ORIGINAL RESEARCH

Classical Cardiovascular Risk Factors and HIV are Associated With Carotid Intima-Media Thickness in Adults From Sub-Saharan Africa: Findings From H3Africa AWI-Gen Study

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Background—Studies on the determinants of carotid intima-media thickness (CIMT), a marker of sub-clinical atherosclerosis, mostly come from white, Asian, and diasporan black populations. We present CIMT data from sub-Saharan Africa, which is experiencing a rising burden of cardiovascular diseases and infectious diseases.

Methods and Results—The H3 (Human Hereditary and Health) in Africa's AWI-Gen (African-Wits-INDEPTH partnership for Genomic) study is a cross-sectional study conducted in adults aged 40 to 60 years from Burkina Faso, Kenya, Ghana, and South Africa. Cardiovascular disease risk and ultrasonography of the CIMT of right and left common carotids were measured. Multivariable linear and mixed-effect multilevel regression modeling was applied to determine factors related to CIMT. Data included 8872 adults (50.8% men), mean age of 50±6 years with age- and sex-adjusted mean (±SE) CIMT of 640±123μm. Participants from Ghana and Burkina Faso had higher CIMT compared with other sites. Age (β=6.77, 95%CI [6.34–7.19]), body mass index (17.6[12.5–22.8]), systolic blood pressure (7.52[6.21–8.83]), low-density lipoprotein cholesterol (5.08[2.10–8.06]) and men (10.3[4.75– 15.9]) were associated with higher CIMT. Smoking was associated with higher CIMT in men. High-density lipoprotein cholesterol (−12.2 [−17.9– −6.41]), alcohol consumption (−13.5 [−19.1–−7.91]) and HIV (−8.86 [−15.7–−2.03]) were inversely associated with CIMT.

Conclusions—Given the rising prevalence of cardiovascular diseases risk factors in sub-Saharan Africa, atherosclerotic diseases may become a major pan-African epidemic unless preventive measures are taken particularly for prevention of hypertension, obesity, and smoking. HIV-specific studies are needed to fully understand the association between HIV and CIMT in sub-Saharan Africa. **(*J Am Heart Assoc*. 2019;8:e011506. DOI: 10.1161/JAHA.118.011506.)**

Key Words: cardiovascular disease • carotid intima-media thickness • epidemiological transition • prevention • sub-Saharan Africa

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*A complete list of the H3Africa AWI-Gen consortium members can be found in the Appendix at the end of the manuscript.

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Clinical Perspective

What Is New?

- This the first study involving indigenous African populations drawn from 4 countries at different stages of epidemiological transition, to demonstrate that classical cardiovascular risk factors such as age, male sex, systolic blood pressure, serum cholesterol, and obesity are major drivers of increased carotid intima-media thickness.
- HIV infection was not associated with higher carotid intima-media thickness levels.

What Are the Clinical Implications?

- Interventions focused on classical, modifiable cardiovascular disease risk factors will attenuate atherosclerotic risk in sub-Saharan African populations.
- HIV infection may not be a risk factor for atherosclerotic diseases in sub-Saharan African.
- Results from recent studies in sub-Saharan African have reported a lower prevalence of cardiovascular disease risk factors in subjects living with HIV and this new paradigm suggests that the HIV care cascade may be an effective resource for the prevention and control of cardiovascular diseases among people living with HIV.

Global morbidity and mortality attributable to noncommunicable diseases are increasing with cardiovascular diseases (CVD) being a significant contributor.[1] A greater proportion of the annual CVD-related deaths occur between 30 to 70 years of age and 85% of these deaths occur in low- and middle-income countries, and are projected to increase further.[2] A major contributor to the burden of cardiovascular morbidity and mortality is the development of atherosclerosis, a continuous process which often starts early in life and progresses with age.[3] Exposure to unfavorable levels of established cardiovascular risk factors such as high systolic blood pressure, smoking, and dyslipidemia leads to the accelerated development of atherosclerosis.

The measurement of sub-clinical atherosclerosis by the assessment of carotid intima-media thickness (CIMT) may provide information about the cardiovascular status of a population.[4–7] However, epidemiological data on the prevalence and determinants of high CIMT arise largely from studies in whites, Asians, and Africans in the diaspora or blacks, which may not reflect the situation among Africans living in sub-Saharan Africa (SSA).[4,8,9]

Africa is currently engulfed in a wave of complex epidemiological transition that is characterized by extensive urbanization with concomitant lifestyle changes such as consumption of calorie dense diets and a decrease in physical activity.[10,11] The surge in CVD risk factors, such as obesity and hypertension, adds to the complex milieu of a high burden of infectious diseases such as HIV, tuberculosis, and malaria.[12] Despite this double burden of non-communicable and infectious diseases in Africa, large cohort studies with harmonized data on CVDs are lacking.[10] To formulate appropriate interventions to decrease CIMT as a proxy for subclinical atherosclerosis, it is important to identify the specific risk factors associated with CIMT in SSA populations.

Therefore, the aim of the study was to measure CIMT and identify risk factors associated with CIMT in a large SSA population. This was achieved by measuring CIMT levels within the AWI-Gen (African-Wits-INDEPTH [International Network for the Demographic Evaluation of Populations and their Health in low- and middle-income countries] Partnership for Genomic studies). This is a large pan-African epidemiological and genetic study that has collected sociodemographic, behavioral, anthropometric, metabolic, and genetic data on close to 12 000 participants from 4 countries within SSA.[13,14]

Materials and Methods

All data and materials for the AWI-Gen study that support the findings in this paper will be made available in the European Genome-phenome Archive under the set of projects related to the Human Heredity and Health in Africa (H3Africa) Consortium. Details about access to data can be found in the document titled "H3Africa Data and Biospecimen Access Committee Guidelines," available in the consortium documents section of the H3Africa website (www.h3africa.org).

Study Design and Study Population

We conducted a population-based cross-sectional study as part of the AWI-Gen partnership, a National Institutes of Health-funded Collaborative Centre of the Human Heredity and Health in Africa (H3Africa) Consortium. Six study sites in 4 sub-Saharan African (SSA) countries were involved in the AWI-Gen study (Figure 1). Three of the sites were in South Africa of which 2 are rural and 1 is urban. The rural sites were the Dikgale health and demographic surveillance site (HDSS)[15] affiliated with the Department of Pathology and Medical Science, University of Limpopo, and the Agincourt Health and Demographic Surveillance System Site (HDSS)[16] managed by the Medical Research Council/Wits Rural Public Health and Health Transitions Research Unit, University of the Witwatersrand. The urban South African site is the MRC/Wits Developmental Pathways for Health Research Unit , University of the Witwatersrand, in Soweto.[17] There was 1 urban site in Nairobi, Kenya: the African Population and Health Research

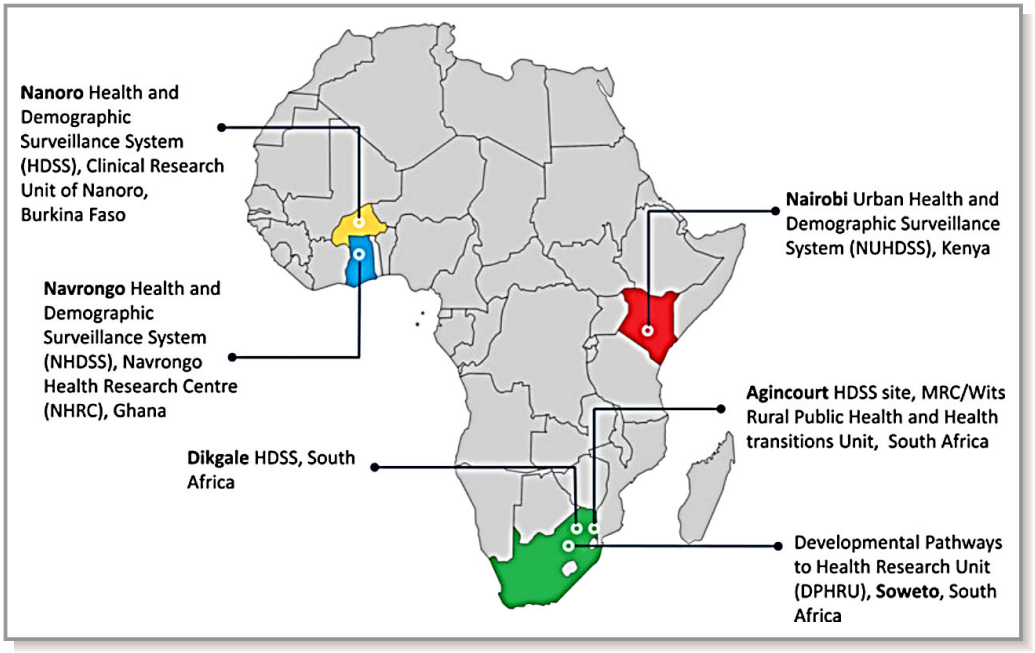

Figure 1. The sites constituting the H3Africa AWI-Gen study. Reprinted from Ramsay et al[13] with permission. Copyright ©2016, Cambridge University Press.

Center HDSS.[18] Finally, there were 2 rural sites in West Africa: the Navrongo HDSS hosted by the Navrongo Health Research Center in Ghana,[19] and the Nanoro HDSS hosted by the Institut de Recherche en Sciences de la Santé Clinical Research Unit of Nanoro in Burkina Faso.[20] Included in the study were adults aged 40 to 60 years resident in the various sites. Exclusion criteria were current pregnancy and inability to complete the prescribed study procedures. Similar numbers of women and men were randomly sampled from each of the sites using existing sampling frames for the respective HDSS sites.[13,14] Only men from Soweto were included in these analyses as women contributing to the study population in Soweto, were the caregivers of the Birth to 20+ Cohort[17] and did not have CIMT measurements. Our study population covers 3 of the 5 subcontinental blocks of Africa and therefore represents a large proportion of the geographical (covering both rural and urban areas) and social variability of the SSA region.

Ethical Considerations

The AWI-Gen study received overall ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa (approval identification numbers: M121029; M170880), as well as from the appropriate ethics committees covering the Dikgale, Navrongo, Nanoro, and Nairobi sites. Community engagement activities were completed at each site to introduce the study to community leaders before commencement of the field work. Written and signed or thumb-printed informed consent was obtained from each participant before performing prescribed study procedures. In compliance with good clinical practice, participants who were found to have clinically overt CVDs were linked to health care by issuing referral letters in accordance with the healthcare system in the particular study site.

Data Collection

Details of data collection methods and procedures have been described elsewhere.[13,14,21] Briefly, a paper-based questionnaire was used to collect information from 5 of the sites while a Computer-Assisted Personalized Interview was used to collect information from the Agincourt site in South Africa. Information collected included demography, family ethnicity, education, household attributes, substance use (tobacco, alcohol, and drugs), infectious disease history (HIV, TB, and malaria), history of cardiovascular and metabolic diseases (diabetes mellitus, stroke, hypertension, angina, heart attack, congestive heart failure, obesity, and high cholesterol), thyroid disease, kidney disease, and physical activity. Data were then entered into the REDCap (Research Electronic Data Capture) system hosted at the University of the Witwatersrand, Johannesburg.[22,23] Data entry quality control to identify outliers, duplicate information, and missing data were completed on 10% of the data per site.

Carotid Ultrasonography

Training

To maintain uniformity across the sites, carotid ultrasonography procedures were standardized, and technicians trained centrally by a certified sonographer at the MRC/Wits Developmental Pathways for Health Research Unit at the Chris Hani Baragwanath Hospital, Soweto, South Africa. The identified technicians from the study sites were clinicians, nurses, or biomedical scientists. To ensure reproducibility and reduce CIMT measurement variability, masked repeated measurements of 15 volunteers were conducted by each trainee and the lead trainer. The coefficient of variation between and within trainees was calculated and maintained at <2%. Subsequently, the same settings and calibrations of the ultrasound equipment (linear-array 12L-RS transducer with a B-mode LOGIQ e ultrasound machine, GE Healthcare, CT, USA) were used for data collection at all sites throughout the entire recruitment period.

Image acquisition

To measure the right carotid, the participant was asked to lie down in a supine position with a pillow underneath the neck for slight extension, head turned towards the left at a 45^{O} angle and gel applied to the exposed neck area. Using the 2 sternocleidomastoid muscles as landmarks, the exposed area was scanned along the longitudinal plane until the common carotid artery (CCA) was found, and an image frozen. The operator then identified a continuous 1-cm segment (10 mm) of the CCA far wall. The operator then placed a cursor between 2 points (10 mm apart) on this identified segment of the far wall with the proximal starting point 1 cm from the bulb of the CCA. The ultrasound machine software then automatically detected the intima-lumen and the media-adventitia interfaces and calculated the minimum, maximum, and mean common CIMT in millimeters and to 2 decimal places. To measure the left carotid, the participant's head was turned to the opposite side, and the process was repeated. This approach was selected over measuring "multiple carotid segments" because it was easier to measure and more reproducible enabling its widespread use at all study sites. A recent study demonstrates that measuring CCA IMT is a good alternative compared with multiple segments in terms of prediction of risk of CVD events.[24] Additional quality control (QC) before analyses included the exclusion of CCA IMT >1.5 mm as this is indicative of plaque. Images with >50% differences between minimum and maximum CCA IMT were also excluded from the analytical data set.[5] The far walls of both the left and right common carotid artery were averaged to determine mean CIMT thickness in millimeters as the main outcome variable. This was then converted to micrometers for the regression analyses.

Assessment of Sociodemographic, Behavioral, Anthropometric, Blood Pressure, Biochemical- and HIV-Related Variables

Age at the time of data collection and sex of participants were self-reported. Highest level of education attained was self-reported and categorized as no formal education, completion of primary, secondary or tertiary education. Household socioeconomic status (SES) was assessed using the INDEPTH health equity tool which is an asset index generated by using principal component analysis to combine data on household possessions (http://indepth-network.org/resources/indepth-health-equity-tool-measuring-socio-economic-status). The asset score generated was categorized into quintiles (Q1=poorest, Q2=poorer, Q3=poor, Q4=less poor and Q5=least poor) and this was computed separately for each of the sites.

Smoking status was assessed by asking subjects if they had ever smoked any tobacco products such as cigarettes, cigars or pipes, and if they were current or past users of such products, Smoking was then categorized as "never," "current," and "past." For the purpose of these analyses current and past were combined as "smokers." Self-reported alcohol use was assessed using the 4-item CAGE (cut-annoyed-guilty-eye) questionnaire[25] and subsequently categorized as current or never/previous use. The Global Physical Activity Questionnaire was used to compute moderate-to-vigorous intensity physical activity (MVPA) in minutes per week. Participants were said to be active if their MVPA was ≥150 min/week or inactive if their MVPA was <150 min/week.[26]

Standing height to the nearest 0.1 cm and weight to the nearest 0.1 kg were measured without shoes and in light clothes using a Harpenden stadiometer (Holtain, Crymych, Wales) fixed to the wall and a digital calibrated weighing scale, respectively. Resting systolic blood pressure (SBP) and diastolic blood pressure were measured using a digital sphygmomanometer (Omron M6, Omron, Kyoto, Japan) with the participant seated with their arm at the level of the chest and with an appropriate-sized cuff. Three readings were taken at 2-minute intervals with the first reading discarded and the average of the final 2 readings taken as the current blood pressure reading.

Overnight fasting serum lipids and glucose were measured using an automated chemistry analyzer (Randox RX Daytona+, Crumlin, Northern Ireland). All serum samples were analyzed at the University of the Witwatersrand Developmental Pathways for Health Research Unit laboratory, Chris Hani Baragwanath Academic Hospital, Soweto, South Africa. The low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation.[27]

Self-reported HIV status was determined at all sites and in addition HIV testing (using locally-available rapid-test kits) was offered to all participants from Kenya and South Africa. In

South Africa all known HIV-positive participants were asked whether they were receiving antiretroviral therapy (ART). In Agincourt, HIV status was determined by use of Vironostika Uniform 11 [Biomeriuex, France] screening assay as part of the HAALSI (Health and Ageing in Africa: a Longitudinal Study of an INDEPTH Community in South Africa) study,[28] several months before performing measurements on a subset of these participants for the AWI-Gen study.[14] The HIV status could therefore have changed at the time of recruitment into the AWI-Gen study. The prevalence of HIV infection at the Burkina Faso and Ghana sites is known to be between 1% to 2%.[29,30]

Statistical Analysis

Continuous data are presented as means±SD while categorical data are presented as proportions. Age- and sex-adjusted mean (with standard error of the mean) CIMT was computed and presented for the various sites stratified by sex. One-way analysis of variance was used to determine the differences in mean CIMT levels between the sites whilst the Student *t*-test was used to determine differences between women and men within the sites. We used various multivariable linear regression models to determine the factors associated with CIMT. In model 1 we adjusted for the classical CVD risk factors. These factors are often used in risk prediction equations[31] to determine the risk of dying from atherosclerotic cardiovascular diseases and include age, sex, current smoking, SBP, fasting glucose, HDL-C, and LDL-C. We replaced total cholesterol with LDL-C because of its key role in the pathogenesis of atherosclerosis and treatment monitoring.[3,32] In model 2, we adjusted for body mass index (BMI), physical activity and alcohol consumption in addition to factors from model 1. In model 3, since household SES and education are a proxy for urbanization and social determinants of health,[33,34] we adjusted for these in addition to factors from model 2. Finally, considering the high burden of HIV infection in SSA, we adjusted for HIV status in model 4 in addition to the variables included in model 3. We also adjusted for the effect of site in all 4 of the multiple linear regression models. The final model (model 4) therefore included age, sex, smoking, SBP, fasting glucose, HDL-C, LDL-C, BMI, alcohol consumption, physical activity, education status, household SES, HIV status and site. We checked this model for multi-collinearity using the variance inflation factor ensuring that the variance inflation factor for each variable was <10. We added multiplicative interaction terms to this model to evaluate whether relations between risk factors and common CIMT differed by sex and between sites. If interaction terms were statistically significant ($P<0.05$), findings were presented for separate strata (men and women; across sites). In a further sub-analysis involving only the South African sites and Kenya we adjusted for objectively measured HIV status and for the South African sites only we adjusted for the effect of ART. This was because only at these sites was HIV status measured objectively and ART status was assessed only in the South African sites.

To fully account for within site differences, we further conducted mixed-effect multi-level (ML) regression using site as a random effect in the final model (model 4) of the multiple linear regression analysis. We also checked for the role of interaction of HIV with age, sex, and household SES in the mixed-effect ML model. A likelihood ratio test was then used to compare the best fitting model between the single multivariable linear regression model, the mixed-effect ML regression model and the mixed-effect ML regression model that included interaction terms. Results are reported as unstandardised β-coefficients with corresponding 95% CIs. Statistical significance was set at a 2-sided $P<0.05$. For educational status and household SES, which had >2 categories, a post estimation test was used to obtain a single *P* value for the estimate in the models. All data were analyzed using STATA 14.2 (College Station, TX 77845, USA) software.

Results

Data were available for 10 363 participants drawn from all 6 sites. However, 1491 of these were excluded from the data analysis because they either had no CIMT data or did not meet quality control criteria. The final analytical data set therefore consisted of 8872 participants.

Sociodemographic Characteristics

The mean (±SD) age of the total study population was 49.9±5.83 years and men comprised 50.8% of study participants (Table 1). Nairobi, Kenya had the youngest (48.5±5.43 years) while Navrongo, Ghana had the oldest (51.1±5.75 years) population. The 2 West African sites, Nanoro in Burkina Faso (83.0%) and Navrongo in Ghana (70.5%), had the highest number of participants with no formal education, while all 3 South African sites (8.45% Agincourt, 3.56% Dikgale and 14.4% among men in Soweto) and Nairobi (3.69%) had the highest number of participants with tertiary education. More than two-thirds of participants in all countries were in the 2 highest quintiles (less and least poor) of household socio-economic status (Table 1).

Behavioral Factors

The prevalence of smoking was higher among men in Soweto (53%) and Dikgale (29.7%) in South Africa and Navrongo,

Table 1. Basic Characteristics of Study Paticipants by Site

	All Sites	Nanoro, BF	Navrongo, GH	Agincourt, SA	Dikgale, SA	Soweto*, SA	Nairobi, KE
	n=8872	n=2081	n=1976	n=795	n=1152	n=936	n=1932
Age, y	49.9±5.82	49.8±5.81	51.1±5.75	50.3±5.79	50.4±5.97	49.4±5.99	48.5±5.43
Men	4506 (50.8)	1043 (50.1)	908 (46.0)	384 (48.3)	355 (30.8)	936 (100)	880 (45.6)
Education status							
No formal	3578 (40.5)	1716 (83.0)	1389 (70.6)	226 (28.5)	93 (8.07)	8 (0.85)	146 (7.55)
Primary	2468 (27.9)	239 (11.5)	376 (19.1)	262 (33.0)	381 (33.1)	105 (11.2)	1105 (57.2)
Secondary	2481 (28.0)	95 (4.63)	168 (8.54)	238 (29.9)	637 (55.3)	688 (73.5)	655 (33.9)
Tertiary	324 (3.69)	18 (0.87)	36 (1.82)	68 (8.56)	41 (3.56)	135 (14.4)	26 (1.34)
Household SES							
Poorest	1242 (14.0)	342 (16.4)	366 (18.5)	130 (16.3)	148 (12.8)	24 (2.57)	232 (12.0)
Very poor	1696 (19.1)	404 (19.4)	356 (18.0)	201 (25.3)	259 (22.5)	45 (4.83)	431 (22.3)
Poor	1676 (18.9)	404 (19.4)	383 (19.4)	101 (12.7)	152 (13.2)	189 (20.2)	447 (23.1)
Less poor	1923 (21.7)	386 (18.5)	462 (23.4)	181 (22.8)	251 (21.8)	248 (26.5)	395 (20.4)
Least poor	2335 (26.3)	548 (26.2)	409 (20.7)	182 (22.9)	342 (29.7)	430 (45.9)	427 (22.1)
Current smoking	1622 (18.3)	142 (6.83)	406 (20.6)	98 (12.4)	249 (29.7)	495 (53.0)	232 (12.0)
Current alcohol consumption	4139 (46.7)	1323 (63.8)	1287 (65.3)	187 (23.5)	318 (27.7)	665 (71.1)	359 (18.6)
Insufficient MVPA (<150 mins/week)	1302 (14.7)	402 (19.3)	293 (14.8)	176 (22.1)	43 (3.73)	256 (27.4)	132 (6.82)
BMI, kg/m^2	23.9±6.09	20.9±3.45	21.6±3.60	26.8±7.69	27.9±8.19	24.9±5.67	25.4±5.76
Systolic blood pressure, mm Hg	123±21.3	116±18.2	124±21.5	131±21.6	126±20.9	132±21.1	120±21.2
Diastolic blood pressure, mm Hg	78.4±13.1	73.5±10.6	76.9±12.7	78.6±12.8	81.1±12.8	89.2±13.2	78.4±12.9
Fasting glucose, mmol/L	5.07±1.69	5.05±1.25	4.54±0.81	5.12±1.83	5.21±2.49	5.28±1.54	5.43±1.99
HDL-C, mmol/L	1.18±0.42	1.12±0.37	1.14±0.38	1.19±0.41	1.19±0.41	1.20±0.46	1.26±0.47
LDL-C, mmol/L	2.21±0.87	1.92±0.76	1.85±0.71	2.23±0.79	2.49±0.89	2.48±0.91	2.58±0.87
HIV+	978 (11.0)	9 (0.43)	16 (0.81)	278 (34.9)	250 (21.0)	188 (20.1)	237 (12.3)
Self-reported ART use	695 (84.7)	…	…	268 (96.4)	138 (55.2)	84 (44.6)	193 (81.4)
Left mean CIMT, μm	649±0.136	669±132	703±145	611±112	632±0.126	637±142	601±121
Right mean CIMT, μm	627±130	659±123	667±132	581±107	640±130	601±129	576±119
Average CIMT μm	640±123	667±118	689±129	598±100	638±117	618±118	590±107

Data presented as absolute numbers and percentages (%) or as means±SD. ART indicates antiretroviral therapy; BF, Burkina Faso; BMI, body mass index; CIMT, carotid intima-media thickness; GH, Ghana; HDL-C, high-density lipoprotein cholesterol; KE, Kenya; LDL-C, low-density lipoprotein cholesterol; MVPA, moderate-to-vigorous physical activity; SA, South Africa; SES, socioeconomic status.

*Data presented are for men only since there was no CIMT measurements for women.

Ghana (20.6%) compared with Agincourt, South Africa (12.4%), Nairobi, Kenya (12.0%) and Nanoro, Burkina Faso (6.83%). Men in Soweto (71.1%) and the 2 West African sites (65.3% in Ghana and 63.8% in Burkina Faso) recorded higher current alcohol consumption than Dikgale (27.7%), Agincourt (23.5%), and Nairobi (18.6%). The total population was fairly active with more than two-thirds of adults across all countries meeting physical recommendations of ≥150 minutes of moderate-to-vigorous intensity physical activity per week (see Table 1).

Anthropometric, Blood Pressure, Biochemical Variables, and HIV Infection

The average BMI was 23.9±6.09 kg/m^2, with the rural sites of Burkina Faso (20.9±3.45 kg/m^2) and Ghana (21.6±3.6 kg/m^2) in West Africa recording lower BMIs than the urban sites in Kenya (25.4±5.76 kg/m^2) and the urban (25.0±5.67 kg/m^2 in Soweto) and rural (26.8±7.69 kg/m^2 in Agincourt and 27.9±8.19 kg/m^2 in Dikgale) sites in South Africa (Table 1). The average SBP and diastolic blood

pressure were highest in all 3 South African sites and Kenya compared with the West African sites. Fasting blood glucose was highest in Kenya (5.43±1.99 mmol/L), followed by the South African sites (5.12±1.83 mmol/L in Agincourt, 5.21±2.49 mmol/L in Dikgale and 5.28±1.54 mmol/L in Soweto), Burkina Faso (5.05±1.25 mmol/L) and Navrongo (4.54±0.81 mmol/L). A similar pattern was observed for HDL-C and LDL-C. The prevalence of HIV was highest in South Africa (34.9% in Agincourt, 21% in Dikgale and 20% in Soweto) followed by Kenya (12.3%) and <1% in Burkina Faso and Ghana (Table 1). Self-reported use of ART among HIV positive participants was lowest at Soweto (44.6%) followed by Dikgale with 55.2% and as high as 81.4% in Nairobi and 96.4% in Agincourt.

CIMT Measurements

Mean CIMT of the left CCA was higher than the right CCA (Table 1) in all 6 sites ($P<0.001$ in all sites). Age and sex adjusted mean (±standard errors) levels of the average CIMT for each sample at the different sites are presented in Figure 1. The average CIMT for the entire population was 640±113 μm. Mean CIMT was significantly different between all sites ($P<0.001$) with Ghana (689±129 μm) and Burkina Faso (667±118 μm) recording higher common CIMT levels than the South African sites (598±100 μm in Agincourt, 638±117 μm in Dikgale and 0.64±0.002 μm in Soweto) and Kenya (590±107 μm). Women in Kenya had higher CIMT compared with men ($P=0.022$) while the reverse was observed in Burkina Faso ($P<0.001$) (Figure 2). In Ghana ($P=0.657$) and South Africa (Agincourt, $P=0.501$ and Dikgale, $P=0.935$), women and men had similar levels of common CIMT.

Factors Associated With Common CIMT

The factors associated with CIMT in the combined population within univariate analyses are shown in Table S1. Adjusted regression models were then built sequentially and the factors associated with CIMT in the various models are displayed in Table 2. These analyses show that of the variables included in model 1, age, SBP, HDL-C and LDL-C remained significant through to model 4, whilst the effect of sex became significant from model 2 onwards. Smoking status was not significantly associated with CIMT in any of the models but its effect did strengthen across the models, whilst the effect of glucose weakened. Among the variables added in model 2, BMI and alcohol use both were significant and remained so, whilst MVPA was not significantly associated with CIMT in any of the models. Educational status and household SES included in model 3 were not significantly associated with CIMT, whilst HIV status, which was added in model 4, was significant. Model 1 explained 23.4% of the variance in CIMT whilst model 4 explained 24.4% of the variance.

To further understand the effect of HIV infection on CIMT, we conducted a sensitivity analysis, where we included

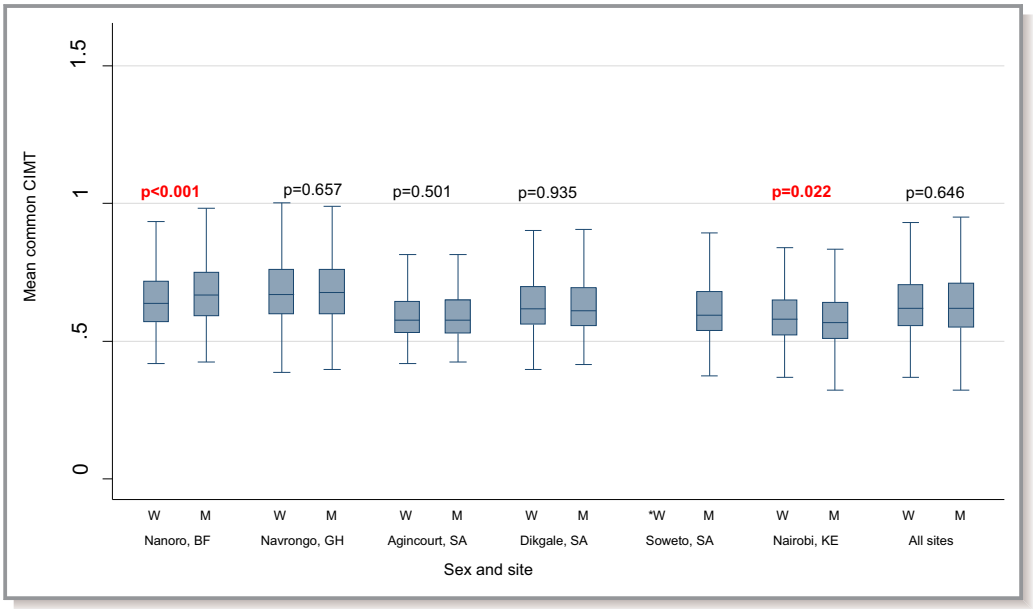

Figure 2. Age- and sex-adjusted distribution of mean levels of common CIMT (in mm) across 4 SSA countries stratified by sex. Differences between women (W) and men (M) were generated using sample *t*-test with equal variance; *Data not available for women in Soweto. CIMT indicates carotid intima-media thickness; SSA, sub-Saharan Africa.

Table 2. Factors Associated With Common CIMT, Presented as Change in Common CIMT in μm Per Increase of the Risk Factors

	Model 1		Model 2		Model 3		Model 4	
Risk Factors	β-Coefficient (95% CI)	*P* Value	β-Coefficient (95% CI)	*P* Value	β-Coefficient (95% CI)	*P* Value	β-Coefficient (95% CI)	*P* Value
Age per y	6.66 (6.24, 7.07)	<0.001	6.79 (6.37, 7.21)	<0.001	6.80 (6.37, 7.23)	<0.001	6.77 (6.34, 7.19)*	<0.001*
Men vs women	4.89 (−0.31, 10.09)	0.065	10.67 (5.25, 16.08)	<0.001	10.62 (5.04, 16.20)	<0.001	10.32 (4.75, 15.90)*	<0.001*
Current vs never/previous smoking	−3.04 (−9.82, 3.73)	0.379	6.22 (−0.86, 13.29)	0.085	6.44 (−0.65, 13.53)	0.075	6.26 (−0.83, 13.35)	0.084
SBP per 10 mm Hg	8.26 (6.98, 9.53)	<0.001	7.59 (6.29, 8.89)	<0.001	7.62 (6.32, 8.92)	<0.001	7.52 (6.21, 8.83)*	<0.001*
Glucose per 1 mmol/L	1.51 (−0.13, 3.16)	0.072	1.01 (−0.60, 2.62)	0.219	0.98 (−0.63, 2.59)	0.232	0.94 (−0.67, 2.56)	0.252
HDL-C per 1 mmol/L	−16.93 (−22.57, −11.28)	<0.001	−11.83 (−17.55, −6.11)	<0.001	−11.99 (−17.73, −6.25)	<0.001	−12.15 (−17.88, −6.41)*	<0.001*
LDL-C per 1 mmol/L	7.85 (4.94, 10.77)	<0.001	5.04 (2.08, 7.99)	0.014	5.08 (2.10, 8.07)	0.001	5.08 (2.10, 8.06) *	0.001*
BMI per 10 kg/m^2	…	…	18.08 (12.99, 23.16)	<0.001	18.21 (13.05, 23.37)	<0.001	17.61 (12.46, 22.76)*	<0.001*
MVPA in mins/week	…	…	−5.68 (−12.46, 1.10)	0.101	−5.50 (−12.29, 1.29)	0.112	−5.58 (−12.37, 1.21)	0.107
Current vs Never/previous alcohol use	…	…	−13.47 (−19.05, −7.89)	<0.001	−13.46 (−19.06, −7.87)	<0.001	−13.51 (−19.11, −7.91)*	<0.001*
Education status								
No formal	…	…	…	…	Ref (value 0)	Ref	Ref	Ref
Primary	…	…	…	…	−4.19 (−11.46, 3.08)	0.589	−4.03 (−11.29, 3.24)	0.625
Secondary	…	…	…	…	−0.65 (−8.54, 7.24)		−7.77 (−8.66, 7.11)	
Tertiary	…	…	…	…	−3.33 (−18.12, 11.46)		−3.81 (−18.60, 10.98)	
Household SES								
Poorest	…	…	…	…	Ref	Ref	Ref	Ref
Poorer	…	…	…	…	−0.26 (−8.42, 7.90)	0.092	−0.11 (−8.27, 8.04)	0.096
Poor	…	…	…	…	−2.73 (−10.94, 5.49)		−2.77 (−10.98, 5.44)	
Less poor	…	…	…	…	−7.17 (−15.20, 0.86)		−7.18 (−15.20, 0.85)	
Least poor	…	…	…	…	1.92 (−6.15, 10.0)		1.78 (−6.29, 9.85)	
HIV+ vs HIV−	…	…	…	…	…	…	−8.86 (−15.70, −2.03)*	0.011*
Variance (R^2)	0.234	…	0.242	…	0. 243	…	0.244	…

Multivariable linear regression analyses of association between risk factors and CIMT. Model 1=age, sex, current smoking, SBP, fasting glucose, HDL-C, LDL-C and site; Model 2=model 1+BMI, alcohol use, physical activity; Model 3=model 2+education status, SES; and Model 4=model 3+HIV infection. ART indicates antiretroviral therapy; BMI, body mass index; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MVPA, moderate-to-vigorous physical activity; SBP, systolic blood pressure; SES, socioeconomic status.

*Factors that are associated with CIMT at a $P<0.05$.

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objectively assessed HIV status from the South African sites and Kenya only. In this model we observed an even stronger inverse association with CIMT (−15.3 [−24.2−−6.31]). We conducted a further sub-analysis on HIV participants who used ART and observed that ART was associated with lower CIMT levels (−70.1 [−165−−25.6] in Agincourt; −5.05 [−9.52−−1.29] in Dikgale and −48.6 [−82.9−−14.2] in Soweto). This model included only participants from South Africa, which was the only country in which ART use was assessed.

To determine the within site variation, we conducted a mixed-effect ML regression analyses. Presented in Table 3 is a comparison of multivariable linear (model 4) and mixed-effect ML regression analyses (model 5) and mixed-effect ML regression analyses including interaction terms (model 6). The likelihood ratio test (LR χ^2=498.02; P<0.001) indicated that the mixed–effect ML model (model 5) had a better fit than the multivariable linear regression model from Table 2 (model 4). In model 5, the association between classical cardiovascular risk factors and CIMT were similar to the multivariable linear regression model. However, HIV, although showing a similar direction of effect (−5.81 [−13.82–2.21]), the observed effect was no longer significant (P=0.156). Further to this, physical activity was associated with lower CIMT levels (−8.17 [−14.81−−1.53]; P=0.016). When interaction terms were introduced into this model (model 6), we noted that HIV did not interact with age (P=0.306), sex (P=0.252) or household SES (P=0.877). The likelihood ratio test (LR χ^2=47.88; P=0.318), showed a better fit for model 5 than for model 6.

In sex stratified analyses (Tables 4 and 5), the observed association of age, SBP, HDL-C, current alcohol consumption and HIV infection with CIMT was similar between men and women. In the pooled analysis (Table 2), the association between smoking and CIMT had a trend towards a positive association (6.26 μm [−0.83, 13.35]; P=0.084). However, in men only current smoking was positively associated with higher CIMT (10.7 μm [2.93, 18.53]). Also in men but not women, a unit elevation in LDL-C (mmol/L) was likely to present with a 6.05 μm [1.97, 10.13] higher CIMT, whilst higher household SES among men but not women was associated with a lower CIMT (P=0.042). We added multiplicative interaction terms to the final model to evaluate whether relations between risk factors and common CIMT differed by sites (Table S2). We observed some significant interactions between site and certain risk factors. We therefore conducted sub-analyses for each site stratified by sex. In these site stratified analyses (Tables 4 and 5), differential effects of some of the independent variables on CIMT were observed. Significant associations of plasma glucose levels with CIMT were observed in women in Nanoro (−7.90 [−13.8−−2.04]) and Dikgale (3.68 [0.75, 6.62]) but the effect was negative in the former and positive in the latter group. In women, BMI correlated significantly and negatively with CIMT in Navrongo (−28.7 [−52.9−−4.56]) but positively in Dikgale (17.8 [7.34–28.2]). Men with primary, secondary, and tertiary education in Soweto were likely to have higher CIMT than men with no formal education. Alcohol consumption was inversely associated with CIMT in men from Nanoro, Burkina Faso. Similarly, high HDL was associated with lower CIMT in women from Dikgale, South Africa and Nairobi, Kenya. The MVPA had similar inverse associations with CIMT in men from Navrongo and Burkina Faso (see Tables 4 and 5).

Discussion

The AWI-Gen study is the first large African study with harmonized data collection in 4 countries across 3 subcontinental African regions to report on the measurement of CIMT and its associated cardiometabolic risk factors. Our study shows both sex and regional differences in CIMT levels and risk factor associations. In pooled analyses, our findings show that the major factors that were consistently associated with higher CIMT were age, men, SBP, BMI, and LDL-C while a high HDL-C, current alcohol consumption, and HIV infection were associated with lower CIMT. In a sex-stratified analysis, smoking was associated with a higher CIMT in men.

The mean CIMT of the left CCA was higher than the right and this has been reported previously in an adult Pakistani population.[35] This could be because of the fact that the left CCA arises directly from the aortic arch and is therefore exposed to greater hemodynamic stress and intimal damage from the systolic pressure from the left ventricles. It may therefore be clinically relevant to use right CIMT for screening purposes. The mean CIMT of 0.64±0.003 mm in our study population was lower than 0.71±0.19 mm reported in adult populations from North America[36] and 0.71±0.12 mm in Europe.[37] The difference is likely explained by the relatively older ages of the North American and European cohorts (mean ages 60.2±8.7 and 58.8±7.6, respectively) compared with our population that had a mean age of 49.9±5.8 years. The observed CIMT in our population was, however, higher than reported in studies from India,[38] China,[39] Pakistan,[35] and South America[40,41] which had a similar age to our population. These observed variations in mean CIMT between white, Asian, and African populations support the notion that CIMT varies by ethnicity[4] and may therefore have a substantive genetic contribution, but it must also be noted that differences in sampling methods, sample size, ratio of men to women and CIMT measurement techniques across these studies may also play a part.

In the combined analysis, mean CIMT levels were similar for men and women. In Nanoro, Burkina Faso where women

Table 3. Comparison of Linear Regression Model and Mixed-Effect Multilevel Model Depicting the Association Between Risk Factors of CIMT in SSA

	Model 4		Model 5		Model 6	
Risk Factors	ß-Coefficients (95% CI)	*P* Value	ß-Coefficients (95% CI)	*P* Value	ß-Coefficients (95% CI)	*P* Value
Age in y	6.77 (6.34, 7.19)	<0.001	6.71 (6.29, 7.13)	<0.001	6.78 (6.34, 7.22)	<0.001
Men vs women	10.32 (4.75, 15.90)	<0.001	13.11 (7.54, 18.69)	<0.001	13.95 (8.22, 19.68)	<0.001
Current vs never/previous smoking	6.26 (−0.83, 13.35)	0.084	3.69 (−3.46, 10.85)	0.312	3.75 (−3.41, 10.91)	0.304
SBP per 10 mm Hg	7.52 (6.21, 8.83)	<0.001	7.78 (6.60, 8.95)	<0.001	7.77 (6.59, 8.94)	<0.001
Glucose per 1 mmol/L	0.94 (−0.67, 2.56)	0.252	0.79 (−0.62, 2.21)	0.269	0.82 (−0.59, 2.23)	0.256
HDL per 1 mmol/L	−12.15 (−17.88, −6.41)	<0.001	−12.71 (−18.42, −6.99)	<0.001	−12.77 (−18.49, −7.06)	<0.001
LDL per 1 mmol/L	5.08 (2.10, 8.06)	0.001	4.35 (1.42, 7.27)	0.004	4.34 (1.42, 7.27)	0.004
BMI per 10 kg/m^2	17.61 (12.46, 22.76)	<0.001	16.86 (12.09, 21.62)	<0.001	16.71 (11.94, 21.48)	<0.001
MVPA in mins/week	−5.58 (−12.37, 1.21)	0.107	−8.17 (−14.81, −1.53)	0.016	−8.06 (−14.70, −1.42)	0.017
Current vs Never/previous alcohol use	−13.51 (−19.11, −7.91)	<0.001	−13.95 (−19.49, −8.41)	<0.001	−13.92 (−19.46, −8.38)	<0.001
Education status						
No formal education	Ref (0)	Ref (0)	Ref (0)	Ref (0)	Ref (0)	Ref (0)
Primary	−4.03 (−11.29, 3.24)	0.625	−7.96 (−15.13, −0.79)	0.175	−8.17 (−15.33, −0.99)	0.156
Secondary	−7.77 (−8.66, 7.11)		−7.17 (−15.36, 1.02)		−7.42 (−15.61, 0.78)	
Tertiary	−3.81 (−18.60, 10.98)		−5.97 (−20.28, 8.33)		−6.27 (−20.57, 8.04)	
Household SES						
Poorest	Ref (0)	Ref (0)	Ref (0)	Ref (0)	Ref (0)	Ref (0)
Poorer	−0.11 (−8.27, 8.04)	0.096	−0.62 (−8.72, 7.48)	0.142	−0.81 (−9.42, 7.79)	0.090
Poor	−2.77 (−10.98, 5.44)		−2.93 (−11.11, 5.25)		−3.78 (−12.39, 4.82)	
Less poor	−7.18 (−15.20, 0.85)		−6.68 (−14.68, 1.32)		−7.84 (−16.2, 0.60)	
Least	1.78 (−6.29, 9.85)		1.83 (−6.25, 9.92)		1.74 (−6.71, 10.20)	
HIV+ vs HIV−	−8.86 (−15.70, −2.03)	0.011	−5.81 (−13.82, 2.21)	0.156	26.80 (−41.40, 95.01)	0.441
Interaction terms						
HIV×sex					−8.82 (−23.91, 6.27)	0.252
HIV×age					−0.69 (−2.01, 0.630)	0.306
HIV×SES						
Poorest vs poorer					2.25 (−23.27, 27.76)	0.877
Poorest vs poor					8.54 (−18.27, 35.34)	
Poorest vs less poor					10.88 (−14.53, 36.29)	
Poorest vs least poor					2.24 (−23.42, 27.89)	
Constant	215.8 (188.6, 242.9)	<0.001	174.4 (132.5, 216.3)	<0.001	171.6 (129.3, 214.0)	<0.001
Observations	8872		8872		8872	
Number of groups	…	…	6	…	6	…
Likelihood ratio (LR) test	…	…	Model 2 vs Model 1 LR χ^2=498.02	<0.001	Model 3 vs Model 2 LR χ^2=47.88	0.318

Model 1=Multivariable linear regression model; Model 2=Mixed effect ML regression analyses; Model 3=Mixed effect ML regression analyses+interaction terms (interactions term, HIV and sex=HIV×sex, HIV and age=HIV×age and HIV vs socioeconomic status=HIV×SES). ART indicates antiretroviral therapy; BMI, body mass index; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MVPA, moderate-to-vigorous physical activity; SBP, systolic blood pressure; SES, socioeconomic status.

and men had similar ages, men had higher CIMT than women, whereas despite being younger, women had higher CIMT than men in Nairobi, Kenya. In other studies where women were observed to have higher CIMT compared with men, the differences were observed in women over the age of 45 years.[42,43] However, when we adjusted for other risk

Table 4. Factors Associated With Common CIMT in Women, Presented as Change in Common CIMT in μm Per Increase of the Risk Factor and Stratified by Sites

	All	Nanoro, BF	Navrongo, GH	Agincourt, SA	Dikgale, SA	Soweto, SA	Nairobi, KE
Factors	β-Coefficient (95% CI)	β-Coefficient (95% CI)	β-Coefficient (95% CI)	β-Coefficient (95% CI)	β-Coefficient (95% CI)	-	β-Coefficient (95% CI)
Age, y	6.48 (5.85, 7.11)*	7.92 (6.72, 9.12)*	6.15 (4.83, 7.48)*	5.18 (3.48, 6.88)*	6.54 (4.86, 8.22)*	…	4.67 (3.37, 5.97)*
Smoking†	1.66 (−20.2, 23.6)	…	29.9 (−9.47, 69.2)	123 (81.5, 165)*	−6.31 (−47.2, 34.6)	…	−11.1 (−46.6, 24.5)
SBP	8.55 (6.67, 10.4)*	6.57 (2.43, 10.7)*	9.57 (6.19, 12.9)*	12.3 (3.84, 20.7)*	5.27 (1.59, 8.95)*	…	11.4 (7.81, 15.0)*
Glucose	1.87 (−0.27, 4.01)	−7.90 (−13.8, −2.04)*	2.16 (−6.92, 11.2)	1.53 (−4.89, 7.94)	3.68 (0.75, 6.62)*	…	1.69 (−1.96, 5.35)
HDL-C	−11.2 (−20.2, −2.19)*	−1.22 (−20.0, 17.6)	−11.9 (−34.9, 11.2)	−12.4 (−33.7, 8.98)	−18.1 (−46.6, 10.3)	…	−7.11 (−20.3, 6.04)
LDL-C	2.09 (−2.26, 6.44)	3.13 (−7.35, 13.6)	−2.18 (−13.4, 9.08)	10.0 (−1.92, 21.9)	−5.38 (−14.3, 3.56)	…	7.53 (−0.24, 15.3)
BMI	4.52 (−1.32, 10.4)	8.30 (−12.7, 29.3)	−28.7 (−52.9, −4.56)*	−0.09 (−9.32, 9.14)	17.8 (7.34, 28.2)*	…	1.99 (−9.25, 13.2)
MVPA	−3.26 (−13.3, 6.77)	−9.73 (−31.2, 11.7)	−6.92 (−26.0, 12.2)	−7.99 (−30.6, 14.6)	18.2 (−29.0, 65.3)	…	−13.3 (−31.9, 5.43)
Alcohol use†	−8.99 (−17.5, −0.50)*	−10.8 (−23.6, 2.05)	−1.69 (−17.2, 13.8)	−6.29 (−41.5, 28.9)	−22.1 (−43.9, −0.15)*	…	−26.9 (−53.5, −0.27)*
Education status							
No formal	Ref	Ref	Ref	Ref	Ref	…	Ref
Primary	−4.97 (−14.5, 4.60)	5.52 (−19.6, 30.7)	−4.78 (−24.3, 14.7)	−24.8 (−45.1, −4.58)*	−0.57 (−28.1, 26.9)	…	−18.8 (−37.6, −0.01)*
Secondary	4.21 (−7.01, 15.4)	8.74 (−52.8, 70.3)	−22.5 (−53.4, 8.46)	−10.7 (−34.1, 12.7)	−5.98 (−34.2, 22.2)	…	−8.76 (−30.1, 12.5)
Tertiary	1.09 (−29.7, 31.9)	−15.9 (−36.7, 4.81)	61.6 (−1.68, 124)	10.1 (−49.3, 69.6)	−31.4 (−73.5, 10.7)	…	−7.4 (−79.8, 64.9)
Household SES							
Poorest	Ref	Ref	Ref	Ref	Ref	…	Ref
Poorer	0.17 (−13.2, 11.3)	6.86 (−14.2, 27.9)	−10.6 (−35.6, 14.3)	3.01 (−27.7, 33.7)	0.87 (−23.5, 25.3)	…	1.67 (−19.9, 23.3)
Poor	−3.48 (−14.6, 7.63)	−3.07 (−23.2, 17.1)	−8.54 (−33.3, 16.2)	−16.6 (−48.4, 15.1)	−3.06 (−31.8, 25.6)	…	1.66 (−19.6, 22.9)
Less poor	−0.12 (−10.9, 10.7)	8.50 (−12.5, 29.5)	−9.16 (−32.7, 14.4)	2.14 (−28.3, 32.6)	12.9 (−13.7, 39.5)	…	−7.79 (−29.2, 13.6)
Least poor	5.64 (−5.63, 16.9)	6.03 (−13.9, 26.0)	7.27 (−18.5, 33.1)	−5.78 (−35.4, 23.9)	29.6 (2.44, 56.7)*	…	−2.82 (−27.2, 21.6)
HIV+‡	−9.07 (−18.9, 0.83)*	−30.4 (−85.0, 24.3)	−6.71 (−38.2, 24.8)	−16.2 (−31.3, 63.8)	−86.8 (−110, −63.6)*	…	−9.94 (−26.6, 6.69)
HIV+ART+‡	…	…	…	−8.13 (−47.0, 63.3)	−14.5 (−38.6, −8.78)*	…	…
Variance (R^2)	0.233	0.197	0.136	0.232	0.211	…	0.174

Multivariable linear regression analyses of factors associated with CIMT among women in the various sites. ART indicates antiretroviral therapy; BMI, body mass index; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MVPA, moderate-to-vigorous physical activity; SBP, systolic blood pressure; SES, socioeconomic status.

*Factors that are associated with CIMT at a $P<0.05$.

†Current vs previous or never.

‡HIV+ vs HIV negative.

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Table 5. Factors Associated With Common CIMT in Men, Presented as Change in Common CIMT in μm Per Increase of the Risk factor and Stratified by Sites

	All	Nanoro, BF	Navrongo, GH	Agincourt, SA	Dikgale, SA	Soweto, SA	Nairobi, KE
Factors	β-Coefficient (95% CI)	β-Coefficient (95% CI)	β-Coefficient (95% CI)	β-Coefficient (95% CI)	β-Coefficient (95% CI)	β-Coefficient (95% CI)	β-Coefficient (95% CI)
Age	7.08 (6.49, 7.68)*	8.50 (7.31, 9.69)*	7.63 (6.12, 9.14)*	6.11 (4.31, 7.91)*	6.91 (4.65, 9.17)*	7.01 (5.76, 8.26)*	4.82 (3.57, 6.08)*
Smoking†	10.7 (2.93, 18.5)*	14.2 (−5.78, 34.2)	−3.66 (−21.0, 13.9)	6.24 (−21.1, 33.6)	38.3 (2.61, 73.9)*	0.45 (−14.8, 15.7)	13.7 (−3.69, 31.0)
SBP	6.03 (4.23, 7.83)*	3.78 (−0.29, 7.83)*	4.69 (0.26, 9.11)*	5.47 (0.41, 10.5)*	6.07 (−0.44, 12.6)*	6.63 (2.96, 10.3)*	10.2 (6.35, 14.1)*
Glucose	−0.47 (−2.76, 1.82)	−2.84 (−6.75, 1.07)	−4.23 (−14.5, 6.00)	−2.95 (−7.43, 1.53)	4.01 (−6.48, 14.5)	0.04 (−4.21, 4.29)	−2.38 (−7.51, 2.74)
HDL-C	−11.9 (−19.6, −4.38)*	1.34 (−17.1, 19.8)	−23.8 (−46.5, −1.14)*	−9.19 (−29.3, 10.9)	−12.4 (−36.8, 12.1)	−16.0 (−29.6, −2.40)*	−9.21 (−25.8, 7.41)
LDL-C	6.05 (1.97, 10.1)*	9.10 (−0.36, 18.6)	9.86 (−2.98, 22.7)	12.0 (−0.53, 24.6)	−1.72 (−17.9, 14.5)	0.24 (−7.09, 7.57)	5.91 (−2.29, 14.1)
BMI	38.1 (28.9, 47.3)*	46.4 (22.7, 70.1)*	12.1 (−20.8, 44.9)	45.9 (19.6, 72.3)*	85.9 (39.2, 132)*	48.7 (34.1, 63.2)*	30.5 (11.2, 49.8)*
MVPA	−3.93 (−13.3, 5.45)	−19.2 (−35.9, −2.40)*	−11.5 (−40.1, 17.1)	−3.72 (−28.6, 21.2)	−7.65 (−77.5, 62.2)	6.83 (−9.18, 22.8)	−9.95 (−46.3, 26.4)
Alcohol use†	−14.9 (−22.5, −7.27)*	−36.9 (−52.9, −20.9)*	−12.4 (−31.2, 6.38)	5.48 (−20.1, 31.0)	−22.2 (−60.1, 15.7)	−14.7 (−30.4, −0.99)	−12.2 (−29.1, 4.69)
Education status							
No formal	Ref	Ref	Ref	Ref	Ref	Ref*	Ref
Primary	−4.21 (−15.1, 6.68)	−15.9 (−34.3, 2.37)	5.06 (−17.4, 27.5)	5.18 (−23.8, 34.2)	−20.2 (−66.2, 25.7)	72.3 (35.2, 109)*	−23.3 (−61.8, 15.1)
Secondary	−3.10 (−14.3, 8.11)	−31.7 (−59.6, −3.77)	−6.85 (−29.3, 15.6)	19.9 (−11.8, 51.5)	−14.3 (−57.7, 29.2)	47.4 (14.5, 80.3)*	−19.3 (−57.9, 19.4)
Tertiary	−7.74 (−25.7, 10.2)	2.92 (−37.5, 43.3)	−15.5 (−63.3, 32.3)	14.3 (−32.9, 61.6)	−51.1 (−117, 14.8)	43.7 (5.92, 81.5)*	1.73 (−86.5, 89.9)
Household SES							
Poorest	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Poorer	−2.11 (−14.1, 9.91)	18.1 (−4.85, 40.9)	−8.45 (−35.4, 18.5)	−26.0 (−58.2, 6.17)	−19.8 (−51.1, 11.5)	22.8 (−18.8, 64.4)	0.77 (−26.6, 28.2)
Poor	−3.43 (−15.6, 8.70)	5.67 (−18.3, 29.6)	−6.30 (−34.8, 22.2)	−42.9 (−75.9, −9.82)*	−24.8 (−63.1, 13.4)	23.8 (−9.47, 56.9)	7.85 (−18.2, 33.9)
Less poor	−15.3 (−27.1, −3.38)*	0.01 (−25.2, 25.2)	−10.9 (−38.3, 16.4)	−40.5 (−73.3, −7.64)*	−20.6 (−62.8, 21.6)	5.91 (−26.5, 38.3)	−17.5 (−43.7, 8.73)
Least poor	−4.52 (−16.27, 7.23)	7.88 (−16.4, 32.2)	1.49 (−26.4, 29.4)	−38.6 (−74.7, −2.39) *	−15.8 (−54.9, 23.3)	13.6 (−18.8, 46.0)	1.29 (−24.9, 27.5)
HIV+‡	−11.7 (−21.0, −2.37)*	−79.2 (−148, −9.37)*	−60.0 (−110, −9.98)*	−42.6 (−137, −31.7)*	−92.2 (−162, −22.0)*	−38.2 (−181, −10.5)*	−3.91 (−26.0, 18.2)
HIV+ART+‡	…	…	…	−161 (−214, −108)*	−69.3 (−86.9, −11.8)*	−49.5 (−83.1, −15.9)*	…
Variance (R^2)	0.279	0.223	0.144	0.238	0.287	0.269	0.157

Multivariable linear regression analyses of factors associated with CIMT among women in the various sites. ART indicates antiretroviral therapy; BMI, body mass index; CI, confidence interval; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MVPA, moderate-to-vigorous physical activity; SBP, systolic blood pressure; SES, socioeconomic status.

*Factors that are associated with CIMT at a $P<0.05$.

†Current vs previous or never.

‡HIV+ vs HIV negative.

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factors including age, men were more likely to present with higher CIMT compared with women. Differences in CIMT levels between men and women have been attributed to differences in exposure to CVD risk factors.[44] In addition, physiological factors, such as lumen diameter, have been suggested as explanations for sex differences, with women generally presenting with smaller blood vessels.[45]

The association between classical CVD risk factors and CIMT has been established in various populations, predominantly white and Asian[46–49] and only in a few studies, with small sample sizes, from African populations.[50,51] Classical CVD factors that have been observed to be associated with CIMT in the literature were similarly associated in the present study, and this provides some level of external validity to our data. Addition of other potential risk factors into a regression model that included these traditional CVD risk factors had a minimal effect on the variance in CIMT explained by the model. These risk factors included BMI, alcohol intake, and HIV, all of which did contribute significantly to the final model but slightly attenuated the association of the other risk factors with CIMT. Our findings are in agreement with the INTERHEART study that showed that, although the magnitude of the relations differed somewhat, established risk factors were associated with an increased risk of acute myocardial infarction across the world.[52] These findings therefore suggest that interventions aimed at reducing the classical risk factors will help prevent the development of atherosclerosis and reduce CVDs and associated mortality in SSA populations.

The association of SBP with high CIMT levels is of particular interest as this presents a worrying phenomenon since a previous AWI-Gen study demonstrated a high prevalence of hypertension across all sites with an associated low awareness and control of high blood pressure.[21] While we advocate for preventive measures that should be targeted to the local situation, early detection and management of hypertension may particularly benefit these SSA populations. Increased awareness, screening, early detection and subsequent management of CVD risk factors should be integrated into current public health systems in SSA.

We observed that current alcohol consumption was associated with lower CIMT and this is contrary to findings from the USE Intima-Media Thickness (USE-IMT) 8 cohorts collaboration conducted among North Americans and Europeans, which reported lower CIMT among participants who consumed little or no alcohol compared with those who consumed >10 g of alcohol daily.[53] A longitudinal study further clarified this by reporting that sustained heavy drinking in midlife was associated with higher CIMT.[54] The observed inverse association of alcohol consumption with CIMT has also been documented in a Korean study.[55] One possible explanation for this relationship comes from a randomized cross-over feeding trial among men which showed that alcohol improves lipid profiles and reduces atherosclerosis-related inflammatory markers in plasma. The phenolic content of alcoholic drinks, which is high in sorghum-based beers, which are consumed widely in the study settings, was found to reduce leukocyte adhesion molecules and inflammatory biomarkers.[56,57] Furthermore, the ARIC (Atherosclerosis Risk in Communities) study, using candidate gene analyses with a Mendelian Randomization methodology, demonstrated that low-to-moderate alcohol consumption improves serum lipid levels.[58] However, it should be noted that in the present study, the inverse association between alcohol intake and CIMT occurred independently of lipid levels. It is possible that the crude assessment of alcohol intake used in the current study may not be sensitive enough to allow more complex investigations of these relationships, and longitudinal studies using more objective measures of alcohol intake may be required.

In our population and according to the mixed-effect ML model, HIV infection showed a non-significant inverse association with lower CIMT after adjusting for age, education status, household SES, and the classical cardiovascular risk factors. This inverse association was shown to be significant in multivariable regression analyses. Both findings are contrary to studies from Brazil[59] and Uganda[60] reporting higher CIMT among HIV-positive compared with HIV-negative individuals. In line with these, a recent meta-analysis based on 17 cohort and case-control studies indicates a 2-fold higher risk ratio for cardiovascular diseases in people living with HIV in comparison with HIV-negative subjects. However, this meta-analysis included only 1 case-control study from Africa including 200 stroke cases and 398 controls.[61] The non-significant association observed in the current study is similar to findings from rural South Africa,[62] North America,[63] and Brazil.[39,40] As HIV was not assessed objectively across all sites, with the exception of the South African and Kenyan sites, we conducted (multivariable linear regression) sub-analyses on data from these sites to assess the effect of HIV on CIMT. These showed a negative association between HIV and CIMT. It is interesting to note that a recent study conducted in rural South Africa among 5059 participants aged ≥40 years has shown that HIV-positive subjects had a lower prevalence of classical CVD risk factors when compared with HIV-negative subjects, in both men and women.[64] This has further been corroborated by more recent studies from South Africa, which demonstrated lower prevalence levels of hypertension and diabetes mellitus among HIV-infected subjects.[65,66] Considerably increased access to ART in SSA in the past decade, particularly so in South Africa, which has the largest ART roll-out program in the world,[67] and application of treatment guidelines to screen people living with HIV for CVD risk,[32,68] may have prompted diagnosis and consequent treatment of identified CVD risk factors, or changes in

lifestyle, in these subjects. These findings may well be indicative of an emerging paradigm reflecting an improved HIV care cascade.

Further to this, studies have reported that the effects of HIV on CIMT are more pronounced in younger than older population because of active viral replication and immune activation and a greater level of high-CVD risk behaviours.[69] Thus, potentially long-term use of ART as noted in our older population may result in chronic viral suppression leading to lower inflammation and reduced CIMT among HIV participants. However, it is possible that the negative association between HIV infection and CIMT observed in our study may be explained by other factors and thus, be attributed to residual confounding. Furthermore, misclassification of HIV status, particularly at sites that did not offer formal HIV testing could be possible, however, the low prevalence of HIV infection observed at such sites is supported by data from the literature.[29,30] It should also be noted that the level of ART coverage varied across the sites ranging from 44.6% in Soweto to 96.4% in Agincourt. Although data on ART regimens were not collected, treatment guidelines in Kenya[68] and South Africa[32] at the time of this study were similar with first line therapies consisting of tenofovir+lamivudine (3TC)+efavirenz/nevirapine and zidovudine (AZT)+lamivudine (3TC)+nevirapine/efavirenz. Despite the heterogeneity across the sites, the negative relationship between HIV infection and CIMT was observed at all study sites in both men and women, suggesting that this is a robust association. The paucity of data on the role of HIV and atherosclerotic CVDs in Africa therefore requires further studies with a wide range of HIV-defining markers, such as viral load, and a larger sample size of subjects with confirmed HIV and ART status.

Several variables demonstrated differential association with CIMT across the sites. Possible reasons for this may include differences across sites in: genetic variance, distribution of the particular effector variables and level of influence of modifying variables. These differential site-specific effects are important to understand but are beyond the scope of the current study and require in depth analysis at individual sites using larger sample sizes and a broader array of input variables.

Limitations to our study include a lack of information on the duration of HIV infection, the ART regimens in use and the duration of therapy, and the absence of measurements of viral load and CD4 counts, all of which may play a role in explaining the association between HIV infection and CIMT. Furthermore HIV status determined in the Agincourt site may have potentially resulted in measurement bias as participants' status may have changed from the time of initial HIV diagnosis to the time of actual recruitment for the AWI-Gen study. The main strength of our study relates to the fact that this is the first large scale study to determine CIMT levels and their association with cardiovascular risk factors in 3 subcontinental blocks in Africa. Measurements of most variables and CIMT were harmonised across all sites minimising variability and making pooled analysis and cross-site comparisons feasible. We were also able to cover the geographical and social variability across these regional blocks by recruiting in both rural and urban sites thus providing representation of the different stages of the epidemiological transition within Africa.

Conclusions

To our knowledge, this is the first large scale study from SSA to report on the levels of, and factors associated with, CIMT. We observed that the main drivers for higher CIMT were the same CVD risk factors associated with CIMT in white and Asian populations. Given the rising prevalence of these CVD risk factors in SSA, atherosclerotic diseases may become a major pan-African epidemic unless preventive measures are taken particularly targeted at prevention of hypertension and reduction in obesity. In addition, differential effects of certain factors on CIMT were observed across the SSA sites. We advocate for HIV-specific studies to fully understand the true association between HIV and CIMT in SSA.

Appendix

H3Africa AWI-Gen Consortium Members

Conception and design of the original AWI-Gen study: Michèle Ramsay (SBIMB, Wits), Osman Sankoh (INDEPTH), Alisha Wade, Stephen Tollman and Kathleen Kahn (Agincourt), Marianne Alberts (Dikgale), Catherine Kyobutungi (Nairobi), Halidou Tinto (Nanoro), Abraham Oduro (Navrongo), Shane Norris (Soweto), and Scott Hazelhurst, Nigel Crowther, Himla Soodyall and Zane Lombard (Wits).

Site specific Investigators: Agincourt, South Africa (Frances Xavier Gómez-Olivé Casas and Ryan Wagner), Dikgale, South Africa (Felistas Mashinya, Ian Cook and Sam Ntuli), Nairobi, Keny (Christopher Khayeka-Wandabwa, Tilahun Nigatu Haregu, Shukri F. Mohammed and Stella Muthuri), Nanoro, Burkina Faso (Palwende R. Boua, Herman Sorgho, Seydou Nakanabo-Diallo, Toussaint Rouamba), Navrongo, Ghana (Godfred Agongo, Cornelius Debpuur, Engelbert A. Nonterah, Eric Fato and Immaculate Anati and Lucas Amega-Etego), Soweto, South Africa (Nomses Baloyi, Juliana Kagura, Richard Munthali and Yusuf Guman) and Wits AWI-Gen Collaborative Centre at SBIMB (Cassandra C. Soo, Freedom Mukomana, Stuart A. Ali, Ananyo Choudhury).

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Author Contributions

Conception of paper (Nonterah, Klipstein-Grobusch, Bots and Crowther), data analysis (Nonterah), writing of original manuscript (Nonterah, PRB, Klipstein-Grobusch, Bots and Crowther), critical review and approval of the manuscript (all authors).

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Univariable estimates for exposure variables and CIMT in the final combined model.

Risk factors	β-coefficient [95%CI]	P-value
Age (years)	7.91 [7.49,8.33]	<0.001
Men vs women	0.99 [-4.12,6.11]	0.704
Current vs Never/previous smoking	-11.93 [-18.45,-5.46]	<0.001
SBP per 10 mmHg	10.49 [9.22,11.75]	<0.001
Glucose per 1mmol/l	0.50 [-1.17,2.18]	0.556
HDL-C per 1mmol/l	-20.24 [-26.34,-14.15]	<0.001
LDL-C per 1mmol/l	-4.04 [-7.05,-1.04]	0.008
BMI per 10 kg/m^2	-2.30 [-6.40,1.79]	0.271
MVPA in mins/week	-17.85 [-25.42,-10.270	<0.001
Current vs Never/previous alcohol use	15.03 [9.91,20.15]	<0.001
Educational status		
No formal education	Ref	
Primary	-49.29 [-55.52,-43.03]	<0.001
Secondary	-58.97 [-64.99,-52.96]	
Tertiary	-49.92 [-64.52,-35.33]	
Household SES		
Poorest	Ref	
Poorer	-8.37 [-17.37,0.63]	0.052
Poor	-8.93 [-17.94,0.08]	
Less poor	-11.11 [-19.93,-2.29]	
Least poor	-2.63 [-11.26,6.00]	
HIV+ vs HIV-	-57.31 [-63.95,-50.68]	<0.001

CI=confidence interval; SES= socio-economic status; MVPA=moderate-to-vigorous physical activity; SBP=systolic blood pressure; BMI=body mass index; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol.

Table S2. Multiplicative interaction terms between sex and site with the risk factors.

Site and risk factor interaction terms	p-value
Site with Age	<0.001
Site with Sex	<0.001
Site with Current smoking	0.844
Site with Systolic blood pressure	0.043
Site with Glucose	0.079
Site with HDL-C	0.619
Site with LDL-C	0.078
Site with BMI	<0.001
Site with MVPA	0.299
Site with Current alcohol	0.281
Site with Educational status	0.003
Site with Household SES	0.108
Site with HIV status	0.113

SES=socio-economic status; MVPA=moderate-to-vigorous physical activity; BMI=body mass index; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol