.29 (0.02 to 0.55)	74	−0.18 (−0.26 to −0.11)	46	−0.13 (−0.33 to 0.07)	33	0.14 (−0.03 to 0.31)	36
BMI, kg/m^2	0.02 (0.02 to 0.03)	Ref	0.05 (0.01 to 0.08)	250	0.02 (0.01 to 0.02)	100	0.02 (0.01 to 0.03)	100	0.04 (0.02 to 0.05)	200
SBP, mm Hg	0.17 (0.16 to 0.19)	Ref	0.13 (0.08 to 0.20)	78	0.06 (0.05 to 0.08)	35	0.13 (0.11 to 0.15)	76	0.09 (0.05 to 0.13)	53
Glucose, mmol/L	0.02 (0.01 to 0.03)	Ref	0.13 (0.06 to 0.19)	650	−0.01 (−0.03 to 0.02)	50	0.04 (0.02 to 0.05)	167	0.06 (0.02 to 0.09)	300
HDL, mmol/L	−0.07 (−0.12 to −0.02)	Ref	0.05 (−0.30 to 0.39)	71	−0.26 (−0.31 to −0.19)	371	−0.31 (−0.42 to −0.21)	443	0.09 (−0.14 to 0.33)	128
LDL, mmol/L	0.16 (0.15 to 0.18)	Ref	0.01 (−0.14 to 0.16)	6	0.06 (0.03 to 0.08)	38	0.13 (0.08 to 0.16)	81	0.14 (0.06 to 0.22)	89

Data presented as β (beta) coefficients (differences in CIMT in mm); beta coefficients also expressed as a percentage of that observed in the European racial group. BMI indicates body mass index; CIMT, carotid intima-media thickness; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ref, reference group with 100% set as the reference value; and SBP, systolic blood pressure.

in the African population. The association of HDL-C with CIMT was negative and significant in European, African, and African American populations whereas LDL-C was positively associated with common CIMT in all groups except the Asian population, being strongest in the European population. When analyzing whether the LDL-C/HDL-C ratio explained more of the variance in CIMT when compared with LDL and HDL, we noticed significant collinearity when LDL-C, HDL-C, and LDL-C/HDL-C were included in the same model. We therefore split these models into 2 with HDL-C and LDL-C in 1 model and LDL-C/HDL-C in the second. A comparison of the adjusted R^2 indicated that the variance explained by HDL-C and LDL-C only was more than that explained by LDL-C/HDL-C ratio (Table S5). In sex-stratified analyses, similar associations of age, BMI, and SBP with CIMT were observed for women and men except for SBP where Asian women (Figure 3) and Hispanic men displayed a marginal association (Figure 4).

When the populations of European ancestry were split into European people residing in North America and in Europe, we observed that the associations were similar except physical activity, which was inversely associated with CIMT in only the European North American racial ethnic group. In assessing the magnitude of the betas, we observed that European North American participants had higher betas for BMI and glucose compared with European participants in Europe.

Within-Race Variation in Strength of the Associated Factors

To account for the within-ethnic group variation in the strength of association of each factor we generated standardized betas presented in Table 4. In these analyses we realized that age was a major driver of subclinical atherosclerosis in African, African American, European, and Hispanic groups whereas SBP was a major driver for the Asian group. In African participants SBP and BMI were next in strength to drive subclinical atherosclerosis. In African American participants SBP and men were next in line to cause increased CIMT. Among Asian participants, hyperglycemia and male sex were important factors that drive atherosclerosis. In people of European ancestry male sex and LDL-C were most likely to drive atherosclerosis next to age. Finally in the Hispanic population, BMI followed by SBP and male sex were important factors driving subclinical atherosclerosis (Table 4).

DISCUSSION

Our study involving a large cohort of adults from different racial or ethnic groups shows that African, African American, Asian, European, and Hispanic individuals

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differ markedly in the levels of CIMT and associated CVD risk factors. African American subjects had significantly higher mean CIMT levels compared with all the other ethnic groups whereas among African subjects, those who were West African had higher levels of CIMT than those who were East and South African. In the pooled individual participant data meta-analyses and adjusted multilevel analyses, age, sex, BMI, and SBP were significantly associated with CIMT in all racial and ethnic groups but with the strength of the associations varying considerably. Compared with European populations, populations of African ancestry (African and African American) had higher strength of association between alcohol, HDL-C, and CIMT whereas all other races or ethnicities had a lower strength of association between LDL-C and CIMT.

It has been observed that racial and ethnic differences in carotid artery thickness, diameter, and stiffness are due to genetic factors as well as anatomical differences in the carotid artery,[30] which may explain the higher CIMT in the African American group in our study. African American people also have disproportionately narrower internal and larger external carotid arteries compared with Asian, European, and Hispanic people.[30] This increases turbulent blood flow around the bifurcation resulting in high shear stress and exposure to risk factors enhances the thickening of the adjoining common carotid artery.[30] African American people are an admixed group with considerably variations in the relative proportions of African, European, and other racial or ethnic group ancestry between individuals. However, the majority of African American individuals are known to have largely originated from Yoruba, Bantu, and Mandeka speaking individuals of West African origin, as well as from Central Africa, who were forcibly moved to North America as part of the slave trade.[31,32] The thicker CIMT in African American people may therefore be due to their ancestry with West African participants having thicker CIMT compared with the other African populations in the AWI-Gen study. In addition, the higher burden of established CVD risk factors among the African American compared with the African populations may be a possible contributor to the greater CIMT observed among the former group.

The independent association of age with increased atherosclerosis in all racial and ethnic groups is consistent with published literature.[6,10] The common carotid artery is highly susceptible to the effects of aging with resultant thickening of the intima-media and increased vascular stiffness.[33] Increasing life expectancy is therefore likely to result in higher CVD-related morbidity and mortalities. The consistent finding of age effects on CIMT across all racial and ethnic groups suggests that screening and management of risk factors should be targeted at older individuals in all populations. The positive association of common CIMT levels with smoking in all races or ethnicities has been previously reported[7,8,10] as has the association of SBP with high CIMT.[6] High blood pressure is reported to cause detrimental effects on the vascular tree by inducing higher pressure overload causing arterial hypertrophy or hyperplasia.[34]

The inverse association of alcohol intake with CIMT in African and African American participants could be attributed to genetic factors and the types of alcohol consumed. Allele frequencies of polymorphic loci in the gene that encodes one of the alcohol dehydrogenase isoforms (ADH1B) differ between populations of African and European ancestry and confer different levels of cardioprotection in both races and ethnicities. Thus, the alcohol-metabolizing ADH1B*3 functional allele, found almost

Table 4. Standardized Relations of the Established CVD Risk Factors Within Racial and Ethnic Groups for the Outcome Common Carotid Intima-Media Thickness

	African	African American	Asia	European	Hispanic
Sample (N)	9428	4182	572	18 817	980
CVD risk factors					
Age	0.35***	0.23***	0.16***	0.23***	0.20***
Men vs women	0.04***	0.11***	0.15**	0.16***	0.13***
Smoking	0.09***	0.03*	0.15***	0.08***	0.04
Alcohol	−0.04***	−0.03*	0.02	−0.01	−0.10
Physical activity	−0.05***	−0.02	0.09	−0.08***	0.05
BMI, kg/m^2	0.11***	0.07***	0.12*	0.05***	0.17***
SBP, mm Hg	0.12***	0.18***	0.20***	0.23***	0.15***
Glucose, mmol/L	0.02	0.07***	0.18***	0.02*	0.09**
HDL-C, mmol/L	−0.09***	−0.09***	0.01	−0.02*	0.03
LDL-C, mmol/L	0.07**	0.08***	0.01	0.13***	0.10**

Data presented as standardised β (beta) coefficients. AA indicates African American; BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

Level of significance, *<0.05, **<0.01, and ***<0.001.

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exclusively in populations with African ancestry, is associated with a higher conversion rate of ethanol to acetaldehyde.[35,36] This should not be regarded as a public health advocacy for the consumption of alcohol as a means of reducing lipid levels. A randomized crossover feeding trial among men of African ancestry showed that alcohol improves lipid profiles and reduces atherosclerosis-related inflammatory markers in plasma.[37] Furthermore, sorghum-based beers are widely consumed in African populations and the high phenolic content of these drinks has been found to reduce the levels of leukocyte adhesion molecules and inflammatory biomarkers.[10] Contrary to our findings the ARIC study observed that African American people who are current drinkers were more likely to develop coronary heart disease than European people.[38] These inconsistent findings further highlight the complex association of alcohol with CVDs and calls for more in-depth longitudinal, gene-alcohol interaction and genome-wide association studies to provide further insight into the relationship of alcohol intake with atherosclerotic diseases in African populations.

African subjects showed the weakest positive association between LDL-C, and one of the strongest negative associations between HDL-C and CIMT compared with the other racial or ethnic groups. Previous studies had demonstrated that African populations have lower lipid levels (especially LDL-C and isolated HDL-C) and this may have resulted in a weaker association with CVD morbidity and mortality compared with other racial or ethnic groups.[39,40] Low LDL-C and weak association of LDL with CIMT may be a driver of the lower level of atherosclerosis in African populations but the effect of HDL-C on CVD risk is uncertain. Lifestyle differences between various racial or ethnic groups may explain some of the observed differences in both the risk factors for CVD and the CIMT measurements.

The raw CIMT levels were higher in men compared with women for all cohorts except those from Africa, where CIMT was similar across genders. Gender differences in CIMT may be related to the relative exposure to CVD risk factors[41] and when CIMT values were adjusted for these risk factors their levels were found to be higher in men than women within the African group and in all the other groups. When CIMT values were adjusted for CVD risk factors, the values fell modestly in all racial or ethnic groups except for the African population where the level rose slightly. This again highlights the differential relationship of CVD risk factors with CIMT across these racial and ethnic groups and suggests that differences in CIMT levels observed between the groups may only partially be explained by the CVD risk factors measured in this study.

Our study has demonstrated that racial and ethnic variations exist in the association of classical cardiovascular risk factors with CIMT. For instance, although SBP and hyperglycemia had the highest strength of association with CIMT in Asian participants, age was found to have the highest strength in all other racial and ethnic groups. These observed differences highlight the importance of further research to elucidate the mechanisms involved in the differential association of CVD risk factors with subclinical atherosclerosis across different population groups.

Strengths and Limitations

In these IPD-MAs, we pooled data from 34 025 adults between the ages of 40 and 60 years from 15 cohorts drawn from Africa, Asia, Europe, and North America. This is the first study to compare the association of CVD risk factors with CIMT in a large population of African people residing in East, West, and South Africa with that in other large cohorts drawn from different ethnic groups. The addition of the African population to the meta-analysis considerably expands our understanding of race and ethnicity and atherosclerotic cardiovascular disease. Using an IPD-MA approach makes this study robust because we have been able to make direct comparison across the various ethnic groups. Harmonization of the outcome measure and the variables used in these analyses limited bias. The use of adjusted multilevel mixed-effect analyses to determine the mean differences in CIMT makes our results reliable and comparable across racial or ethnic groups. We also acknowledge that because of the relatively small number of Asian and Hispanic subjects included in this study, our results may not be generalizable to these races and ethnicities as a whole. Furthermore, the Hispanic population and a large majority of the Asian population were resident in the United States and therefore any data should not be extrapolated to such racial or ethnic groups residing outside of the United States.

Adjustment of the mean CIMT levels for the effect of established CVD risk factor enabled us to determine whether observed variations in mean CIMT across racial and ethnic groups were due to differential patterning of CVD risk factors. We were also able to account for across and within racial and ethnic group differences conferred by the different cohorts included in the IPD-MA while preserving the original design and composition of the cohort. The H3Africa AWI-Gen study was conducted recently (2013–2015) whereas studies in the USE-IMT cohorts were mainly conducted between 1990 and 2000. This however should not affect the observed relationships because evidence from the Framingham study demonstrates significant relations that were observed in the baseline cohort 73 years ago still exist.[42]

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A recent review by Mitchell et al. (2021) reported that over time changes in technology have improved image resolutions of CIMT measurements.[25] This may therefore affect cross-cohort comparisons due to differences in the ultrasound technologies used based on the year data were collected. We believe however that the use of *Z* scores, a method previously described by Den Ruijter et al. (2012), may offer a measure of standardization owing to the different ultrasound protocols used by the various studies[11] and minimize bias in the observed associations of CIMT with CVD risk factors. Further to this a binary variable of older and newer technology was generated and there was no difference in the mean CIMT *Z* scores between the 2 technologies. When we further introduced this dummy variable as a multiplicative interaction term with race or ethnicity, we found no statistical interaction in the model. This is further proof that the reported associations in this paper are not significantly affected by the differences in technologies of the ultrasound machines.

A limitation of any meta-analysis is that analyses can be performed only on variables that are common to all the studies. In the present meta-analysis, dietary intake data was not available across all the studies and this is a limitation because previous investigations have shown associations between nutrient intake and CIMT. Thus, a recent meta-analysis of clinical trials focusing on the reduction of CIMT demonstrated that dietary interventions significantly slowed CIMT progression.[43] In addition, we did not have medication use for all the included studies and data on the self-reported history of a diagnosis of diabetes or hypertension were available only from the African sites. We also acknowledge that residual confounding from several other unmeasured factors that may contribute to some of the observed ethnic differences could not be dealt with in these analyses.

CONCLUSIONS

The differences in the magnitude of the associations of CVD risk factors with CIMT has implications for ethnic specific primary prevention strategies and also offer insights into racial- and ethnic-specific mechanisms involved in the pathogenesis of CVD. The current study does suggest that high CIMT levels in African American people could be the result of genetics, with alleles predisposing to higher CIMT levels possibly originating in West Africa. However, it cannot be excluded that differences in lifestyle (eg, diet), and metabolic factors (such as BMI, SBP, hyperglycemia, and LDL) may also contribute to these differences in CIMT levels and that gene-environment interactions may also be involved.

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Author contributions: Nonterah, Klipstein-Grobusch, Crowther, and Bots conceived the paper and designed the data analyses plan. Nonterah analyzed the data and wrote the first draft with contributions from Klipstein-Grobusch, Crowther, and Bots. Investigators responsible for AWI-Gen study data collection and quality control were Nonterah, G. Agongo, G. Asiki, Boua, Choma, Crowther, Micklesfield, Oduro, Tollman, and Ramsay Investigators responsible for the USE-IMT data include Anderson, Couper, Engström, de Graaf, Kavousi, Kauhanen, Lonn, Mathiesen, Okazaki, Polak, Rundek, Salonen, Tuomainen, Grobbee, and Bots. The PIs responsible for the AWI-Gen and USE-IMT consortia are Ramsay and Bots respectively.

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S5

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SUPPLEMENTAL MATERIAL

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Data S1.

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Table S1: Baseline characteristic of the cohorts in the USE-IMT and AWI-Gen collaborative study

Cohorts	Country	Women	Men	Age, years	CIMT, mm	Smoking %	Alcohol %	PA %	BMI, kg/m^2	SBP, mm Hg	DBP, mm Hg	Glucose, mmol/l	LDL, mmol/l	HDL, mmol/l
ARIC[14]	USA	6920	5355	52 ±5	0.66 ±0.14	27	75	98	27.6 ±5.3	120±18	74±11	5.96 ±2.14	3.53 ±1.02	1.34 ±0.44
AWI-Gen[12]	SSA	4745	4683	50 ±6	0.64 ±0.12	29	38	89	24.1 ±6.1	124±22	79±13	5.06 ±1.62	2.30 ±0.99	1.18 ±0.41
	*SA**	758	515	51 ±6	0.61 ±0.09	20	21	83	27.1 ±6.7	134±23	80±13	4.99 ±1.63	2.33 ±0.93	1.20 ±0.39
	SA†	804	356	51 ±6	0.64 ±0.12	31	28	79	30.0 ±8.2	126±21	81±13	5.18 ±2.26	2.54 ±1.03	1.19 ±0.40
	SA‡	-	965	49 ±6	0.62 ±0.12	69	51	75	24.9 ±5.7	132±21	89±13	5.29 ±1.54	2.37 ±0.92	1.21 ±0.46
	Kenya	1056	884	49 ±5	0.59 ±0.11	28	19	89	25.4 ±5.8	120±21	78±13	5.43 ±1.99	2.86 ±0.93	1.26 ±0.47
	BF	1038	1043	50 ±6	0.66 ±0.12	13	64	84	20.9 ±3.5	116±18	74±11	5.05 ±1.24	2.20 ±0.95	1.12 ±0.37
	Ghana	1089	920	51 ±6	0.69 ±0.13	31	65	89	21.6 ±3.6	124±22	78±13	4.54 ±0.81	1.72 ±0.74	1.14 ±0.38
FATE[13]	Canada	1	1112	49 ±5	0.71 ±0.16	14	100	-	28.8 ±3.6	127±16	82±10	5.34 ±1.01	3.38 ±0.83	1.24 ±0.28
KIHD[17]	Finland	-	1055	50 ±5	0.76 ±0.16	42	100	80	26.5 ±3.5	132±16	88±10	4.72 ±1.16	3.93 ±0.97	1.29 ±0.29
Malmö[18]	Sweden	1920	1331	54 ±4	0.74 ±0.14	25	100	79	25.4 ±3.8	137±18	86±9.5	5.08 ±1.23	4.06 ±0.98	1.39 ±0.37
MESA[15]	USA	1631	1433	53 ±5	0.68 ±0.14	18	72	85	28.8 ±5.8	119±18	72±10	5.20 ±1.66	3.08 ±0.83	1.29 ±0.37
NBS[20]	NLD	327	66	56 ±3	0.79 ±0.09	21	90	40	26.2 ±4.0	124±14	77±10	5.04 ±0.81	3.77 ±0.93	1.47 ±0.39
NOMAS[16]	USA	210	144	57 ±2	0.69 ±0.08	20	69	47	28.7 ±5.2	133±19	82±11	5.37 ±2.17	3.22 ±0.86	1.21 ±0.35
OSACA2[21]	Japan	84	114	55 ±5	0.84 ±0.13	31	100	98	23.9 ±3.3	135±20	83±11	5.88 ±1.48	3.52 ±0.66	1.43 ±0.40
Tromsø[19]	Norway	1235	1459	55 ±5	0.74 ±0.13	36	79	69	26.1 ±3.7	139±19	83±12	4.84 ±1.13	4.84 ±1.23	1.52 ±0.43
Combined	-	17073	16952	52 ±5	0.69 ±0.14	27	78	90	26.4 ±5.3	125±20	78±12	5.41 ±1.81	3.34 ±1.22	1.33 ±0.43

Data presented as mean ±standard deviation (SD) or %; ARIC, Atherosclerosis Risk in Communities study; AWI-Gen, African-Wits-INDEPTH Genomic study; BF, Burkina Faso; BMI, body mass index in kg/m^2; CIMT, carotid intima-media thickness; FATE, Firefighters and Their Endothelium Study; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; Malmö, Malmö Diet and Cancer Study; MESA, Multi-Ethnic Study of Atherosclerosis; NBS, Nijmegen Biomedical Study; NLD, Netherlands; NOMAS, Northern Manhattan Study; OSACA2, Osaka Follow-up Study for Carotid Atherosclerosis 2; PA, Physical activity; *SA, South Africa -Agincourt; †SA, South Africa – Dikgale; ‡SA, South Africa – Soweto; USA, United States of America; USE-IMT, USE Intima-Media Thickness collaboration.

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Table S2: Adjusted mean common carotid intima-media thickness (with 95% CIs) for the various ethnicities in the USE-IMT AWI-Gen collaborative study and stratified by women and men

	Asian (n=572)	**African (n=9428)**	**African American (n=4182)**	**European (n=11477)**	**European American (n=7340)**	**Hispanic (n=980)**	**P-value**
Combined sample							
Model 1	0.72 (0.68, 0.76)	0.64 (0.53, 0.75)	0.78 (0.74, 0.82)	0.75 (0.73, 0.77)	0.68 (0.65, 0.70)	0.73 (0.69, 0.77)	-
Model 2	0.72 (0.68, 0.76)	0.66 (0.55, 0.77)	0.78 (0.74, 0.81)	0.73 (0.72, 0.75)	0.66 (0.64, 0.68)	0.72 (0.68, 0.75)	< 0.001
Model 3	**0.73 (0.61, 0.74)**	**0.67 (0.59, 0.76)**	**0.75 (0.72, 0.77)**	**0.72 (0.70, 0.74)**	**0.66 (0.63, 0.69)**	**0.69 (0.66, 0.72)**	**0.001**
Women							
Model 1	0.69 (0.65, 0.74)	0.64 (0.53, 0.75)	0.76 (0.72, 0.81)	0.74 (0.70, 0.76)	0.66 (0.63, 0.69)	0.72 (0.67, 0.76)	-
Model 2	0.68 (0.64, 0.72)	0.66 (0.55, 0.76)	0.75 (0.71, 0.79)	0.72 (0.69, 0.74)	0.64 (0.62, 0.67)	0.70 (0.66, 0.74)	-
Model 3	**0.65 (0.62, 0.69)**	**0.66 (0.58, 0.75)**	**0.72 (0.68, 0.75)**	**0.71 (0.68 0.74)**	**0.64 (0.61, 0.67)**	**0.67 (0.64, 0.71)**	-
Men							
Model 1	0.74 (0.70, 0.78)	0.64 (0.53, 0.75)	0.79 (0.75, 0.83)	0.76 (0.74, 0.78)	0.69 (0.67, 0.72)	0.74 (0.70, 0.78)	-
Model 2	0.73 (0.69, 0.77)	0.66 (0.55, 0.77)	0.78 (0.75, 0.82)	0.75 (0.74, 0.76)	0.68 (0.66, 070)	0.73 (0.69, 0.77)	-
Model 3	**0.72 (0.69, 0.76)**	**0.69 (0.61, 0.77)**	**0.76 (0.73, 0.78)**	**0.73 (0.71, 0.75)**	**0.68 (0.65, 0.70)**	**0.70 (0.67, 0.74)**	-

Model 1 is crude unadjusted; model 2 is adjusted for age, sex and sex*ethnicity interaction (sex stratified analyses were adjusted for only age) and model 3, model 1 + smoking, alcohol, physical activity, SBP, BMI, glucose, HDL-C and LDL-C; BMI, body mass index, HDL-C, high density lipoprotein cholesterol, LDL-C, low density lipoprotein cholesterol and SP, systolic blood pressure; P-value denotes ethnicity*sex interaction

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Table S3: Multiplicative interaction terms between race-ethnicity and sex

Multiplicative interaction terms	**Coefficient (95%CI)**	**SE**	**X^2 (p-value)**
Ethnicity x Sex for whole sample			
African x Women	-0.59 (-1.77, 0.58)	0.599	1204.88 (<0.00001)
African x Men	-0.58 (-1.75, 0.59)	0.599	
African American x Women	0.60 (0.53, 0.66)	0.032	
African American x Men	0.99 (0.92, 1.07)	0.037	
Asian x Women	-0.16 (-0.34, 0.03)	0.094	
Asian x Men	0.64 (0.42, 0.87)	0.113	
European x Women	Ref (0)	Ref (0)	
European x Men	0.69 (0.50, 0.87)	0.094	
Hispanic x Women	0.17 (0.03, 0.31)	0.070	
Hispanic x Men	0.43 (0.28, 0.57)	0.073	
HIV x Sex for Africans only			
HIV negative x Women	Ref (0)	Ref (0)	60.41 (0.169)
HIV negative x Men	0.048 (-0.003, 0.101)		
HIV+ART+ x Women	-0.213 (-0.111, 0.314)		
HIV+ART+ x Men	-0.324 (-0.212, 0.436)		

ART, antiretroviral therapy

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Table S4: Individual Participant Data-Meta-analysis on ethnic differences of the association between classical CVD risk factors and carotid intima-media thickness in the combined sample, women and men

Factors	**African**	**African American**	**Asian**	**European**	**European American**	**Hispanic**	***I^2, P-value***
	β (95%CI)	**β (95%CI)**	**β (95%CI)**	**β (95%CI)**	**β (95%CI)**	**β (95%CI)**	
Combined population							
Age	**0.07 (0.06, 0.07)**	**0.08 (0.07, 0.09)**	**0.04 (0.02, 0.07)**	**0.08 (0.07, 0.08)**	**0.07 (0.07, 0.08)**	**0.05 (0.04, 0.07)**	*64%; p=0.026*
Men vs. women	**0.09 (0.03, 0.15)**	**0.36 (0.26, 0.46)**	**0.37 (0.13, 0.61)**	**0.46 (0.42, 0.50)**	**0.42 (0.36, 0.47)**	**0.31 (0.16, 0.46)**	*96%; p<0.001*
Smoking	**0.24 (0.19, 0.29)**	**0.12 (0.03, 0.21)**	**0.72 (0.29, 1.16)**	**0.25 (0.21, 0.30)**	**0.22 (0.17, 0.28)**	0.13 (-0.06, 0.31)	*95%; p<0.001*
Alcohol	**-0.09 (-0.16, -0.04)**	**-0.20 (-0.38, -0.03)**	0.06 (-0.22, 0.33)	-0.05 (-0.14, 0.04)	**-0.36 (-0.43, -0.26)**	-0.03 (-0.16, 0.15)	*97%; p<0.001*
Physical activity	**-0.18 (-0.26, -0.11)**	-0.13 (-0.33, 0.07)	0.29 (0.02, 0.55)	**-0.39 (-0.47, -0.33)**	**-0.12 (-0.23, -0.01)**	0.14 (-0.13, 0.31)	*70%; p<0.001*
BMI (kg/m^2)	**0.02 (0.01, 0.02)**	**0.02 (0.01, 0.03)**	**0.05 (0.01, 0.08)**	**0.02 (0.02, 0.03)**	**0.03 (0.02, 0.03)**	**0.04 (0.02, 0.05)**	*90%; p<0.001*
SBP (mmHg)	**0.06 (0.05, 0.08)**	**0.13 (0.11, 0.15)**	**0.13 (0.08, 0.20)**	**0.17 (0.16, 0.19)**	**0.14 (0.12, 0.15)**	**0.09 (0.05, 0.13)**	*94%; p<0.001*
Glucose (mmol/l)	-0.01 (-0.03, 0.02)	**0.04 (0.02, 0.05)**	**0.13 (0.06, 0.19)**	**0.02 (0.01, 0.03)**	**0.04 (0.03, 0.06)**	**0.06 (0.02, 0.09)**	*91%; p<0.001*
HDL-C (mmol/l)	**-0.26 (-0.31, -0.19)**	**-0.31 (-0.42, -0.21)**	0.05 (-0.30, 0.39)	**-0.07 (-0.12, -0.02)**	**-0.13 (-0.19, -0.06)**	0.09 (-0.14, 0.33)	*93%; p<0.001*
LDL-C (mmol/l)	**0.06 (0.03, 0.08)**	**0.13 (0.08, 0.16)**	0.01 (-0.14, 0.16)	**0.16 (0.15, 0.18)**	**0.11 (0.08, 0.13)**	**0.14 (0.06, 0.22)**	*97%; p<0.001*
Women							
Age	**0.07 (0.06, 0.08)**	**0.07 (0.06, 0.08)**	**0.05 (0.02, 0.08)**	**0.07 (0.06, 0.08)**	**0.07 (0.06, 0.07)**	**0.05 (0.03, 0.08)**	*0.0%; p=0.437*
Smoking	0.05 (-0.12, 0.21)	0.13 (-0.01, 0.26)	0.05 (-0.08, 0.09)	**0.17 (0.12, 0.23)**	0.19 (0.12, 0.26)	0.13 (-0.12, 0.38)	*63%; p=0.029*
Alcohol	**-0.20 (-0.31, -0.18)**	-0.18 (-0.41, 0.04)	-0.01 (-0.37, 0.35)	**-0.13 (-0.24, -0.03)**	**-0.43 (-0.54, -0.31)**	0.06 (-0.13, 0.25)	*96%; p<0.001*
Physical activity	**-0.23 (-0.34, -0.12)**	-0.14 (-0.40, 0.11)	0.25 (-0.07, 0.56)	**-0.24 (-0.35, -0.13)**	-0.09 (-0.23, 0.04)	0.14 (-0.07, 0.34)	*89%; p<0.001*
BMI (kg/m^2)	**0.08 (0.03, 0.14)**	**0.09 (-0.01, 0.18)**	**0.04 (0.02, 0.08)**	**0.12 (0.07, 0.18)**	**0.02 (0.01, 0.03)**	**0.26 (0.09, 0.42)**	*93%; p<0.001*
SBP (mmHg)	**0.08 (0.06, 0.09)**	**0.15 (0.12, 0.17)**	0.05 (-0.02, 0.12)	**0.12 (0.05, 0.18)**	**0.13 (0.11, 0.14)**	**0.11 (0.07, 0.16)**	*87%; p<0.001*
Glucose (mmol/l)	0.01 (-0.01, 0.03)	**0.05 (0.03, 0.07)**	**0.14 (0.05, 0.24)**	**0.06 (0.04, 0.08)**	**0.05 (0.03, 0.07)**	**0.05 (0.01, 0.09)**	*78%; p=0.001*
HDL-C (mmol/l)	**-0.22 (-0.30, -0.13)**	**-0.38 (-0.52, -0.24)**	-0.08 (-0.45, 0.29)	**-0.07 (-0.13, -0.04)**	**-0.09 (-0.17, -0.12**	0.25 (-0.03, 0.52)	*81%; p<0.001*
LDL-C (mmol/l)	**0.05 (0.01, 0.08)**	**0.11 (0.05, 0.16)**	**0.25 (0.16, 0.55)**	**0.14 (0.12, 0.16)**	**0.07 (0.04, 0.12)**	**0.11 (0.04, 0.22)**	*81%; p<0.001*
Men							
Age	**0.08 (0.07, 0.09)**	**0.09 (0.08, 0.11)**	**0.04 (0.07, 0.08)**	**0.09 (0.08, 0.11)**	**0.08 (0.07, 0.09)**	**0.05 (0.02, 0.08)**	*63%; p=0.028*
Smoking	**0.08 (0.01, 0.14)**	0.12 (-0.02, 0.26)	**0.85 (0.32, 1.39)**	**0.34 (0.27, 0.40)**	**0.27 (0.018, 0.36)**	0.12 (-0.15, 0.39)	*77%; p=0.002*
Alcohol	**-0.14 (-0.22, -0.06)**	-0.24 (-0.52, 0.03)	0.09 (-0.31, 0.50)	0.06 (-0.09, 0.21)	**-0.32 (-0.49, -0.15)**	-0.07 (-0.34, 0.19)	*93%; p<0.001*
Physical activity	**-0.12 (-0.22,- 0.02)**	-0.08 (-0.39, 0.26)	0.29 (-0.12, 0.71)	**-0.38 (-0.48, -0.28)**	-0.19 (-0.39, 0.01)	0.11 (-0.17, 0.39)	*0.0%; p=0.460*
BMI (kg/m^2)	**0.03 (0.02, 0.04)**	**0.04 (0.03, 0.06)**	**0.04 (-0.02, 0.11)**	**0.04 (0.02, 0.04)**	**0.05 (0.04, 0.06)**	**0.06 (0.04, 0.09)**	*67%; p=0.016*
SBP (mmHg)	**0.06 (0.05, 0.08)**	**0.11 (0.08, 0.14)**	**0.30 (0.17, 0.42)**	**0.19 (0.17, 0.20)**	**0.16 (0.14, 0.18)**	0.05 (-0.01, 0.12)	*97%; p<0.001*
Glucose (mmol/l)	-0.09 (-0.32, 0.14)	**0.03 (0.01, 0.06)**	**0.12 (0.03, 0.20)**	**0.67 (0.45, 0.89)**	**0.46 (0.21, 0.71)**	**0.09 (0.06, 0.13)**	*82%; p<0.001*
HDL-C (mmol/l)	**-0.26 (-0.33, -0.18)**	-0.15 (-0.32, 0.03)	0.15 (-0.50, 0.80)	**-0.12 (-0.21, -0.03)**	**-0.27 (-0.37, -0.14)**	-0.27 (-0.71, 0.17)	*0.0%; p=0.444*
LDL-C (mmol/l)	**0.06 (0.02, 0.09)**	**0.15 (0.08, 0.21)**	0.06 (-0.18, 0.31)	**0.20 (0.17, 0.23)**	**0.17 (0.13, 0.21)**	**0.18 (0.05, 0.31)**	*95%; p<0.001*

I^2, is the between-study variance as a percentage of total variance; BMI, body mass index, CI, confidence interval; HDL-C, high density lipoprotein cholesterol, LDL-C, low density lipoprotein cholesterol and SP, systolic blood pressure

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Table S5: Comparing the variance explained by modeling the association of LDL, HDL and LDL/HDL ratio with common carotid intima-media thickness

	Variance inflation factor for model 1	**R^2 for model 2**	**R^2 for model 3**	**Comment**
African ancestry	7.32	0.18	0.18	No change in R^2
African American	8.29	0.17	0.17	No change in R^2
Asians	12.6	0.26	0.26	No change in R^2
European ancestry	8.41	0.16	0.16	No change in R^2
Hispanic	10.04	0.24	0.24	No change in R^2

Model 1included the following independent variables: age, sex, smoking, physical activity, alcohol, BMI, SBP, Glucose, HDL-C, LDL-C and LDL-C/HDL-C ratio; Model 2 included age, sex, smoking, physical activity, alcohol, BMI, SBP, Glucose, LDL-C and HDL-C and Model 3 included age, sex, smoking, physical activity, alcohol, BMI, SBP, Glucose, LDL-C/HDL-C ratio

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