**Title: Defensive active coping facilitates chronic hyperglycemia and early structural vascular changes in African men: the SABPA study.**

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**ABSTRACT**

**Background:** Defensive active coping (AC) responses have been associated with disturbed vascular function but whether it applies to early structural vascular changes, is uncertain. We therefore aimed to determine receiver operating characteristic (ROC) carotid intima media far wall (CIMTf) cut offs best associated with risk markers namely 24h BP, -silent ischaemia and glycated hemoglobin (HbA1c).

**Methods:** We included 317 Africans and Caucasians without pre-existing stroke or atrial fibrillation, aged 45 ± 9 years. Significant interaction on main effects necessitated selection of AC responders above mean (Coping Strategy Indicator). We collected ultrasound CIMTf, 24h BP, -silent ischaemia and overnight fasting blood samples.

**Results:** Between 69-77% of AC African men showed above normal diastolic BP and HbA1c levels compared to 44–48% of AC Caucasian men. AC African women, 41-60% showed above normal BP, silent ischaemia and HbA1c levels compared to 17-44% of their Caucasian counterparts. From ROC curve analyses the optimal cut points detecting early structural changes, yielding maximum sum of sensitivity and specificity, ranged between 0.57-0.65 mm (BP) and 0.71-0.74 mm (silent ischaemia) in AC ethnic-gender groups. Only HbA1C (>5.7%) with a sensitivity/specificity 47%/74% after controlling for confounders, predicted early structural vascular changes at an optimal cut point of 0.69 mm in AC African men (OR 4.5; 95% CI 2.93 - 18.73).

**Conclusion:** Behavioral resilience was apparent in the African female despite a high prevalence of risk markers. A defensive coping strategy facilitated chronic hyperglycemia and early structural vascular changes in the African male, possibly increasing stroke risk.

## INTRODUCTION

Defensive active coping responses (AC) have been associated with vascular hyperresponsivity and elevated resting glucose in urban Africans [1,2] These findings however, are contradictory to previous work which demonstrated that emotional avoidance responses have been associated with cardiometabolic pathology and "loss of control"[3,4] Urban African males seem to be more at risk as they reported behavioral control with active problem solving coping responses [2]. On the other hand though, they demonstrated physiological pathology with vascular hyperresponsivity, hypertension and increased metabolic syndrome markers [2,5,6]. An apparent dissociation evidently occurs between behavioral and physiological stress responses indicating loss of physiological control [7]. It could further imply that defensive coping responses in an overly challenging urban environment, where chronic stress is experienced[2], may exhaust "physiological" resources if control can not be exerted.

A recent meta-analysis showed that chronic stress is associated with increased cardiovascular disease (CVD) burden and hyperglycaemic responses in populations of developing countries [8,9]. Long-lasting stressful events can lead to an abnormal wall-to-lumen ratio of the vasculature and thereby an increase in resistance to flow and acceleration of the progression of atherosclerosis and risk for stroke [5,8-12].

Data from 2005 showed that stroke accounted for 200-300 per 100 000 deaths in sub-Saharan Africans [13,14]. It is not clear whether AC responses during chronic psychosocial stress contributes to stroke risk in Africans. To our knowledge, the association between AC, early structural vascular changes and associated stroke risk markers have never been studied in Sub Saharan Africans. We aim to show the notion of defensive coping facilitating early structural vascular changes. Therefore, we will evaluate these responses applying the discriminatory ability

of a risk predictor model based on the area under the non-parametric receiver operating characteristic (ROC) curve to determine the CIMTf cut offs best associated with atherosclerotic risk markers in ethnic-gender specific groups.

## MATERIALS AND METHODS

### Study design and population

Our sub-study is nested in the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) study conducted between February 2008 – May 2009. The participants comprised 409 urban African and Caucasian men and women working in the Dr Kenneth Kaunda Education district in the North West Province, South Africa. The reason for this selection was to obtain a homogenous sample from similar socio-economic class. Exclusion criteria were pregnancy, lactation, psychotropic substance users, ear temperature > 37.5°C, being vaccinated or donating blood within 3 months prior to participation. For the purpose of our sub-study, we additionally excluded participants with pre-existing stroke events (N=1), atrial fibrillation (N=16), HIV positive status (N=19) and clinically diagnosed diabetes (N=13). The final participant sample with defensive coping scores above mean comprised 317 participants.

The SABPA study abided by the institutional guidelines and terms of the Declaration of Helsinki 1975 (revised 2008) and was approved by the Ethics Review Board of the North-West University (0003607S6). The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [15]. The nature, benefits, and risks of the study were explained to the volunteers, and their written, informed consent was obtained prior to participation.

### Procedures

Each morning of the working week the 24h ambulatory blood pressure and ECG apparatus as well as accelerometers were fitted to four participants. At 1630h they were transported to the Metabolic Unit Research Facility of the North West University and familiarized with the experimental setup. Completion of the coping questionnaire commenced under supervision of registered clinical psychologists. Participants were advised to go to bed at 2200h, fasting overnight. At 0600h the 24h apparatuses were disconnected followed by anthropometric measurements. Participants were ~ 2h in semi-recumbent position for the resting 12-lead electrocardiogram (ECG) and venous blood sampling, followed by ultrasound scanning of common CIMT.

**Lifestyle confounders**

All anthropometric measures were determined in triplicate by trained personnel. Body weight and height were measured according to appropriate methods [16] and used to calculate body mass index (BMI) with the formula $kg/m^2$. The Mosteller formula determined body surface area (BSA ($m^2$) = ([height (cm) x weight (kg)] / 3600) [17]. The Actical® (Montréal, Québec) omnidirectional accelerometer monitor determined physical activity. It was initialized using 15-s epochs which were converted to 1-min epochs for data analysis. Serum cotinine levels were determined to evaluate exposure to first- and second-hand smoking [18]. Serum gamma glutamyl transferase (γ-GT) was determined as a marker of alcohol consumption, with normal cut points of ≤ 65 u/l for men and ≤ 45 u/l for women [19].

**Questionnaires**

*The Amirkhan Coping Strategy Indicator (ACSI)*

The ACSI is a 33-item self-report measure of coping responses and has been used in the African context [20] with three sub-scales of 11 items each [21]. Cronbach alpha reliability coefficients

were determined for the three subscales in each ethnic and gender group and ranged between 0.81-0.87 for defensive problem solving, 0.61-0.85 for avoidance and 0.83-0.90, for seeking social support. “Defensive active coping (AC) responses” imply problem solving, being-in-control, acceptance of the stressor as reality and endeavouring to eliminate the stressor actively; “seeking social support” implies an active coping process for comfort and advice in stressful times and lastly, “avoidance or loss of control” implies defeat, with physical and psychological withdrawal. Responses were rated on a three-point Likert scale: a lot (3), a little (2), or not at all (1), with a recent stressful event in mind.

**Cardiovascular measurements**

We obtained 24h ambulatory blood pressure (ABPM) and 2-lead ECG measurements with the Cardiotens CE120® apparatus (Meditech, Budapest, Hungary) validated by the British Hypertension Society in 2003. Each morning at ~0700-0800 hours the apparatus and leads were fitted, applying suitable cuffs on the non-dominant arm. The Cardiotens oscillometrically measured blood pressure at 30-min intervals during the day (0800-2200 hours) and 60-min intervals at night (2200–0600 hours) [22]. The successful mean 24h inflation rate was 79.2%. Participants were asked to continue with normal daily activities and record any abnormalities such as visual disturbances, headache, nausea, fainting, palpitations and stress on their ambulatory diary cards.

**ECG measures**

A resting 12-lead ECG (strip lead II) was obtained during 6 cardiac cycles and identified atrial fibrillation and RaVL data (NORAV Medical Ltd PC 1200, software version 5.030, Kiryat Bialik, Israel). Two-lead 24h ECG recordings were made according to a preset program for 20 s at 5-min intervals assessing silent ischaemic events. Software was initialized to document ischaemic

events according to the 1-1-1 rule: 1) More than 1 mm horizontal or descending ST-segment, 2) The ST-segment event occurs for at least 1 minute (duration), and 3) Two consecutive ST-episodes must have an interval of at least 1 minute (thus counted as independent episodes) [23]. The data was analyzed using the CardioVisions 1.15.2 Personal Edition software (Meditech®, Budapest, Hungary).

**Subclinical atherosclerosis**

High resolution ultrasound CIMT scans were used to determine structural vascular changes. CIMT images, from at least two optimum angles of the left and the right common carotid artery segments were acquired using a Sonosite Micromaxx ultrasound system (SonoSite Inc., Bothell, WA, USA) and 6-13 MHz linear array transducer, using the Rudy Meijer protocol [24]. The images were digitized and imported into the Artery Measurement Systems automated software (AMS) II v1.139 (Gothenburg, Sweden) for dedicated analysis of CIMT. Cross-sectional wall area (CSWA) which confirm structural and not functional changes in the luminal diameter was measured as follows: $CSWA = \pi(d/2 + CIMT)^2 - \pi(d/2)^2$, where d denotes luminal diameter. For the purpose of this study, the far wall CIMT measurements were used (CIMTf) [25]. Intra-observer variability was 0.04 mm between two measurements made 4 weeks apart on 10 participants.

**Biochemical analysis**

Serum, EDTA whole blood and NaF glucose blood samples were obtained and handled according to standardized procedures and stored at - 80°C until analysis. EDTA whole blood turbidometric inhibition immunoassay analyses determined glycated haemoglobin (HbA1c) and estimated average glucose (eAG) values. The HbA1c and eAG values reflect an average capillary glucose equivalent for the preceding 2-3 months or 1-2 weeks, respectively (Integra 400 Roche,

Switzerland). Fasting sodium fluoride glucose and serum samples for total cholesterol, γ-GT, cotinine and ultrahigh-sensitivity C-reactive protein (Hs-CRP) were analyzed using the sequential multiple analyzer computer (Konelab 20i; Thermo Scientific, Vantaa, Finland) and by immunoassay (Integra 400, Roche, Switserland).

**Data analysis**

Data analyses were performed with Statistica 10 (StatSoft, Inc., 2011) and ROC analyses with SPSS 19 for Windows. Departure from normality was evaluated and hs-CRP and γ-GT were normalised. Means of continuous variables were compared using the Student t tests for independent samples (mean ± standard deviation). Chi-square tests were performed to compare categorical variables (%). A priori covariates included age, body surface area (BSA) and lifestyle factors (alcohol abuse, smoking habits and physical activity). We computed 2 x 2 x 2 analyses of covariance (ANCOVA) adjusting for covariates, to test for significant interactions on main effects (coping, ethnicity and gender) for early vascular risk markers. Interaction effect analyses (between coping, ethnic and gender) for early vascular risk markers were repeated for each of the three dichotomised coping strategies namely defensive problem solving, avoidance and social support (using mean cut points) [21]. Subsequent one-way ANCOVAs were performed to compare ethnic-gender groups. Mean values, adjusted for covariates, were obtained by using least square means .

Hereafter, to demonstrate the notion of defensive coping responses facilitating early structural vascular changes, we computed non-parametric receiver operating characteristic (ROC) curves [26]. The AC ethnic-gender groups' ROC curves were computed together with the area under the curve (AUC) to explore the association between CIMTf and different atherosclerotic or stroke

risk markers, using different cut points. Sensitivity and specificity values for different cut points, together with the AUC (with 95% CI intervals) were computed. The optimal cut point was chosen where the sum of the numbers of true positive and true negative predictions was maximized. The ROC analyses predicted optimal cut points for CIMT responses in AC ethnic-gender groups, with and without atherosclerotic risk markers [27,28]: 24h SBP hypertension (≥ 125 mmHg), DBP hypertension (≥ 80 mmHg); HbA1c (≥ 5.7%), hs-CRP (>3mg/l) and 24h silent ischaemia (events, yes/no).

These analyses were followed by logistic regression analyses to predict pathological CIMTf for each atherosclerotic risk marker cut point in the respective AC ethnic-gender groups. Odds ratios (OR) were also specifically computed to test if covariates influences the discriminatory power of the ROC CIMTf cut point [29]. Covariates for all models included age, BSA, physical activity, cotinine, log γ-GT, log hs-CRP and total cholesterol. Statistical significance was set at $P \leq 0.05$.

**RESULTS**

Despite being of similar age, Africans revealed lower body surface areas and were less active (Table 1). They further reported on using less avoidance coupled to higher social support coping strategies ($P \leq 0.05$). Atherosclerotic risk markers were also more pronounced in Africans compared to Caucasians ($P \leq 0.05$) with mean values exceeding known cut offs, including HbA1c (> 5.7%), eAG (> 7.0 mmol/l), BP (24h SBP > 125 mmHg and 24h DBP > 80 mmHg), Hs-CRP (> 3 mg/l) and γGT (45-65 u/l) [19,27,28]. Silent ischaemic events, CIMT and CSWA values were more pronounced in all Africans.

Interaction on main effects (defensive coping x ethnicity x gender) demonstrated significance for CSWA ($F(1, 317)$, 5.21; $P = 0.02$) and a trend toward silent ischemia ($F(1, 317)$, 2.95; $P = 0.09$). No significant interactions existed for avoidance and/or social support coping strategies

pertaining to any of the atherosclerotic risk markers. This necessitated selection of only participants above mean (cut off 26) defensive coping (AC) [21], within each ethnic and gender group (Tables 2-3; Figures 1-2). Higher responses on seeking social support coupled to less avoidance were viewed as supportive of defensive AC responses.

In Table 2, the AC African men and women overall demonstrated similar trends when compared to their Caucasian counterparts. AC African men showed ($P \leq 0.05$) a less active lifestyle but both men and women apparently abused more alcohol, had higher 24h heart rate, -BP, chronic hyperglycemia (eAG, HbA1c), inflammatory status (hs-CRP) as well as lower cholesterol levels when compared to Caucasians. The AC African men revealed higher 24h silent ischaemic events whilst CIMT values were only higher in AC African women compared to AC Caucasians. In both gender African groups, defensive coping responses were supported by less avoidance coping (PC) and more social support coping responses ($P \leq 0.05$).

In Table 3, between 69-77% of AC African men showed above normal diastolic BP and HbA1c levels compared to 44-48% in AC Caucasian men. AC African women showed above normal BP, silent ischemia and HbA1c levels with 41-60 %, compared to 17-44% in their counterparts.

*Predictors of early structural vascular changes*

ROC curves indicated that AC responses facilitated early structural vascular changes as depicted by lower CIMT cut offs. The suggested optimal cut off values for CIMTf was determined by using a risk predictor model including 24h SBP (Fig 1a), 24h DBP (Fig 1b), HbA1c (Fig 2a), silent ischaemia (Fig 2b) and hs-CRP values as reference of morbidity in gender-ethnic groups [29]. The respective ROC cut off values, yielding maximum sum of sensitivity and specificity ranged between 0.57-0.65 mm (BP), 0.64-0.70 mm (HbA1c) and 0.71-0.74 mm (ST) in AC ethnic-gender groups. In Fig 1-2, the areas under the curve (AUC) for these variables were > 0.5

and closer to 1, indicating accuracy and not random chance [30]. Risk marker Hs-CRP revealed AUC values less than 0.5 in all ethnic groups i.e., 0.47 – 0.68 (95% CI: 0.33, 0.72) indicating low discriminatory ability and probability of false positives. Adjusting for CIMT confounding factors had to be considered and therefore we commenced with odds ratios in order to obtain the best predictor for pathological CIMTf. Only increased HbA1c significantly predicted early structural vascular changes in AC African men according to a suggested ROC cut off of 0.69 mm (OR 4.5; 95% CI 2.93 - 18.73) with 46 % sensitivity and 74 % specificity. It implies that the odds of the high CIMTf group (≥ 0.69 mm) to the low CIMTf group (< 0.69 mm) within the high HbA1c group is 4.5 times larger than that obtained in the low HbA1c group, but can be as low as 2.93 and as high as 18.73 with high probability to predict early structural vascular changes. Odds ratios for risk markers BP and silent ischemia predicting pathological CIMTf, were not significant.

**DISCUSSION**

We aimed to determine whether defensive coping responses facilitated early structural vascular changes possibly caused by endothelial alteration, by calculating the ROC CIMTf cut offs best associated with ambulatory BP, - silent ischaemia and HbA1c. Overall, AC Africans demonstrated a more vulnerable atherosclerotic profile with higher prevalence of risk markers especially DBP and HbA1c. Our main finding showed that chronic hyperglycemia predicted early structural vascular changes in the AC African male although not in Caucasians.

Atherosclerotic risk markers and associated defensive coping responses were further supported by less avoidance and more social support coping responses. According to our results it implies that if defensive coping responses are utilized *habitually* it could facilitate hypertension, hyperglycemia [31] and ischaemic events. Defensive coping hyperresponsivity has been implicated in the development of essential hypertension [31,32]. It is also assumed that the

pathways subserving the defense responses become markedly facilitated and hyperresponsiveness of the sympathetic nervous system (SNS) becomes greater in hypertensive than in normotensives [33]. To support our notion of a defensive coping pathway and not ethnicity *per se* facilitating early structural vascular changes, we repeated ROC and adjusted OR analyses in all African men, independent of coping responses. However, at a suggested CIMT cut off of 0.77 mm, the HbA1c did not predict early structural vascular changes (P = 0.57) as were seen in the AC men only.

Although 24h BP and -silent ischaemia did not predict early structural vascular changes, levels were higher in the African men attempting to cope actively with his circumstances. The sympathoexcitatory effects of indirect markers of SNS such as increased heart rate, 24h ischaemic events and chronic hyperglycaemia, in the AC African men could potentiate adrenergic overdrive reinforcing metabolic overdrive and structural alterations [33]. In another sub-study of SABPA we have demonstrated attenuated baroreceptor sensitivity in the African male possibly supporting the adrenergic overdrive notion [34]. Further evidence for potential associations between SNS and endothelial function comes from disease states associated with impairments in both systems [34,35]. For example, hypertension and diabetes are associated with abnormalities in SNS regulation of the cardiovascular system. Both these disease states have been associated with impairments in endothelial function [36]. Whether they affect each other negatively or whether both systems undergo dysregulation as a consequence of disease process, is uncertain.

In African Americans larger CIMTs' and stiffer carotid arteries were found compared to their Caucasian counterparts [37] supporting data seen in our African subjects, although gender differences were not taken into account. Considering AC responses though, it was only African females revealing increased CIMTf values compared to their Caucasian counterparts. There

seems to be an apparent behavioral resilience in the African female despite being more centrally obese [38] as well as having a higher prevalence of structural vascular changes.

Current guidelines suggest that CIMTf values ≥ 1mm should be used as an indication of subclinical atherosclerosis [28]. Studies on the risk of coronary and cerebrovascular events demonstrated that the risk of first myocardial infarction increases with a CIMT of 0.82 mm or more and the risk of stroke increases with a CIMT of 0.75 mm or more [39]. Our cut point predicting pathological progression rates of the far-wall common carotid artery varied between 0.66 – 0.71 in the AC African male and AC Caucasian female which is far less than the measures suggested above. However, an interaction effect (ethnic x gender x coping) for the CSWA (P = 0.02), support a facilitating defensive pathway relating to early structural vascular changes.

In the United Kingdom Prospective Diabetes Study, HbA1c levels above 6.2 % were associated with increases in macrovascular disease risk which implies that for each 1 percent elevation in HbA1c, coronary heart disease increases by 11% [40]. Our AC African males may therefore demonstrate increased risk for macrovascular disease complying with the set criteria with a mean value of 6.28% (Table 2). Conversely, chronic hyperglycaemia could adversely affect vascular function if coupled to an increased prevalence for silent ischaemia [11]. Acute hyperglycaemia increases osmolality, ischaemic damage and decreases cortical blood flow [41,42]. Subsequently, hyperglycaemic states impair compensatory changes in vascular diameter in response to altered blood viscosity. Autoregulation becomes defective augmented by lower cardiac output and vasoconstriction in vascular smooth muscle [42].

Furthermore, endothelial dysfunction via vascular alterations may contribute to the higher prevalence of ischaemic events as seen in our AC African groups as it could imply reduced supply to the heart. Reduced supply if coupled to increased SNS responses could set a

hyperkinetic stage further increasing ischaemia and potentiating impeding regulation of cerebral microvascular tone and blood flow [11]. Hyperglycemia and increased hs-CRP values may initially increase oxidative stress through increased superoxide anion production and adhesion protein-1 activity [43,44]. Schutte et al. [45] demonstrated vascular dysfunction and decreased anti-oxidant capacity in African men, linking vascular changes to early atherosclerosis. This could happen through a possible impairment of endothelium-dependent relaxation in human conduit arteries [33]. Even if only HbA1c predicted early structural changes, their risk for atherosclerosis and stroke could, therefore, be increased [27].

The study has several limitations. The cross sectional design of the study cannot infer causality and prospective data is needed to substantiate our findings or progression of disease. Functional markers of nitric oxide metabolites and cellular adhesion molecules need to be addressed in future studies as markers of impaired endothelial function. Strengths of the study include the novelty of a defensive coping pathway facilitating early structural changes in the endothelium predicting the possibility of increased stroke risk through chronic hyperglycemia (Fig 3). The well-controlled design of the study for psychophysiological stress testing, which is a first in sub-Saharan Africa, contributes to novel data associated with structural vascular changes and stroke risk in a cohort of Africans.

**Perspectives**

The present study lends support to previous findings of a facilitated defensive coping strategy in African males. Vulnerability may emerge in a too demanding westernized society where efforts to take control will drain their psychophysiological resources. Behaviourally, African males report AC responses aimed at taking control of a stressor, but physiologically they are losing control which may be “masked” before pathology sets in. Less avoidance coping and more social

support responses should have a protective effect on their cardiovascular status [4] but this was not the case. A possible facilitated defensive pathway and "*loss of control"* could therefore potentially increase their risk for CVD and stroke. A behavioral resilience in the African female despite a high prevalence of structural vascular risk markers can not be explained and further studies are needed.

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**Disclosures**

None.

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Table 1: Baseline characteristics (mean ± SD) by ethnic status.

| Variables | Africans (N = 151) | Caucasians (N = 166) |
|---|---|---|
| *Confounders* | | |
| Age, y | 44.28 ± 8.01 | 44.92 ± 10.86 |
| Body surface area, $m^2$ | 1.92 ± 0.23 | 2.11 ± 0.28* |
| Body mass index, $kg/m^2$ | 30.13 ± 7.01 | 27.61 ± 5.94* |
| Physical activity, kcal/h | 2682.37 ± 795.41 | 3112 ± 1596.54* |
| Cotinine, ng/ml | 27.24 ± 60.94 | 22.71 ± 77.47 |
| γ-Gluthamyl transferase, u/l | 66.34 ± 82.39 | 26.91 ± 33.91* |
| *Psychological variables* | | |
| Problem solving score | 28.15 ± 4.09 | 28.83 ± 3.87 |
| Social support score | 25.67 ± 5.01 | 18.76 ± 4.79* |
| Avoidance score | 21.07 ± 3.78 | 24.00 ± 5.16* |
| *Variable potentially affecting the endothelium* | | |
| hs-C-reactive protein, mg/l | 8.51 ± 10.51 | 3.09 ± 3.88* |
| Cholesterol, mmol/l | 4.60 ± 1.19 | 5.54 ± 1.28* |
| HbA1c, % | 6.08 ± 1.21 | 5.51 ± 0.42* |
| eAG, mmol/l | 7.02 ± 1.92 | 6.18 ± 0.67* |
| Glucose, mmol/l | 5.64 ± 2.06 | 5.67 ± 0.81 |
| 24hr SBP, mmHg | 133 ± 16.18 | 124 ± 12.04* |
| 24hr DBP, mmHg | 84 ± 10.70 | 77 ± 8.04* |

| | | |
|---|---|---|
| 24h silent ischaemia, events | 6.04 ± 15.48 | 2.56 ± 5.94* |
| CIMTf, mm | 0.69 ± 0.15 | 0.64 ± 0.15* |
| Cross sectional wall area, $mm^2$ | 14.30 ± 4.07 | 13.26 ± 3.91* |
| Hypertensive, N (%) | 137 (83.03) | 102 (52.31)* |
| *Medications* | | |
| Hypercholesterolemia, N (%) | 2 (1.21) | 9 (4.62)* |
| Hypertension, N (%) | 43 (26.06) | 18 (9.23)* |

**Table 1 caption**

Data are presented as arithmetic mean ± SD or number of participants (%). *P ≤ 0.05.

Table 2: Comparing ethnic defensive active coping (AC) responses characteristics in men and women, adjusting for confounders.

| | **AC African males (N = 77)** | **AC Caucasian males (N = 84)** | **AC African females (N = 74)** | **AC Caucasians females (N = 82)** |
|---|---|---|---|---|
| *Confounders* | | | | |
| †Age, y | 43.18 ± 8.05 | 44.96 ± 11.08 | 44.99 ± 7.51 | 45.88 ± 10.45 |
| †Body surface area, $m^2$ | 1.94 ± 0.23* | 2.18 ± 0.21* | 1.88 ± 0.22 | 1.82 ± 0.24 |
| †Body mass index, $kg/m^2$ | 27.72 ± 5.98 | 28.87 ± 4.99 | 32.31 ± 6.58 | 26.34 ± 6.49* |
| †Physical activity, kcal/h | 2714.85 ± 800.12 | 3674.35 ± 2059.15* | 2547.93 ± 695.55 | 2588.35 ± 653.37 |
| †γ-Gluthamyl transferase, u/l | 84.84 ± 91.70 | 34.72 ± 29.51* | 47.41 ± 74.12 | 20.87 ± 40.76* |
| †Cotinine, ng/ml | 35.46 ± 65.01 | 30.89 ± 96.69 | 13.75 ± 36.08 | 7.87 ± 36.03 |
| *Coping strategies, scores* | | | | |
| Defensive problem solving | 30.17 (29.6,30.8) | 30.52 (30.1,31.1) | 30.24 (29.7,30.7) | 30.06 (29.6,30.5) |
| Social support | 25.28 (24.1,26.6) | 17.95 (16.7,19.2)* | 26.60 (26.5,27.7) | 19.21 (18.2,20.2)* |
| Avoidance | 20.7 (19.7,21.8) | 24.46 (23.5,25.5)* | 21.03 (19.8,22.2) | 25.06 (24.1,26.2)* |

| | | | | |
|---|---|---|---|---|
| *Variable potentially affecting endothelium* | | | | |
| Cholesterol, mmol/l | 4.67 (4.4,5.0) | 5.6 (5.4,5.9)* | 4.44 (4.1,4.7) | 5.40 (5.1,5.7)* |
| hs-C-reactive protein, mg/l | 6.19 (4.6,7.8) | 1.47 (-0.1,3.0)* | 11.63 (9.7,13.6) | 4.33 (2.5,6.1)* |
| Glucose, mmol/l | 6.13 (5.7,6.5) | 5.89 (5.7,6.3) | 5.14 (4.8,5.5) | 5.41 (5.1,5.7) |
| HbA1c, % | 6.28 (6.1,6.5) | 5.59 (5.4,5.8)* | 5.71 (5.6,5.9) | 5.41 (5.3,5.6)* |
| eAG, mmol/l | 7.28 (6.8,7.7) | 6.30 (6.0,6.7)* | 6.51 (6.2,6.8) | 6.01 (5.8,6.3)* |
| 24hr SBP, mmHg | 139 (136,142) | 126 (122,129)* | 127 (124,130) | 120 (118,123)* |
| 24hr DBP, mmHg | 89 (87,91) | 78 (76,80)* | 78 (76,80) | 74.27 (73,76)* |
| 24h Heart rate, beats/minute | 80 (77,83) | 71 (68,74)* | 79 (77,81) | 76 (74,78)* |
| 24h ischaemia, events | 8.49 (5.4,11.6) | 0.83 (-2.1,3.8)* | 3.20 (1.9,4.5) | 2.63 (1.4,3.9) |
| CIMTf, mm | 0.71 (0.67,0.74) | 0.68 (0.65,0.71) | 0.67 (0.6,0.7) | 0.60 (0.60,0.62)* |
| Cross sectional wall area, $mm^2$ | 15.62 (14.7,16.5) | 14.68 (13.8,15.6) | 13.04 (12.4,13.6) | 11.56 (11.0,12.1)* |
| Hypertensive, N (%) | 62 (80.5) | 60 (71.4) | 38 (51.4) | 24 (29.3)* |
| *Medications* | | | | |
| Hypercholesterolemia, N (%) | 1 (1.3) | 5 (6.1) | 1 (1.4) | 3 (3.6)* |

| | | | | |
|---|---|---|---|---|
| Hypertension, N (%) | 16 (20.8) | 8 (9.5)* | 15 (20.3) | 7 (8.5)* |

Table 2 caption

†, Data presented as arithmetic mean ± SD; other data as N (%) and adjusted mean (± 95% CI, confidence interval). Covariates included age, body surface area (BSA), physical activity, γ-GT and cotinine. * $P \leq 0.05$ vs the African gender.

Figure 1a

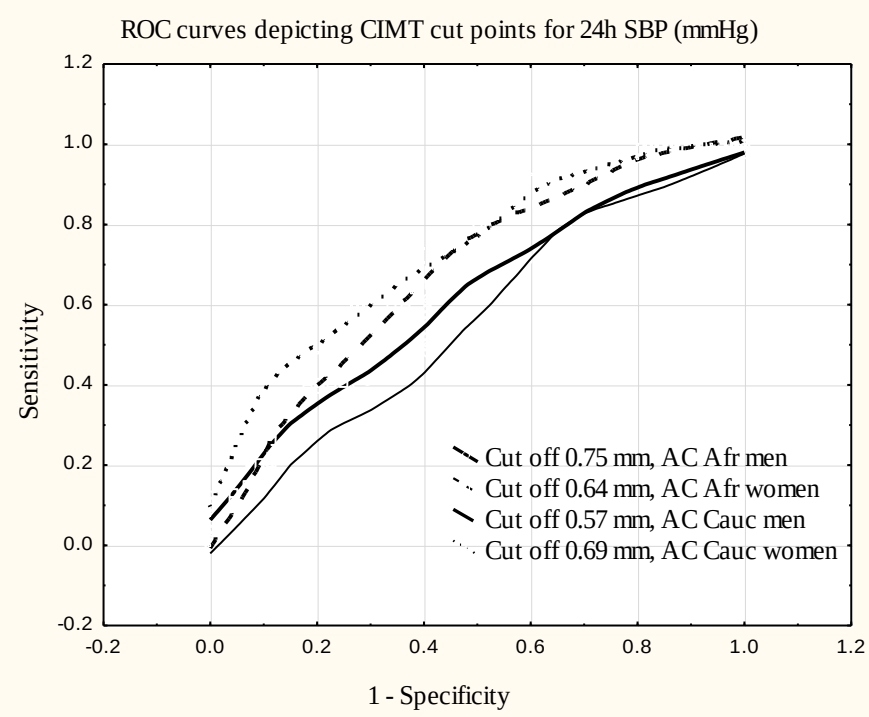


Figure 1a: ROC curves depicting CIMT cut points for 24h SBP in AC ethnic-gender groups: Afr, Africans and Cauc, Caucasians. The area under the curve (AUC) (95%CI) was 0.62 (0.50, 0.74) for Afr men; 0.68 (0.58, 0.79) for Afr women; 0.55 (0.44, 0.67) for Cauc men and 0.73 (0.63, 0.84) for Cauc women.

Figure 1b

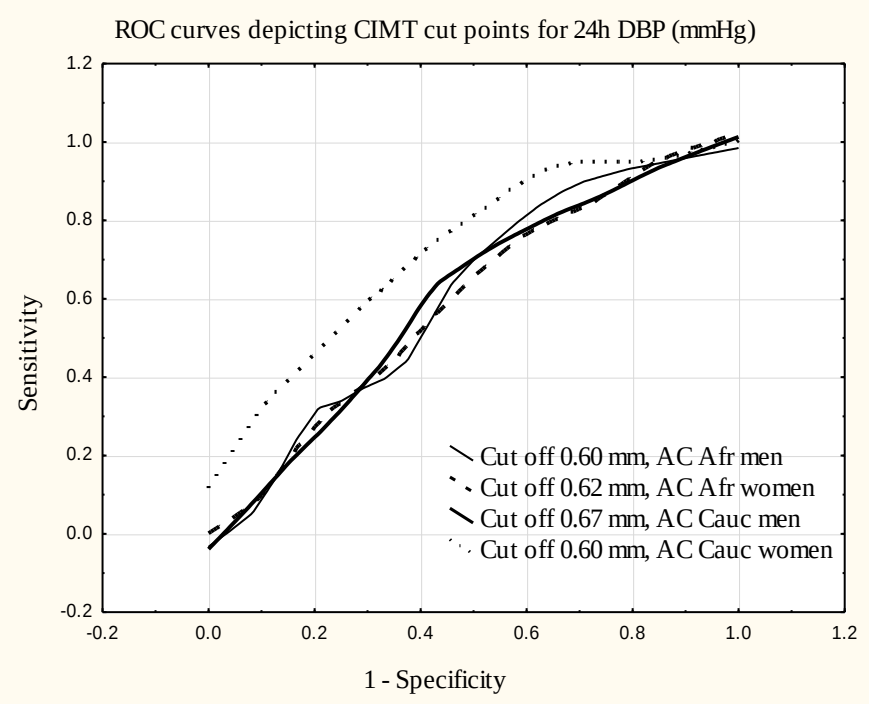


Figure 1b: ROC curves depicting CIMT cut points for 24h DBP in AC ethnic-gender groups: Afr, Africans and Cauc, Caucasians. The area under the curve (AUC) (95%CI) was 0.60 (0.46, 0.75) for Afr men; 0.59 (0.48, 0.71) for Afr women; 0.60 (0.49, 0.71) for Cauc men and 0.73 (0.61, 0.84) for Cauc women.

Figure 2a

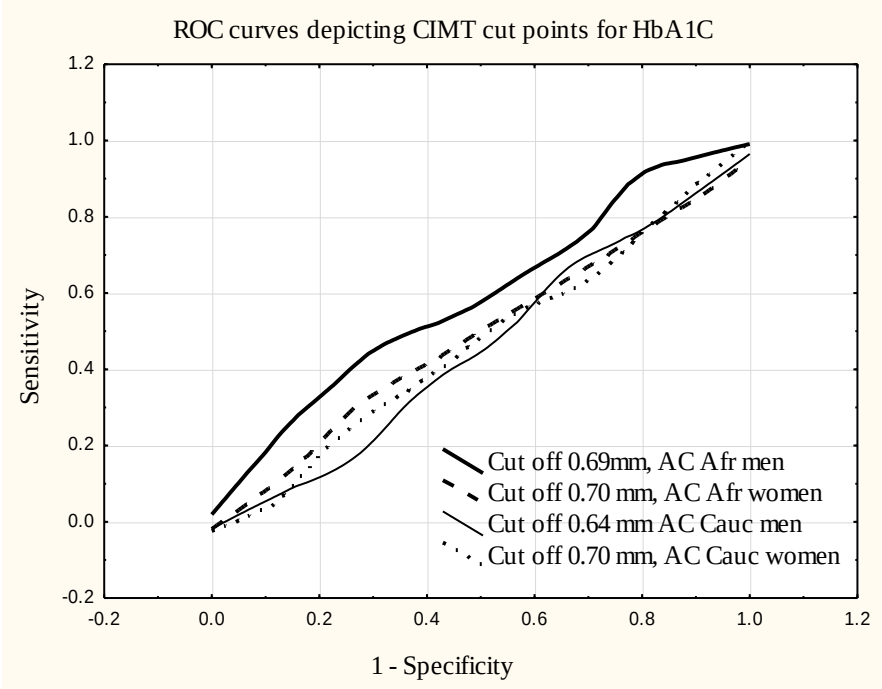


Figure 2a: ROC curves depicting CIMT cut points for HbA1c in AC ethnic-gender groups: Afr, Africans and Cauc, Caucasians. The area under the curve (AUC) (95% CI) was 0.59 (0.46, 0.72) for Afr men; 0.49 (0.34, 0.63) for Afr women; 0.46 (0.31, 0.60) for Cauc men and 0.59 (0.46, 0.72) for Cauc women.

Figure 2b

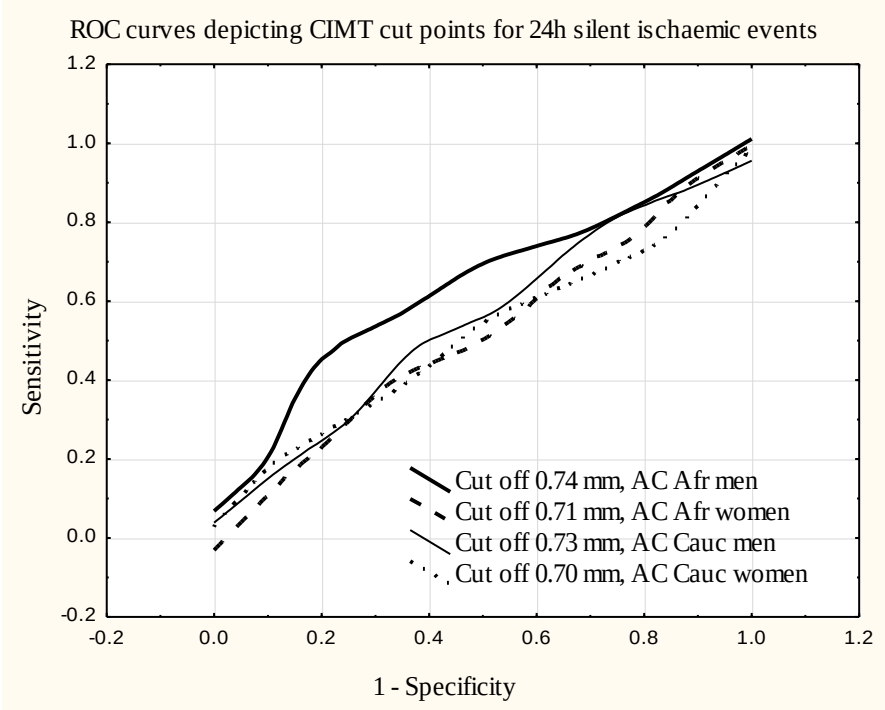


Figure 2b: ROC curves depicting CIMT cut points for 24h silent ischaemia events in AC ethnic-gender groups: Afr, Africans and Cauc, Caucasians. The area under the curve (AUC) (95% CI) was 0.63 (0.53, 0.75) for Afr men; 0.52 (0.40, 0.63) for Afr women; 0.55 (0.43, 0.67) for Cauc men and 0.64 (0.53, 0.75) for Cauc women.

Table 3: Comparing prevalence (%) of earlier structural vascular risk markers in defensive active coping (AC) African and Caucasian responders.

| Prevalence, % | **AC African males (N = 77)** | **AC Caucasian males (N = 84)** | **AC African females (N = 74)** | **AC Caucasians females (N = 82)** |
|---|---|---|---|---|
| 24h SBP (≥125 mmHg) | 74.03 | 61.90 | 50.00 | 23.17** |
| 24h DBP (≥80 mmHg) | 76.62 | 47.62** | 40.54 | 17.10** |
| HbA1c (≥5.7%) | 68.83 | 44.05** | 47.30 | 20.73** |
| 24h ST (events) | 44.16 | 34.52 | 59.46 | 43.90* |

* $P \leq 0.05$; **$P \leq 0.01$

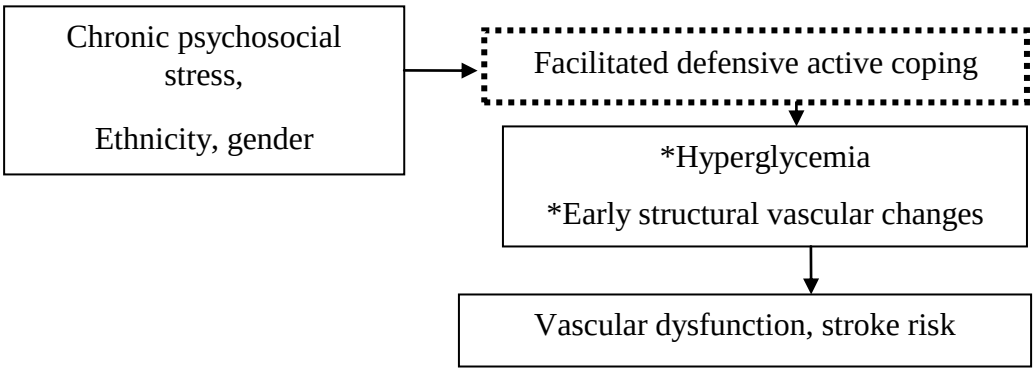


Figure 3: Defensive active coping responses in an urban environment facilitate chronic hyperglycemia predicting early structural endothelial changes. Vascular dysfunction and stroke risk may increase.