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Cardiometabolic disease risk factors in pre- and postmenopausal women from four sub-Saharan African countries: A cross-sectional study

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Appendix A. Supplementary data

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Declaration of competing interest

The authors declare that they have no competing interest.

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Abstract

Objective: To compare the risk factors for cardiometabolic disease between pre- and postmenopausal women from four sub-Saharan African countries.

Study design: This cross-sectional study included 3609 women (1740 premenopausal and 1869 postmenopausal) from sites in Ghana (Navrongo), Burkina Faso (Nanoro), Kenya (Nairobi), and South Africa (Soweto and Dikgale). Demographic, anthropometric and cardiometabolic variables were compared between pre- and postmenopausal women, within and across sites using multivariable regression analyses. The sites represent populations at different stages of the health transition, with those in Ghana and Burkina Faso being rural, whilst those in Kenya and South Africa are more urbanised.

Main outcome measures: Anthropometric and cardiometabolic variables.

Results: The prevalence rates of risk factors for cardiometabolic disease were higher in South (Soweto and Dikgale) and East (Nairobi) Africa than in West Africa (Nanoro and Navrongo), irrespective of menopausal status. Regression models in combined West African populations demonstrated that postmenopausal women had a larger waist circumference ($\beta = 1.28$ (95 % CI: 0.58; 1.98) cm), log subcutaneous fat ($\beta = 0.15$ (0.10; 0.19)) diastolic ($\beta = 3.04$ (1.47; 4.62) mm Hg) and log systolic ($\beta = 0.04$ (0.02; 0.06)) blood pressure, log carotid intima media thickness ($\beta = 0.03$ (0.01; 0.06)), low-density lipoprotein cholesterol ($\beta = 0.14$ (0.04; 0.23) mmol/L) and log triglyceride ($\beta = 0.10$ (0.04; 0.16)) levels than premenopausal women. No such differences were observed in the South and East African women.

Conclusions: Menopause-related differences in risk factors for cardiometabolic disease were prominent in West but not East or South African study sites. These novel findings should inform cardiometabolic disease prevention strategies in midlife women specific to rural and urban and peri-urban locations in sub-Saharan Africa.

Keywords

Pre-menopause; Postmenopause; Cardiometabolic disease risk; Sub-Saharan Africa; AWI-Gen

1. Introduction

Sub-Saharan Africa (SSA) is experiencing a health transition [1] characterised by an increased life expectancy that is associated with a growing population of peri- and postmenopausal women [2]. This parallels a rising prevalence of cardiometabolic diseases (CMDs), including obesity [3,4], hypertension [4], and diabetes mellitus [5] within the SSA region.

Data from a number of studies have demonstrated anthropometric and cardiometabolic differences between pre- and postmenopausal women, with CMD risk increasing on the approach of menopause [6–8]. The menopause transition is associated with shifts in body fat distribution, particularly increased deposits of abdominal fat, independent of body mass index (BMI) [6]. Although the association of CMD risk factors with menopause stage has been studied in detail in high income countries, only a small number of such studies have been conducted in SSA. These include cross-sectional investigations in pre- and postmenopausal women from South Africa [9,10], Ghana [11], and the Democratic Republic of Congo (DRC) [12]. These studies included premenopausal women with a wide age range (from 20 years onwards) [10,11] and modest sample sizes: 590 (South Africa) [9], 206 (South Africa) [10], 250 (Ghana) [11], and 200 (DRC) [12].

Therefore, the aim of the current study was to measure and compare CMD risk factors between pre- and postmenopausal women from four SSA countries i.e., Ghana, Burkina Faso, Kenya, and South Africa. Study participants were from the Africa-Wits International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) Partnership for Genomic studies (AWI-Gen) [13] which allowed us to perform the first pan-SSA analyses of the relationship between menopause stage and CMD risk factors. Furthermore, the populations within AWI-Gen arose from different demographic strata varying from rural subsistence farmers to more urbanised communities and therefore included SSA populations at different stages of the health transition [14]. This allowed us to determine if any differences observed in CMD risk factors between pre- and postmenopausal women were similar across SSA populations with varying health and demographic profiles. Our hypothesis was that the same biological processes in all populations drive the increase in CMD risk that is observed during the menopause transition and therefore the prevalence of CMD risk factors would be higher in post- than premenopausal women at all the study sites irrespective of differences in sociodemographic factors.

2. Methods

2.1. Study design and setting

This cross-sectional population-based study on midlife women is a sub-study of the AWI-Gen study [13] from five different sites across four African countries namely: South Africa (Dikgale and Soweto), East Africa (Nairobi, Kenya) and West Africa (Nanoro, Burkina Faso, and Navrongo, Ghana) (Fig. 1). These sites included a mixture of urban (Soweto and Nairobi), peri urban (Dikgale) and rural (Nanoro and Navrongo) environments. In the main study, recruitment was performed using random sampling in the general population of women aged 40–60 years at each of the study centres [13]. The recruitment target for each site was at least 1000 women, thus 5184 women were recruited for this study.

Using a questionnaire, data on demography, behaviour, and health history were collected from all study participants. Menopause was staged by asking each woman about her menstrual bleeding patterns. The premenopausal group was then defined as women with regular menstrual cycles, the perimenopausal group was those having irregular menstrual cycles within the past 12 months, whilst the postmenopausal group was those who had had amenorrhea for twelve consecutive months or more. A total of 1575 women had

unknown menopausal stage, were perimenopausal, on hormonal therapy or were <40 and >60 years of age and were excluded resulting in 3609 women being included in the final analyses. Perimenopausal women were excluded to effectively separate individuals who had experienced the menopause transition and those that had not.

The recruitment process and collection of anthropometric measurements by trained staff has been detailed previously [14]. Waist, and hip circumference measurements were taken using a tape measure (SECA, Hamburg, Germany). Height was measured using a Harpenden digital stadiometer (Holtain, Wales) fixed to a wall. Weight was measured using digital Physician Large Dial 200 kg capacity scales (Kendon Medical, South Africa) whilst abdominal subcutaneous (SAT), visceral fat (VAT) and carotid intima media thickness (cIMT) of both the right and left layers of the common carotid arteries were measured using a LOGIQ e ultrasound system (GE Healthcare, CT, USA). All ultrasound readings were taken by trained field workers and to validate the measurement of SAT, VAT and cIMT, each of them was asked to perform repeated measurements on 15 volunteers. The coefficient of variation between and within trainees was <2 %. Self-reported information on age, physical activity, socioeconomic status, dietary intake, alcohol intake, and smoking were also obtained. Moderate-vigorous intensity physical activity (MVPA) was assessed in minutes per week using the Global Physical Activity Questionnaire (GPAQ) [15]. The MVPA was calculated from the accumulation of occupation, travel-related and leisure time physical activity. Socio-economic status was estimated from household assets and categorised into either of the five quintiles namely, “poorest”, “poorer”, “poor”, “less poor” and “least poor”. Dietary intake focused on questions regarding consumption of fruits and vegetables, bread, soft drinks (i.e., sugar-sweetened beverages) and fruit juices. Participants were requested to provide the number of days per week in which each of these items were consumed. Smoking and alcohol intake were defined by three categories: “never”, “current”, and “former”.

Systolic blood pressure and diastolic blood pressure were measured using a digital sphygmomanometer (Omron M6, Omron, Kyoto, Japan). Three readings were taken within two-minute intervals and the last two readings averaged for the final blood pressure level. Measurements of serum triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C), fasting glucose and creatinine levels were performed on the Randox Plus clinical chemistry analyser (Randox Laboratories Limited, Dublin, UK) through colorimetric methods. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation [16]. For the assessment of kidney function, estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation without the African American ethnicity correction formula [17].

Body mass index (BMI) was calculated from weight in kg/height in m². The homeostatic model assessment insulin resistance index (HOMA-IR) was calculated using the formula fasting insulin (μIU/L) × fasting glucose (mmol/L) / 22.5 [18]. Diabetes mellitus was defined as a fasting plasma glucose ≥ 7.0 mmol/L [19], and/or use of anti-diabetic agents and/or previous diagnosis by a health care professional. Obesity was defined as BMI ≥ 30 kg/m² [20], hypertriglyceridemia as triglycerides ≥ 1.69 mmol/L [21], and

hypercholesterolaemia as cholesterol ≥ 5.18 mmol/L and/or treatment with anti-lipid agents [21]. Insufficient physical activity was defined as MVPA <150 min/week [22], and hypertension as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and/or use of anti-hypertensive agents and/or previous diagnosis by a healthcare professional [23].

2.2. Statistical analyses

All statistical analyses were performed using Stata version 16.1 (StataCorp LP, College Station, TX, USA). Continuous variables were presented as means \pm standard deviations (SD) or medians and interquartile ranges (IQR) for data with normal or skewed distribution, respectively, and as proportions (%) for categorical variables. Non-parametric continuous dependent variables were log transformed to normality before being analysed using multivariable linear regression analysis. Categorical variables were compared across groups using the chi-squared test. Continuous variables were compared between two groups (e.g., pre- vs postmenopausal) or more (e.g., between study sites) using the appropriate parametric (Student's *t*-test or one-way ANOVA) or non-parametric (Mann–Whitney *U* test or Kruskal–Wallis) statistical tests. The level of significance of all statistical analyses was set at $p < 0.05$.

Multivariable linear regression was used to compare the relationship of CMD risk factors, namely systolic and diastolic blood pressure, BMI, waist and hip circumference, VAT and SAT, triglycerides, LDL-C, HDL-C, blood glucose, HOMA-IR and average cIMT (dependent variables) with menopausal stage (independent variable; post- compared to premenopausal group). Additional independent variables were chosen based on scientific plausibility (Supplemental Table 1). In the univariate (unadjusted) models, each CMD risk factor was regressed against menopause stage. In the adjusted model, age, and other independent variables (Supplemental Table 1) were incorporated into a multivariable model. Multivariable linear regression analyses were performed for each individual study site and for the sites combined, against each CMD risk factor. In addition, we performed a sub-analysis on participants who were not receiving therapy by removing participants who reported use of anti-hypertensive medication or therapies for the treatment of diabetes.

Unstandardised β coefficients (with 95 % CIs) were used in all the regression models. In cases where the dependent variable was log-transformed to obtain a normal distribution, the unstandardised β coefficient represents the fractional increase in the dependent variable for every 1 unit increase in the independent variable. Thus, a β coefficient of 0.10 signifies a 10 % increase. Collinearity of variables within each regression model was assessed using the variance inflation factor (VIF): all regression models included independent variables with $VIF < 3$. Assumptions of constant variance for the residuals from each regression model were checked by the Breusch-Pagan/Cook-Weisberg test and correction for unequal co-variances was accomplished using robust standard errors.

3. Results

3.1. Participant characteristics

A total of 3609 women (1740 premenopausal and 1869 postmenopausal) were recruited across the five study sites (Fig. 1). The number of study participants and variables collected are shown in Supplemental Table 2. Table 1 and Fig. 2 show that the women at the West African sites had a more favourable cardiometabolic profile, whilst those from South Africa had the worst. Thus, Table 1 shows the prevalence of behavioural CMD risk factors and of CMDs across all five study sites for all women (i.e., pre-, and postmenopausal combined). Smoking was rare at all sites, whilst alcohol intake was highest at the two West African sites. Insufficient physical activity varied across sites being more prevalent in Soweto. Obesity, hypertension, diabetes, and dyslipidaemia had the lowest prevalence at the two West African sites and the highest prevalence at one or both South African sites (except for diabetes). Table 1 shows that study participants from West and East Africa consumed more vegetables than those from South Africa. In addition, South and East African women consumed more fruits, soft drinks, and bread than their counterparts in West Africa. However, data on alcohol and dietary intake, and cIMT measurements were missing in Soweto (Table 1).

In Fig. 2, selected CMD risk factors are expressed as continuous variables and presented for all women per study region i.e., West Africa (Navrongo with Nanoro), East Africa (Nairobi) and South Africa (Dikgale with Soweto). Again, these data highlight the tendency for these risk factors to be lowest in the West African region. Similar patterns were observed for the other CMD risk factors i.e., waist circumference, VAT, SAT, and HDL-C (data not shown). When systolic and diastolic blood pressure, BMI, waist circumference, LDL-C, and triglycerides were stratified by menopausal stage (Supplemental Table 3), the same patterns shown in Fig. 2 were observed in both menopausal groups across the three regions.

3.2. Comparison of anthropometry and CMD risk factors across menopause groups

When data were combined from all sites and stratified by menopause stage, all anthropometric measures except BMI were higher in post- than in premenopausal women (Table 2).

Anthropometric and cardiometabolic risk factors were then compared between menopause groups at the individual sites (Supplemental Tables 4–8). The differences observed in the combined analyses were the same at each of the individual sites except for height, weight, BMI, VAT, SAT, and hip circumference which were lower in the postmenopausal groups at one or more study sites. The BMI was lower in postmenopausal women in the West African sites, Nanoro and Navrongo, compared to their premenopausal counterparts, but was not different between the menopausal groups at any of the other sites. Compared to premenopausal women, postmenopausal women in Dikgale and Nairobi had lower SAT, in Nanoro and Nairobi had lower VAT, and in Dikgale, Nanoro and Navrongo had lower hip circumference.

The cardiometabolic variables (cIMT, blood pressure, lipids, glucose, and HOMA-IR) were higher in post- vs premenopausal women when data from all sites were combined (Table

2) and at individual sites (Supplemental Tables 4–8). The only exceptions were HOMA-IR, which was only higher in post- vs. premenopausal women in Nairobi (Supplemental Table 8), HDL-C levels which were only higher in Dikgale, Nanoro and Nairobi (Supplemental Tables 5, 6 and 8) and glucose levels which were only higher in the postmenopausal group in Dikgale, Soweto and Nairobi (Supplemental Tables 4, 5 and 8).

3.3. Multivariable linear regression analyses

Due to differences between sites in the levels of CMD risk factors (Table 1), univariate and multivariable linear regression models were performed for each risk factor at each site. In the univariate models (Table 3), each CMD variable was regressed against menopause stage alone (the unadjusted model), whilst in adjusted models age and other independent variables were selected depending on the identity of the dependent variable (Supplemental Table 1). Only significant models are presented in Table 3. Supplemental Table 9 includes all the multivariable regression models for all CMD risk factors at each site. These results clearly show that nearly all the associations between the different CMD risk factors and menopausal stage were observed in the West African sites, Nanoro and Navrongo. Thus, at either one or both sites postmenopausal stage was positively associated with waist circumference, SAT, diastolic and systolic blood pressure, LDL-C, triglycerides, glucose and cIMT, whilst postmenopausal stage was inversely associated with BMI at both Nanoro and Navrongo. In addition to the West African sites, postmenopausal stage was associated with elevated triglycerides in Dikgale and inversely associated with systolic blood pressure in Nairobi.

The data in Table 3 demonstrates that associations between menopause stage and CMD risks factors are observed predominantly at the individual West African sites. We therefore ran multivariable regression models for each CMD risk factor in which the two West African sites were combined, and we also combined the East and South African sites. We hoped that these combinations would reveal new significant associations that could not be observed at the individual sites (as shown in Table 3) due to a lack of power. There was only one East African site i.e., Nairobi, and therefore it was decided to combine it with the South African sites. These three sites also share some similarities particularly the high prevalence of CMDs (Table 1) and as shown in Table 3, very few associations of menopausal stage with CMD risk factors. In addition, we combined all five sites to enhance the ability to identify associations that may not have been observable in the lower-powered regional models; the results are shown in Table 4. The adjusted regression models for waist circumference, BMI, SAT, systolic and diastolic blood pressure, glucose, cIMT, LDL-C and triglycerides demonstrate associations with menopause stage in West Africa but not in combined sites from East and South Africa. In the models for LDL-C, associations were observed with menopause stage in both the regional models, but the association was stronger for West Africa. The models for HOMA-IR demonstrated an association with menopause stage only when all five study sites were combined, whilst for hip circumference, VAT and HDL-C no associations were observed in any of the models.

To determine the effect of anti-hypertensive and diabetic medication on the observed associations we removed all participants who reported use of these therapies from the regression models and the above associations between menopausal groups and CMD risk

factors were not altered. The number of participants taking lipid-lowering medication was very low ($n = 20$) and therefore associated adjustments to the regression models were not warranted.

4. Discussion

This study demonstrates that the CMD risk factor profile of midlife African women is more favourable for those women from West Africa compared to those from South and East Africa, irrespective of menopausal stage. When comparing CMD risk factors between menopausal groups, many of these risk factors are higher in postmenopausal West African women compared to their premenopausal counterparts, with differences observed less frequently in the East and South African study populations.

In the current study, the staging of menopause was determined by asking participants about their menstrual bleeding patterns. The use of self-reported bleeding patterns is considered to be the most appropriate technique for the staging of menopause [24,25] and is universally used. A study conducted in Soweto, South Africa confirmed the accuracy of the staging in an African population using both estradiol and follicular stimulating hormone (FSH) serum level trends as supportive criteria across menopause stages determined from self-reported bleeding patterns [9,26].

The lower level of CMD risk factors in the West African women may be due to differences in environmental and/or lifestyle related factors [13,14]. Thus, both West African populations were predominantly subsistence farmers whereas the East and South African sites were more urbanised [14]. In addition, the West African study participants had a lower dietary intake of bread, soft drinks and fruit than observed at the other study sites and obesity was far less prevalent in the West African population.

The current analyses demonstrate that differences in CMD variables between pre- and postmenopausal women were observed more frequently at the West African than the East or South African sites. No other studies have been conducted in SSA comparing CMD risk factors across menopausal groups within different countries. The few studies that have been undertaken were restricted to individual countries. Thus, a study in women of mixed ancestry from South Africa demonstrated higher levels of CMD risk factors in post-compared to premenopausal women; however, the premenopausal group varied in age from 20 to 49 years (median age of 39) and no adjustment for age was made when comparing variables between the menopausal groups [10]. A second study from South Africa [9], which included data from participants who were part of the Soweto cohort in the current study, observed no differences in anthropometric and body composition variables between pre- and postmenopausal women after adjusting for confounders. A study from Ghana (West Africa) [11] demonstrated that metabolic syndrome was more prevalent in post- than premenopausal women, but the premenopausal group varied in age from 20 years and upwards (mean age, 34.5 years) and age was shown to be a major determinant of metabolic syndrome. A similar study from the DRC (Central Africa) [12] demonstrated a higher prevalence of metabolic syndrome in post-compared to premenopausal women, which was maintained after adjustment for age.

A major characteristic of the West African sites are much lower levels of CMD risk factors, particularly the lower prevalence of obesity (1.5–5.4 %) in comparison to East (32.0 %) and South Africa (51.3–66.2 %). This may be significant because Tufano et al. showed that cholesterol levels were higher in lean women post menopause compared to lean premenopausal women, but these differences were not observed between obese pre- and postmenopausal groups [27]. The authors suggested that in the obese women, body fat was a more important determinant of CMD risk than menopausal stage. It should be noted however, that the sample size in this study was low ($n = 92$). In addition, a large cross-sectional study in rural China reported associations between postmenopausal stage and elevated glucose, blood pressure, triglycerides, and abdominal obesity amongst women with mean BMI 24.9–25.2 kg/m² [28]. Furthermore, cross-sectional studies from Indian populations with mean BMI ≥ 25 kg/m² demonstrated that postmenopausal stage was positively associated with waist circumference [29] and mean arterial pressure [30]. The data from these studies therefore suggest that differences in CMD risk factors between pre- and postmenopausal women may be greater in lean than obese women. It must be noted that several studies have demonstrated increased levels of metabolic syndrome and its individual components in post- compared to premenopausal women [31]; however, none of these studies have examined these differences within study sub-groups based on BMI or other anthropometric measures.

Another difference between the West and the East and South African populations is that those in West Africa are residing in a more rural location. This may explain the lower prevalence of obesity in the West African sites, but it is also possible that rural residence could influence the relationship between menopausal stage and CMD risk factors independent of its association with lower BMI. Thus, the studies described above that showed an increase in CMD risk factors in post- compared to premenopausal women in populations with low BMI were all conducted at rural sites [28–30]. However, a study conducted in a large rural population ($N = 4743$) in China demonstrated a higher prevalence of CMD risk factors in post- than premenopausal women, but with a prevalence of obesity at close to 22 %, which is far higher than that observed in the West African populations [32]. In addition, a study from Poland comparing rural to urban postmenopausal women, demonstrated a higher prevalence of metabolic syndrome in the rural (70 %) than the urban group (22 %) [33]. Furthermore, two recent studies from Mexico [34] and China [35] have demonstrated that age at menopause is lower in rural than urban women. Earlier age at menopause is known to be associated with a higher risk of cardiovascular disease [36]. The study from China also showed that rural women had a higher prevalence of menopausal symptoms and that these were associated with a higher risk of non-communicable diseases [35]. These studies suggest that rural residence may be associated with a higher risk of CMDs in postmenopausal women, but longitudinal studies are required to determine whether the menopause transition is differentially associated with CMD risk in rural and urban populations.

The reason why lower BMI or a rural environment may be associated with greater differences in CMD risk factors between pre- and postmenopausal women is not known. However, regarding low BMI, it is possible that this may be related to the hormonal changes that occur during menopause. It is well known that estrogen levels (specifically estradiol)

decline during the menopause transition [37]. As estradiol (E₂) levels fall, circulating C₁₉ steroids i.e., testosterone, androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) become the major substrate for E₂ biosynthesis in extra-gonadal tissues [38]. Studies have shown that the expression of the enzyme aromatase, which is responsible for the production of E₂ in adipose tissue, increases with age and BMI [38]. Therefore, it is possible that the lower BMI in West African women could be associated with lower postmenopausal E₂ levels when compared to the women from East and South Africa, who have much higher levels of obesity. The lower postmenopausal E₂ levels in the West African females may then lead to enhanced CMD risk, as studies have shown that the fall in the serum concentrations of estrogens across the menopause transition is associated with higher levels of CMD risk factors [38].

In West Africa, although postmenopausal women have a higher prevalence of CMD risk factors than their premenopausal counterparts, CMD risk factor levels are still lower than those of both pre- and postmenopausal women in East or South Africa. Thus, in these latter two regions emphasis must be placed on prevention of obesity and related comorbidities in both pre- and postmenopausal women. In West Africa, our data demonstrate that the menopause transition is a critical window for the attenuation of CMD risk, and therefore the potential benefits of menopausal hormone therapy (MHT) become apparent. Data from previous studies suggest that when prescribed in healthy women early in menopause, MHT may help decrease the risk of CMD [7]. Unfortunately, data on the use of hormone therapy in sub-Saharan African women and its relation to CMD risk factors are absent.

4.1. Strengths and limitations

The main limitations of this study are its cross-sectional design, limited dietary data, lack of data on sex hormone levels and the fact that populations at the study sites may not be representative of the national population. The time available for collecting data by interviews was restricted and therefore an in-depth analysis of dietary intake using a food frequency questionnaire was not feasible. Therefore, we focused on some key dietary constituents such as fruit and vegetables and high carbohydrate-containing foods and drinks that have been associated with obesity and cardiometabolic diseases i.e., sugar sweetened soft- drinks, fruit juices and bread. Although regional differences were noted in consumption of these dietary items, their inclusion in the regression models did not modify any of the observed associations. A further limitation of this study was that food and alcohol intake were not recorded at the Soweto site and cIMT data were also not available.

Despite the shortcomings of a cross-sectional design, comparable findings to those observed in the West African populations were found in longitudinal studies where the menopausal transition was associated with increased levels of total cholesterol and LDL-cholesterol [39,40], and increased waist circumference [40]. One of the largest longitudinal studies of the health consequences of the menopause transition, SWAN, also demonstrated similar findings to those observed in the West African population with regards lipid levels, body fat distribution and cIMT whereas menopausal increases in blood pressure, glucose and insulin levels were found to be related to chronological aging [40]. The data from longitudinal studies therefore demonstrate that the menopause transition is associated with the worsening

of cardiometabolic health, which suggests that the data from the South and East African sites are not representative of the current literature and warrant further investigation.

The strengths of the study are the large sample size, the use of multiple sites representing different stages of the health transition across SSA and the measurement of a wide array of appropriate anthropometric, metabolic, demographic, and behavioural data. Furthermore, standardised methodologies were implemented across the study sites and all blood analytes were measured at a central laboratory.

5. Conclusions

The current study shows that the difference in the levels of CMD risk factors between pre- and postmenopausal women varied across geographical regions within SSA. In the more rural West African populations with a lower prevalence of obesity and other CMD risk factors, there were differences in the levels of CMD risk factors according to menopausal stage, but these differences were largely absent in the more urbanised and more obese South and East African populations. This indicates a need for context specific interventions to lower the risks of CMD in these populations. Thus, public health measures to curb the obesity epidemic in urban SSA populations, and clinical trials to assess the effects of hormone therapy in both urban and rural midlife women on menopause symptomology and CMD and cancer risk, are required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Ethical approval

Ethics approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand for the AWI-Gen study (M121029 and M170880) and for the current sub-study (M2010106). In addition, local ethics approval was obtained in the respective AWI-Gen study sites. All study participants provided written informed consent.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The data have been submitted to the European Genome-Phenome Archive (EGA), accession number EGA00001002482 [41]. The Human Heredity and Health in Africa (H3Africa) Data and Biospecimen Access Committee (DBAC) will review requests for the AWI-Gen phenotype dataset. Related documents including study protocol and statistical analysis plan will be available upon request from the corresponding author.

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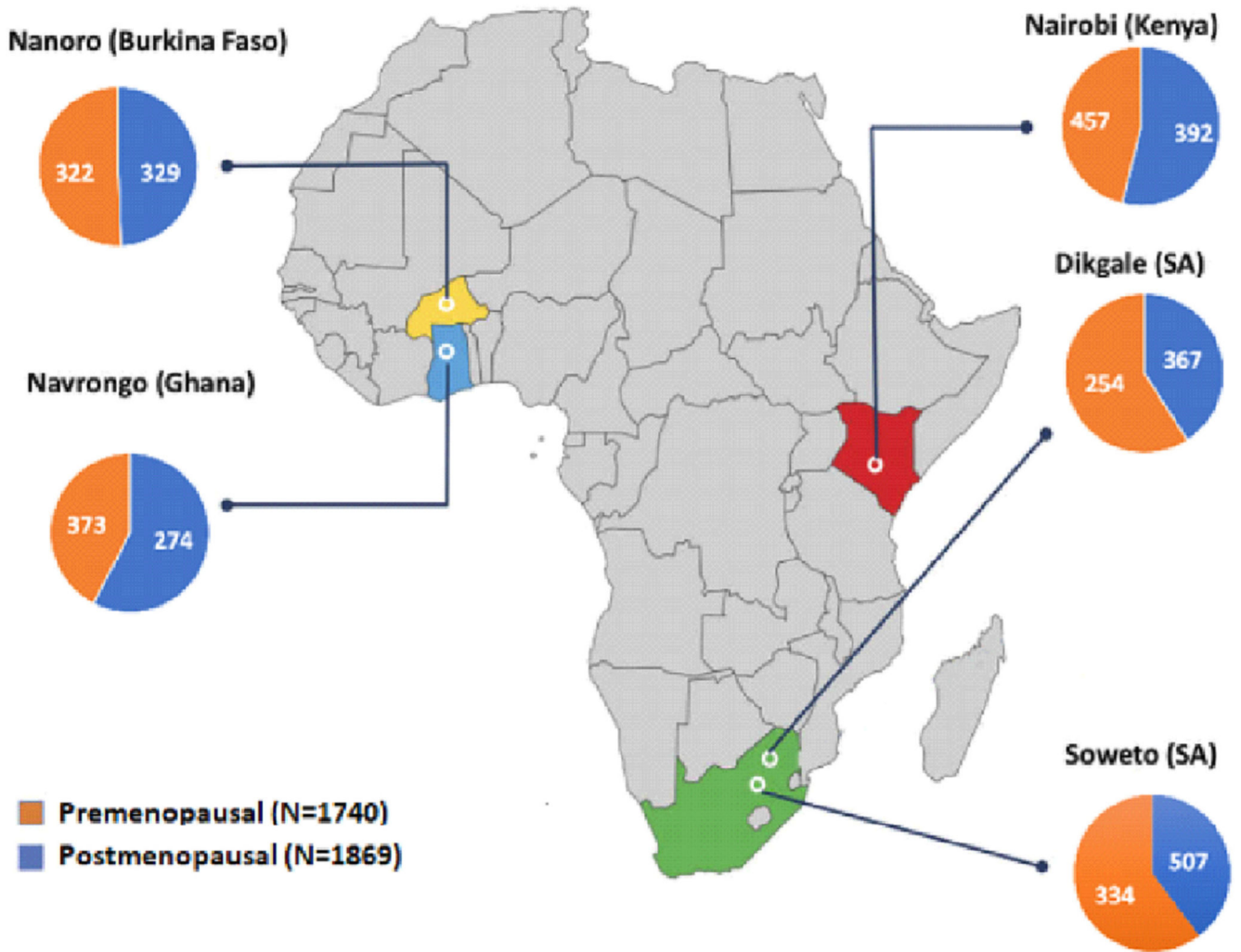


Fig. 1. Distribution of women according to menopausal stage across the five AWI-Gen Study Centres. Adapted from Ali et al. [13].

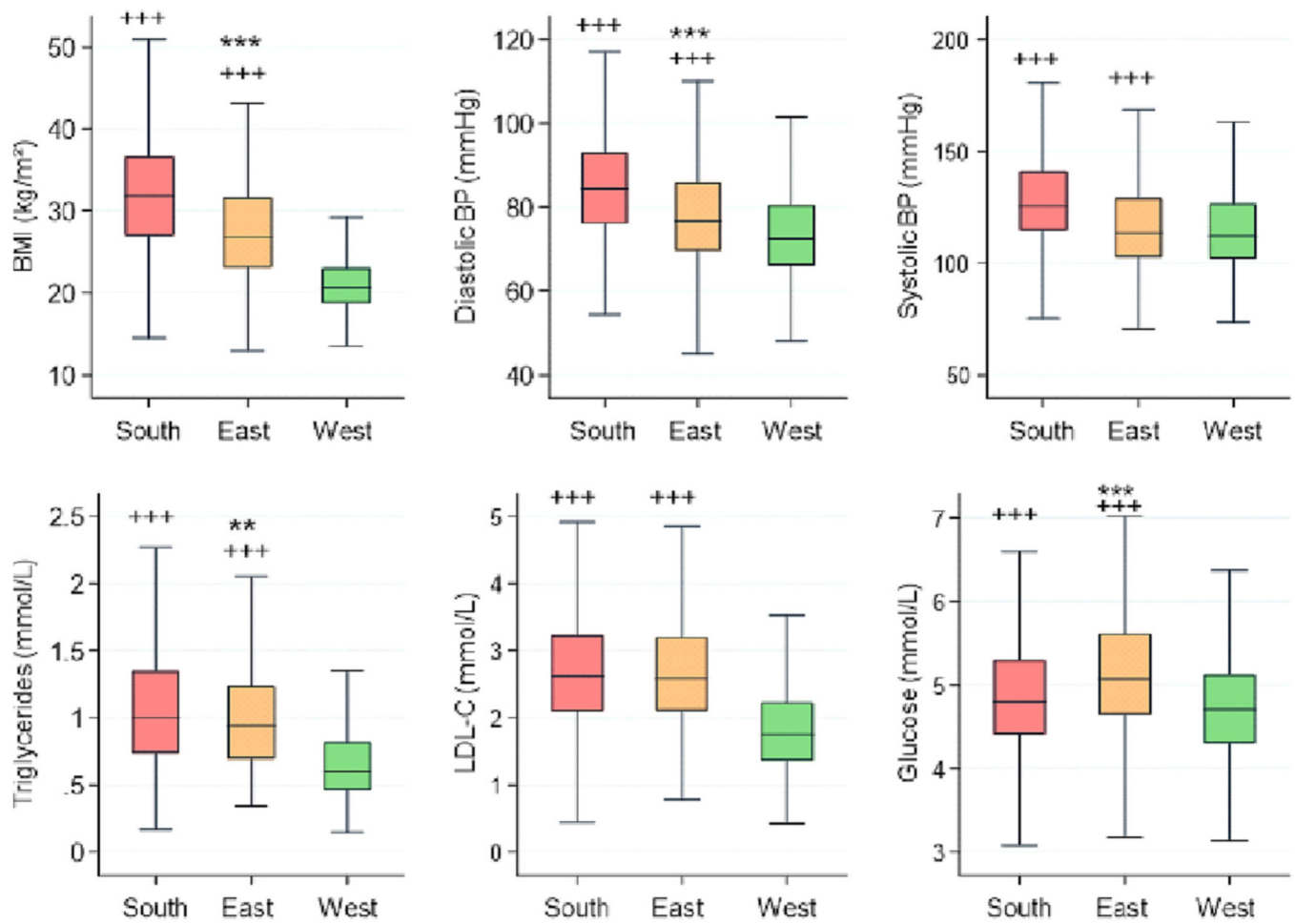


Fig. 2. CMD risk factor levels across South, East and West Africa. CMD risk factor levels (BMI (body mass index), diastolic and systolic BP (blood pressure), triglycerides, LDL-C (low density lipoprotein cholesterol) and glucose) compared across the three regions by Tukey post hoc analysis. ***p < 0.001, **p < 0.01 vs South Africa. +++p < 0.001 vs West Africa.

Prevalence of cardiometabolic diseases and risk factors in women at each AWI-Gen study site.

Table 1

Risk factors	All sites (n = 3609)	Nanoro, West Africa (n = 651)	Navrongo, West Africa (n = 647)	Nairobi, East Africa (n = 849)	Dikgale, South Africa (n = 621)	Soweto, South Africa (n = 841)	p value
Age in years	49.3 ± 5.8	49.1 ± 5.8	50.1 ± 5.8	48.3 ± 5.5	50.3 ± 6.2	49.3 ± 5.8	0.03
Current smoking	90 (3)	0 (0.0) ^a	2 (0.3)	23 (3)	22 (4)	43 (5)	<0.001
Current alcohol consumption	865 (31)	389 (60)	344 (53)	50 (6)	82 (13)	...	<0.001
Insufficient MVPA	659 (18)	79 (12)	125 (19)	84 (10)	24 (4)	347 (41)	<0.001
Obesity	1193 (33)	10 (2)	35 (5)	272 (32)	319 (51)	557(66)	<0.001
Hypertension	1221 (34)	76 (12)	146 (22)	250 (29)	290 (47)	459 (55)	<0.001
Diabetes mellitus	160 (5)	11 (2)	2 (0.3)	67 (8)	36 (7)	44 (6)	<0.001
Hypertriglyceridemia	388 (11)	19 (3)	27 (4)	93 (11)	84 (14)	165 (20)	<0.001
Hypercholesterolaemia	582 (16)	23 (4)	21 (3)	179 (21)	107 (17)	252 (30)	<0.001
Diet (days consumed per week)							
Vegetables	4.1 ± 2.3	3.2 ± 2.8	4.7 ± 2.0	5.1 ± 1.7	3.1 ± 1.8	...	<0.001
Fruits	2.0 ± 2.2	0.8 ± 1.8	1.0 ± 1.2	3.5 ± 2.4	2.1 ± 1.8	...	<0.001
Soft drinks	0.7 ± 1.9	0.1 ± 0.5	0.1 ± 0.3	0.5 ± 1.1	2.0 ± 3.2	...	<0.001
Fruit juices	0.5 ± 1.4	0.1 ± 0.2	0.3 ± 0.9	0.2 ± 0.7	1.5 ± 2.4	...	<0.001
Bread	1.9 ± 2.3	0.6 ± 1.4	0.7 ± 1.3	2.2 ± 2.2	4.0 ± 2.4	...	<0.001

Data presented as mean ± standard deviation or numbers (percentage), MVPA: moderate-vigorous intensity physical activity. Significance testing across the sites completed by one-way ANOVA or chi squared test. Definitions were as follows; insufficient MVPA: <150 min/week, obesity: BMI ≥ 30 kg/m², hypertension: systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, diabetes mellitus: fasting plasma glucose ≥ 7.0 mmol/L, hypertriglyceridemia: triglycerides ≥ 1.69 mmol/L and hypercholesterolaemia: cholesterol ≥ 5.18 mmol/L.

^aThere were no smokers in Nanoro and data on alcohol consumption and diet were missing for Soweto.

Table 2

Comparison of age, anthropometry and cardiometabolic risk factors between menopause groups for all AWI-Gen study sites combined.

Variables	Premenopause	Postmenopause	p value
Age (years)	45.4 ± 4.0	53.0 ± 4.8	<0.001
BMI (kg/m ²)	25.2 (10.3)	26.4 (12.1)	0.19
Hip circumference (cm)	101.8 ± 16.0	102.9 ± 17.6	0.05
Waist circumference (cm)	86.5 ± 15.4	89.3 ± 16.3	<0.001
SAT (cm)	1.65 (1.61)	1.86 (1.69)	<0.001
VAT (cm)	4.43 (2.35)	4.55 (2.50)	<0.001
Systolic BP (mm Hg)	114.5 (23.5)	123 (29.5)	<0.001
Diastolic BP (mm Hg)	77.5 ± 13.0	81.6 ± 13.0	<0.001
Total cholesterol (mmol/L)	3.71 ± 1.08	4.15 ± 1.23	<0.001
LDL-C (mmol/L)	2.22 ± 0.86	2.51 ± 0.94	<0.001
Triglycerides (mmol/L)	0.74 (0.51)	0.90 (0.60)	<0.001
HDL-C (mmol/L)	1.10 (0.43)	1.13 (0.43)	<0.001
Glucose (mmol/L)	4.75 (0.80)	4.90 (0.95)	<0.001
HOMA-IR	1.04 (1.97)	1.24 (2.11)	<0.001
cIMT average (mm)	0.59 (0.12)	0.65 (0.15)	<0.001

Data presented as mean ± standard deviation or median (interquartile range); BMI (body mass index), VAT (abdominal visceral fat), SAT (abdominal subcutaneous fat); LDL-C (low-density lipoprotein cholesterol), HDL-C (high-density lipoprotein cholesterol), HOMA-IR (homeostatic model for assessment of insulin resistance), cIMT average (average of left and right carotid intima-media thickness).

Table 3

Multivariate linear regression models showing relationship of menopausal stage with CMD risk factors for individual sites.

Dependent variable	Site	Menopausal stage ^a (unadjusted)	Menopausal stage ^a (adjusted) ^b
Waist circumference (cm)	Nanoro	0.24 (-1.00; 1.48)	1.54 (0.63; 2.45) **
	Navrongo	-0.88 (-2.38; 0.63)	1.06 (0.07; 2.06) *
Visceral fat (log; mm)	Nanoro	-0.05 (-0.09; -0.01) *	-0.06 (-0.12; -0.004) *
Subcutaneous fat (log; mm)	Nanoro	0.09 (0.02; 0.16) *	0.13 (0.05; 0.21) **
	Navrongo	0.05 (-0.03; 0.12)	0.14 (0.08; 0.20) ***
BMI (log; kg/m ²)	Nanoro	-0.05 (-0.07; -0.03) ***	-0.03 (-0.07; -0.004)
	Navrongo	-0.06 (-0.09; -0.04) ***	-0.04 (-0.07; -0.01) *
Diastolic blood pressure (mm Hg)	Nanoro	2.85 (1.34; 4.36) ***	2.62 (0.549; 4.69) *
	Navrongo	3.04 (1.15; 4.93) **	3.26 (0.918; 5.61) *
Systolic blood pressure (log; mm Hg)	Nairobi	0.05 (0.03; 0.07) ***	-0.03 (-0.06; -0.003) *
	Navrongo	0.06 (0.04; 0.09) ***	0.05 (0.02; 0.08) **
LDL-C (mmol/L)	Nanoro	0.17 (0.07; 0.26) **	0.16 (0.01; 0.30) *
	Navrongo	0.18 (0.07; 0.29) **	0.14 (0.14; 0.28) *
Triglycerides (log; mmol/L)	Dikgale	0.27 (0.20; 0.35) ***	0.20 (0.09; 0.31) ***
	Navrongo	0.13 (0.06; 0.21) ***	0.11 (0.03; 0.20) *
Glucose (reciprocal, mmol/L)	Navrongo	-0.004 (-0.01; 0.001)	-0.01 (-0.01; -0.002) *
Average cIMT (log; mm)	Navrongo	0.10 (0.07; 0.12) ***	0.05 (0.02; 0.08) **

Data is unstandardised β (95 % confidence interval); additional adjustments were made for specific variables as shown in Supplemental Table 1.

^aPost- vs pre-menopause; BMI, body mass index, LDL-C, low-density lipoprotein cholesterol, cIMT average, carotid intima-media thickness average of left and right cIMT.

^bAll models adjusted for age, physical activity, socioeconomic status, HIV status, level of education, smoking status, alcohol, vegetable, fruit, soft drink, fruit juice, and bread intake.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

Table 4

Univariate and multivariate linear regression models showing relationship of menopausal stage with CMD risk factors for all sites combined, for West African sites and for South and East African sites combined.

Dependent variable	Sites included in model	Menopausal stage ^a (unadjusted)	Menopausal stage ^a (adjusted) ^b
Waist circumference (cm)	All Sites	2.83 (1.79; 3.86) ***	1.10 (0.49; 1.73) ***
	West Africa	-0.39 (-1.36; 0.58)	1.28 (0.58; 1.98) ***
	South and East Africa	2.51 (1.26; 3.77) ***	0.92 (-0.09; 1.93)
Hip circumference (cm)	All Sites	1.12 (0.02; 2.21)	-0.35 (-0.88; 0.19)
	West Africa	-2.83 (-3.73; -1.93) ***	-0.40 (-1.10; 0.30)
	South and East Africa All Sites	0.86 (-0.43; 2.21)	-0.17 (-0.97; 0.63)
BMI (log; kg/m ²)	All Sites	(-0.01; 0.03)	-0.02 (-0.04; 0.0002)
	West Africa	-0.06 (-0.08; -0.05) ***	-0.03 (-0.06; -0.01) **
	South and East Africa	0.01 (-0.01; 0.03)	0.0004 (-0.03; 0.03)
VAT (log; mm)	All Sites	0.03 (0.01; 0.06) *	-0.01 (-0.04; 0.02)
	West Africa	0.0003 (-0.03; 0.03)	-0.01 (-0.04; 0.03)
	South and East Africa	0.02 (-0.01; 0.06)	-0.02 (-0.06; 0.02)
SAT (log; cm)	All Sites	0.11 (0.07; 0.15) ***	0.07 (0.04; 0.11) ***
	West Africa	0.06 (0.01; 0.11) *	0.15 (0.10; 0.19) ***
	South and East Africa	0.04 (-0.001; 0.08)	0.03 (-0.01; 0.08)
Systolic blood pressure (log; mm Hg)	All Sites	0.07 (0.06; 0.08) ***	0.01 (-0.01; 0.03)
	West Africa	0.06 (0.04; 0.08) ***	0.04 (0.02; 0.06) ***
	South and East Africa	0.07 (0.05; 0.08) ***	-0.02 (-0.04; 0.01)
Diastolic blood pressure (mm Hg)	All Sites	4.09 (3.21; 4.98) ***	1.44 (0.20; 2.68) *
	West Africa	2.44 (1.19; 3.69) ***	3.04 (1.47; 4.62) ***
	South and East Africa	3.98 (2.87; 5.09) ***	0.06 (-1.79; 1.92)
Glucose (reciprocal, mmol/L)	All Sites	-0.01 (-0.01; -0.01) ***	-0.002 (-0.01; 0.001)
	West Africa	-0.01 (-0.01; -0.001) **	-0.0060 (-0.01; -0.002) *
	South and East Africa	-0.01 (-0.01; -0.003) **	0.002 (-0.004; 0.007)
Average cIMT (log; mm)	All Sites	0.09 (0.07; 0.10) ***	0.01 (-0.003; 0.03)
	West Africa	0.09 (0.08; 0.11) ***	0.03 (0.01; 0.06) *
	South and East Africa	0.09 (0.07; 0.11) ***	-0.003 (-0.024; 0.02)
LDL-C (mmol/L)	All Sites	0.31 (0.24; 0.36) ***	0.13 (0.05; 0.20) ***
	West Africa	0.16 (0.09; 0.23) ***	0.14 (0.04; 0.23) *
	South and East Africa	0.29 (0.22; 0.37) ***	0.10 (-0.01; 0.22)
Triglycerides (log; mmol/L)	All Sites	0.19 (0.16; 0.22) ***	0.08 (0.04; 0.12) ***
	West Africa	0.16 (0.11; 0.21) ***	0.10 (0.04; 0.16) **
	South and East Africa	0.16 (0.12; 0.20) ***	0.05 (-0.01; 0.11)

Dependent variable	Sites included in model	Menopausal stage ^a (unadjusted)	Menopausal stage ^a (adjusted) ^b
HOMA-IR (log)	All Sites	0.13 (0.05; 0.21) **	0.16 (0.04; 0.28) *
	West Africa	0.06 (−0.09; 0.21)	0.18 (−0.02; 0.37)
	South and East Africa	0.13 (0.04; 0.22) **	0.16 (0.001; 0.32)
HDL-C (log; mmol/L)	All Sites	0.04 (0.02; 0.06) ***	0.01 (−0.02; 0.04)
	West Africa	0.04 (0.01; 0.08) *	0.01 (−0.04; 0.05)
	South and East Africa	0.03 (0.002; 0.06) *	0.01 (−0.03; 0.05)

Data is unstandardised β (95 % confidence interval); West African sites: Navrongo and Nanoro, South African sites: Soweto and Dikgale, East African site: Nairobi, all sites: Navrongo, Nanoro, Soweto, Dikgale and Nairobi. BMI, body mass index, VAT, abdominal visceral fat and SAT, abdominal subcutaneous fat, LDL-C, low-density lipoprotein cholesterol, HDL-C, high-density lipoprotein cholesterol, HOMA-IR, homeostatic model for assessment of insulin resistance, cIMT average, carotid intima-media thickness average of left and right cIMT; additional adjustments were made for specific variables as shown in Supplemental Table 1.

^aPost- vs pre-menopause.

^bAll models adjusted for age, physical activity, socioeconomic status, HIV status, level of education, smoking status, study sites, alcohol, vegetable, fruit, soft drink, fruit juice and bread intake.

* p < 0.05.

** p < 0.01.

*** p < 0.001.