Double product and psychological distress in a bi-ethnic urban South African cohort: the SABPA study

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Lastly, I would like to thank my family and my girlfriend for the endless support and motivation.

Opsomming

Probleemstelling: Hipertensie dra aansienlik by tot die ontwikkeling van kardiovaskulêre siektes. Verskeie faktore dra by tot die ontwikkeling van hipertensie soos obesiteit, alkoholmisbruik en psigologiese spanning. Swart Afrikane ly aan hipertensie as gevolg van lewenstylveranderings of verstedeliking wat moontlik psigologiese distres of spanning kan verhoog. Kroniese spanning kan simpatiese hiperaktiwiteit sneller om die hipotalamiese pituïtêre adrenale as (HPAA) stresbaan te aktiveer wat die streshormoon, kortisol, vrystel wat tydens kroniese toestande kardiometaboliese risiko kan verhoog. Dubbelproduk (DP) is ideaal om werkslading van die hart te meet aangesien dit die produk van sistoliese bloeddruk en harttempo is wat dien as ’n indeks van suurstofverbruik. DP wat harttempo ook inkorporeer, kan ’n sterker verband hê met metaboliese faktore waar ’n verhoogde harttempo gedurende simpatiese ooraktiwiteit dus kan bydra tot verhoogde kardiometaboliese risiko.

Doel: Ons doel is om assosiasies tussen dubbelproduk, stil iskemiese insidente en kardiometaboliese risiko-merkers, spesifiek kortisol en adrenokortikotropiese hormoon (ACTH), te assesseer in etniese geslagsgroepe asook om die assosiasies tussen laasgenoemde faktore tydens psigologiese distres waar te neem.

Metodiek: Ons sub-studie is gegrond op die Simpatiese aktiwiteit en Ambulatoriese Bloeddruk in Afrikane- (SABPA) studie (2008-2009). Die proefgroep het bestaan uit 'n Sosio-ekonomiese soortgelyke populasie van 409 onderwysers van die Dr Kenneth Kaunda onderwys distrik in die Noordwes Provinsie van Suid-Afrika. Kortisoon-gebruikers (n=3), deelnemers gediagnoseer met atriale fibrilasie (n=16) en klinies gediagnoseerde diabete (n=12) is uitgesluit. Die finale groep bestaan uit 378 individue waarvan 92 Swart mans, 90 Swart vroue, 94 Wit mans en 102 Wit vroue is. Ambulatoriese bloeddruk, elektrokardiogram- en fisieke-aktiwiteitsvlak-waardes is verkry in die 48-uur kliniese data-insamelingsproses.

Vastende bloedmonsters is ingesamel en het gamma glutamiel transferase-, hoë sensitiewe C-reaktiewe proteïen- (CRP), kotinien, HbA1c., kortisol- en kortikotropien-monsters ingesluit. Onafhanklike *t*-toetse en Chi-kwadraat-toetse is gebruik om Swart en Wit groepe te vergelyk gevolg deur 'n kovariansie-analise (ANCOVA). ANCOVAS is gekorrigeer vir *a priori* veranderlikes (ouderdom, middelomtrek, fisieke aktiwiteit, gamma glutamiel transferase en kotinien). Onafhanklike assosiasies tussen DP, stil iskemiese insidente, kortisol en kardiometaboliese risikomerkers is bepaal in die totale kohort asook in matig tot erg depressiewe etniese geslagsgroepe.

Resultate: Swartes het 'n swakker kardiovaskulêre profiel vertoon met hoër bloeddrukwaardes, 'n verhoogde harttempo, hoër HbA1c-vlakke, meer iskemie asook meer laegraadse inflammasie (CRP > 3 mg/l) getoon as die Wit geslagsgroep. Laer kortisol- asook hoër ACTH-waardes het voorgekom by Swart mans teenoor ander etniese en geslagsgroepe. Middel-omtrek was kleiner by Swart mans en groter by Swart vroue as by Wit mans en vroue. Stratifisering in ras x geslagsgroepe het lae kortisol en hoër ACTH asook meer stil iskemie in Swart mans vertoon, maar in geeneen van die ander groepe nie. Die Swart vroue het, soos by die swart mans, hoër ACTH-waardes getoon as wat die geval was by Wit vroue. Assosiasies is gevind tussen middelomtrek en dubbel produk by Swart mans [Aangepas R^2 0.36; β 0.35 (0.17,0.51); p<0.001], Swart Vroue [Aangepas R^2 0.11; β 0.27 (0.06,0.48); p=0.014]; Wit mans [Aangepas R^2 0.33; β 0.52 (0.35,0.69) p<0.001]; en by Wit vroue [Aangepas R^2 0.36; β 0.37 (0.10,0.60); p=0.007]. Ná stratifisering van die deelnemers in matig en erg depressiewe (MDED) en nie-MDED groepe, is assosiasies gedemonstreer tussen DP en stil iskemie (ST) [Adj R^2 0.19; β 0.41 (0.40,0.42); P = 0.025] asook tussen ST en kortisol [Adj R^2 0.19; β 0.37 (0.25,0.48); P = 0.043] slegs by Swart mans.

Gevolgtrekking: Emosionele spanning kan outonome disfunksie of simpatiese hiperaktiwiteit in die huidige Swart manlike groep fasiliteer. Dus tydens kroniese spanning

kan kortisolvlakke dubbelproduk negatief beïnvloed. Dit kan die voorkoms van ST verhoog wat disregulering van die HPA-aksis en risiko vir kardiovaskulêre siekte verhoog. Dit dui daarop dat hoër emosionele eise 'n invloed kan hê op kardiometaboliese gesondheid waar vatbaarheid vir emosionele spanning 'n onderliggende faktor vir die waargenome verskille by die groep Swart mans kan wees.

Sleutelwoorde: Kortisol; Dubbelproduk; stil iskemiese insidente

Summary

Argument: Hypertension contributes to the development of cardiovascular diseases. Several factors contribute to the development of hypertension, such as obesity, alcohol abuse and psychological distress. Black Africans suffer from hypertension due to life-style changes or urbanisation which can possibly increase psychological distress. Chronic distress can trigger sympathetic hyperactivity to activate the hypothalamic-pituitary-adrenal axis (HPAA) stress channel which releases the stress hormone, cortisol, which can increase cardiometabolic risk during chronic conditions. Double product (DP) is ideal for measuring workload of the heart since it is the product of systolic blood pressure and heart rate which serves as an index of oxygen consumption. DP, which also incorporates heart rate, can have a stronger relation with metabolic factors where an increased heart rate can contribute to increased cardiometabolic risk during sympathetic over-activity.

Aim: We aim at assessing associations between DP, silent myocardial ischemia (ST), cortisol and Adrenocorticotropic hormone (ACTH) in different ethnic sex groups, and at assessing associations between DP, cortisol and ST during psychological distress.

Methodology: Our sub-study is founded on the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) study (2008-2009). The sample group comprised a Socio-economically matching population of 409 teachers of the Dr Kenneth Kaunda Education District in North-West Province of South Africa. Cortisone users (n=3), participants diagnosed with atrial fibrillation (n=16) and clinically diagnosed diabetes (n=12) were excluded. The final group comprised 378 individuals which consisted of 92 Black men, 94 Black women, 94 White men and 102 White women. Ambulatory blood pressure, electrocardiogram and physical activity level values were obtained during the 48-hour clinical data collection process. Fasting Blood samples were collected and included

gamma glutamyl transferase, high sensitivity C-reactive protein (CRP), cotinine, HbA1c, cortisol and corticotropin samples. Independent *t*-tests and Chi-square tests were used with a view to compare Black and White groups, followed by a covariance analyses (ANCOVA). ANCOVAs were corrected for *a priori* variables (age, waste circumference, physical activity, gamma glutamyl transferase and cotinine). Independent associations between DP, silent ischemic incidents, cortisol and cardiometabolic risk markers were determined in the total cohort as well as in moderate to severely depressive ethnic gender groups.

Results: Blacks demonstrated a poorer cardiovascular profile with higher blood pressure values, an increased heart rate, higher HbA1c levels, more ischemia as well as more low-grade inflammation (CRP > 3 mg/l) than the White gender group. Lower cortisol as well as higher ACTH values occurred in Black men than in other ethnic and gender groups. Waist circumference was lower in Black men and higher in Black women than in White men and women. Stratification on race x gender groups showed low cortisol and higher ACTH as well as more silent ischemia in Black men, but in none of the other groups. The Black women, similar to the black men, showed higher ACTH values than was the case with White women. Associations were found between waist circumference and double product in Black men [Adj R^2 0.36; β 0.35 (0.17,0.51); p<0.001], Black women [Adj R^2 0.11; β 0.27 (0.06,0.48); p=0.014]; White men [Adj R^2 0.33; β 0.52 (0.35,0.69) p<0.001]; and in White women [Adj R^2 0.36; β 0.37 (0.10,0.60); p=0.007]. Following stratification of the participants in moderate and severely depressive (MDED) and non-MDED groups, associations were demonstrated between DP and silent ischemia (ST) [Adj R^2 0.19; β 0.41 (0.40,0.42); P = 0.025] as well as between ST and cortisol [Adj R^2 0.19; β 0.37 (0.25,0.48); P = 0.043] only in Black men.

Conclusion: Emotional distress can facilitate autonomous dysfunction or sympathetic hyperactivity in the current Black male group. Hence, during chronic distress cortisol levels can influence double product negatively. It can increase the occurrence of ST, which

increases down-regulation of the HPA axis and risk for cardiovascular disease. This indicates that higher emotional demands can influence cardiometabolic health where susceptibility to emotional distress can be an underlying factor for the observed differences in the group of Black men.

Key words: Cortisol; Double product; Silent Ischemia

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Abbreviations

ABPM	Ambulatory blood pressure
ACTH	Adrenocorticotropic hormone / Corticotropin
BP	Blood pressure
CAR	Cortisol awakening response
CRH	Corticotropin-releasing hormone
CRP	High sensitivity C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DP	Double product
DSM	The Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
ESH	European Society of Hypertension
GGT / γ-GT	Gamma glutamyl transferase
GR	Glucocorticoid receptor
HbA1c	Glycated haemoglobin
HIV	Human immunodeficiency virus
HPAA	Hypothalamic-pituitary-adrenal axis
MDSD	Moderately- and severely depressed
MR	Mineralocorticoid receptor

PHQ	Patient Health Questionnaire
SABPA	Sympathetic Activity and ambulatory Blood Pressure in Africans
SANHANES	The South African National Health and Nutrition Examination Survey
SBP	Systolic blood pressure
ST	Silent ischemia

Chapter 1:

Preface

Double product and psychological distress in a bi-ethnic urban South African cohort: the SABPA study

Preface

This dissertation has been completed in fulfilment of the requirements for the degree *Master of Science in Physiology* at the Potchefstroom Campus of the North-West University and is presented in article format. The article manuscript in Chapter Three has been submitted to the peer-reviewed *Journal of Human Hypertension*, and is therefore presented in the prescribed journal format. At the end of Chapters Two, Three, and Four of this dissertation, the relevant references cited therein are indicated. The reference format throughout this dissertation is consistent with the guidelines for publishing in the afore-mentioned journal, according to the journal's bibliographic style (see *Instructions for Authors* in Chapter Three of this dissertation for further information). Skills acquired during postgraduate training are presented on page 14.

POSTGRADUATE STUDENT SKILLS 2015

STUDENT NAME:	Tick if accomplished
Optional: Clinical Pharmacology course (16 credit module)	
Optional: Honours student mentorship *(indicate number of students)*	
Ethical consent: Sub-study application under Umbrella-study	✓
Obtained and interpreted medical history & medications *Including duration of stay, education, marital status, alive family members, health (cardiometabolic, inflammation, depression, renal, arthritis, cancer, reproduction), sleep apnoea, ambulatory & dietary diary, mental stress perception*	✓
Good clinical practice: lifestyle habits; participant handling *Objective & Self-reported smoking & alcohol habits*	✓
Dietary intake and questionnaire	✓
Observed Collection of psychosocial battery measures *Measures with known heritability:* Life orientation, Personality	✓
Predictors of developing/worsening hypertension: Coping, Depression, Cognitive distress	✓
Moderating effects of the environment: Fortitude, Mental Health, Self-regulation, Job stress	✓
Observed anthropometry measurements *Height, Body mass, Waist circumference, BMI*	✓
Cardiovascular assessments, download and interpretation of data Resting Blood Pressure [*Riester CE 0124® & 1.3M TM Littman® II S.E. Stethoscope 2205*]	✓
*Finometer [*Finapres Medical Systems*®]	✓
12-lead resting ECG [*NORAV PC-ECG 1200*®] 24 ambulatory BP & -ECG [*Cardiotens® & Cardiovisions 1.19®, Meditech*]	✓
Pulse Wave Velocity and Pulse Wave Analysis [*Sphygmocor EXCEL, AtCor*]	✓
Laboratory skills (sample handling and analyses) 24h Urine/blood/saliva: **1**collection/**2**sampling/**3**aliquoting/**4**waste material	1 ✓ 2 ✓ 3 ✓ 4 ✓
Rapid tests (cholesterol, glucose, urine dipstick and blood type)	✓
Laboratory analyses of samples (ELISA, RIA, ECLIA, etc.)	✓
Whole blood HIV status *[PMC Medical, Daman, India; Pareekshak test, BHAT Bio-Tech, Bangalore, India]*	✓
Accomplished training & measuring of ultrasound Carotid Intima Media Thickness (CIMT) *[Sonosite Micromaxx®, SonoSite Inc., Bothell, WA]*	✓
Statistical analyses **1**Normal distribution & T-tests, **2**General linear models, **3**Multiple regression analyses **4**ROC analyses; **5**prospective data analyses and risk prediction	1 ✓ 2 ✓ 3 ✓ 4 ✓ 5 ✓
Publication: Preparation, submission and addressing rebuttal of manuscript to peer-reviewed journal	✓ N=1

*Including sympathetic nervous system (SNS) responses (laboratory stressors namely the cold pressor & colour-word-conflict tests)

Prof L Malan (RN, HED, PhD) Principal Investigator of the SABPA study	Dr CMC Mels (PhD Biochemistry) Manager HART Laboratory	Sr A Burger (RN, MCur) Head of the Hypertension Research and Training Clinic

Authors' contributions:

Christiaan Ernst Schutte (BSc Hons. Physiology) was responsible for the literature review, data collection and analysis from the SABPA study as well as the planning, design and interpretation of the manuscript.

Prof L Malan, as supervisor and principal investigator of the SABPA study, supervised the planning, design, data collection and -analysis, postgraduate skill development form, as well as giving recommendations regarding the writing and construction of the manuscript.

Prof NT Malan (DSc) and **Mrs M Cockeran**, as co-supervisors, provided recommendations regarding the data analyses and with the writing and construction of the manuscript.

Mr C E Schutte	Prof L Malan
Prof NT Malan	Mrs M Cockeran

Chapter 2:

Introduction and Literature study

Double product and psychological distress in a bi-ethnic urban South African cohort: the SABPA study.

Introduction

There are various factors that contribute to the risk of hypertension during chronic psychosocial stress including alcohol abuse, obesity and urbanisation.[1,2] Hypertension is a significant contributing risk factor for CVD, stroke and ischemic heart disease.[3] Ambulatory hypertension is defined by systolic blood pressure (SBP) values of ≥ 130mmHg and/or diastolic blood pressure (DBP) levels of ≥ 80mmHg (ESH).[4] The South African National Health and Nutrition Examination Survey (SANHANES) estimated that systolic hypertensive rates ranged from 19.0% to 29.4% and diastolic hypertensive rates ranged from 8.3% to 19.4% in the provincial areas of South Africa.[3]

Various risk factors contribute to the development of hypertension. These risk factors can be defined within two categories such as non-modifiable and modifiable factors.[5] Examples of non-modifiable factors are age, gender and ethnicity. With increased age the artery walls tend to become stiffer resulting in a decrease in compliance and an increase in blood pressure.[6] Gender also influences hypertension as it is observed that men usually have higher blood pressure than do pre-menopausal women of the same age. The blood pressure of pre-menopausal women tends to be lower than that of post-menopausal women. Furthermore, the blood pressure of postmenopausal women may even rise to levels exceeding that of their male counterparts. This is normally attributed to attenuated postmenopausal estradiol and increased androgen levels in postmenopausal women.[7] Ethnicity also plays a role in hypertensive risk, not necessarily genetically but rather through biosocial factors such as alcohol consumption, smoking and obesity.[8] A recent study explained the differences in sub-clinical vascular disease between Africans and Caucasians in South Africa (hereafter referred to as Blacks and Whites). An excess burden of sub-clinical vascular disease development in urban Blacks compared to urban Whites was observed which was largely explained by health behavioural

and conventional risk factors.[9] Health behavioural factors may be influenced by urbanisation and subsequent psychological distress.

2.1 Urbanisation and psychological distress

Psychological distress and hypertension risk has been associated with urbanisation and disruption of cultural identity. Urbanisation as a global trend has doubled in developing countries from 18% to 40% between the year 1950 and 2000.[10] Urbanisation in Africa is high with an estimated level of 64% by 2050 where it seems that Africa's urbanisation is demographically and not socio-economically driven. Africa's urbanisation is uneven across various sub-regions with Southern Africa at the highest. In urban-dwelling citizens hypertension levels is increasing rapidly whereas psychological distress and other lifestyle factors contribute toward this trend.[2,9] It has been observed that urban Blacks have increased levels of hypertension of 25% compared to 9% for those of rural Blacks.[8] Lifestyle changes such as psychological distress contribute significantly towards the increased risk of developing CVD. Psychological or emotional distress has been related to hypertension, coronary heart disease, left ventricular wall remodelling and stroke.[12,13] Taking ethnic groups into consideration, an individualistic urban environment may contribute to chronic stress in Blacks where it has been observed that the driving force for early sub-clinical vascular changes[11,14] can be coping disability which facilitates autonomic dysfunction. When looking at the SABPA study, previous results revealed overall poorer cardiovascular health in Blacks.[15-17] One of the reasons for the poorer health could be explained by the impact of stress as stress impacts physiological functioning but the severity partly depends on coping style applied for managing psychosocial stress such as the fight or flight defensive coping response. Blacks may experience the individualistic urban environment as too demanding and may experience a loss of control. Defensive coping in Blacks enhanced renovascular risk, especially in those with lower cortisol levels and possible HPA axis dysregulation.

Batty 2014 stated that the presence of emotional distress may increase CVD risk.[14] Long-term psychological distress may have a stronger association with atherosclerosis than short-term distress.[12] It is suggested that the increased risk is not only as a result of an unhealthy lifestyle, but may also be attributed by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.[12]

2.2 HPA axis

A major pathway in regulating the stress response is the HPA axis. Psychological distress is a reliable trigger of the HPA axis which induces corticotropin-releasing hormone (CRH) secretion when triggered.[19] This leads to the release of adrenocorticotropic hormone (ACTH) which stimulates the synthesis and secretion of glucocorticoids with cortisol as the end product in the stress response.[20] As cortisol follows a circadian cycle, sampling times to avoid the cortisol awakening response (CAR) have considerable clinical significance. The CAR is the change in cortisol levels 20-45 minutes after waking up in the morning.[21]

There are three systems involved in the homeostasis of the stress response. The first two, namely the suprachiasmatic and the hypothalamic paraventricular nuclei, allow for diverse defensive stress responses such as physical or emotional stress.[22] The third mechanism involves a feedback inhibition, as seen in figure 1, to prevent toxic glucocorticoid levels where the inhibition revolves around the down-regulation of CRH and ACTH and which may occur during chronic emotional distress.[23,24]

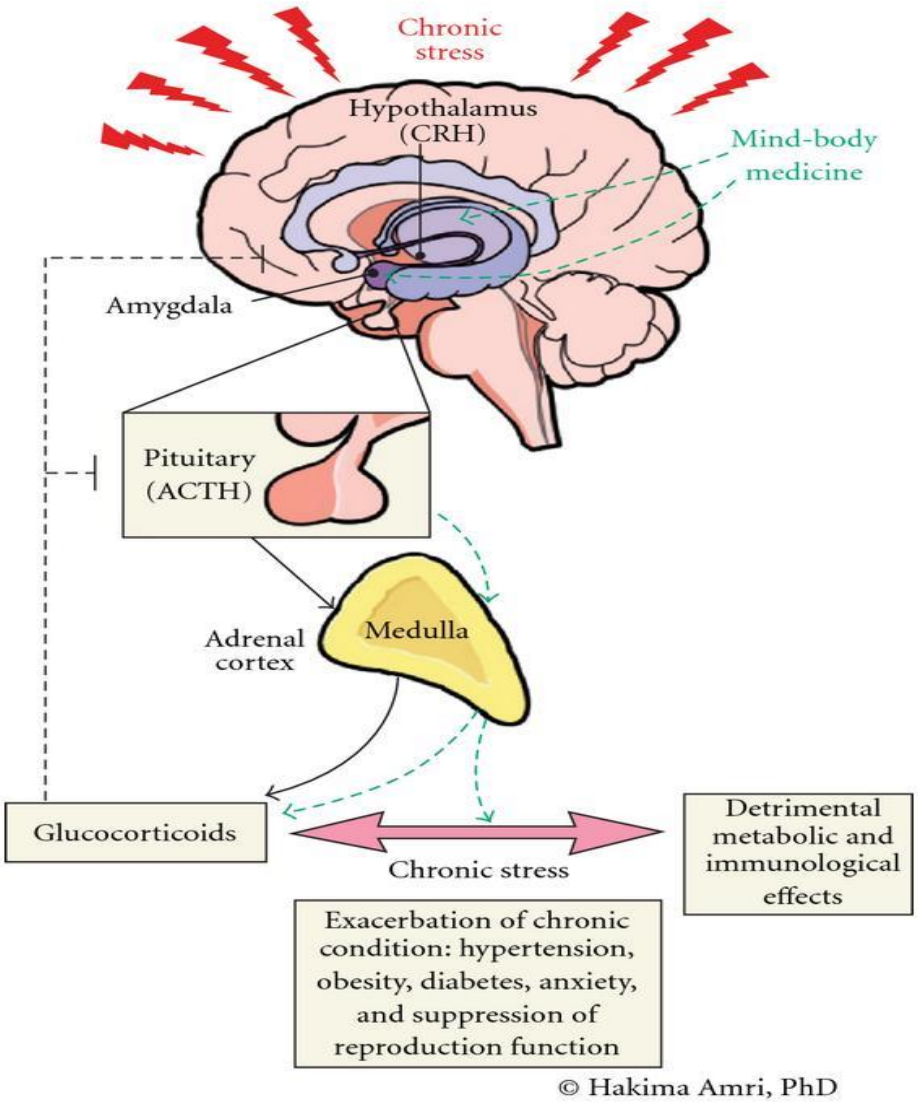

Figure 1: Schematic representation of the regulation of the HPA axis under chronic stress. Excerpt adapted from Smith & Vale.[25]

Prolonged exposure to a taxing emotional stress environment, such as an urban-dwelling lifestyle, disrupts homeostasis by increasing the physiological stress response. Thus maintaining normal levels is difficult, which may lead to the experience of chronic stress.[26] Chronic stress triggers sympathetic hyperactivity which increases the release of catecholamine and subsequently increases cardiometabolic risk.[13,27] Blacks have a preference for a collectivistic cultural environment and when exposed to an individualistic environment the lack of anticipated support may exacerbate their stress levels.[28] It may further imply the

cumulative effects of stress that may result in higher allostatic load and may eventually increase cardiovascular disease.[29]

Therefore an individualistic urban environment might contribute to chronic stress in Blacks where defensive responses facilitate autonomic dysfunction which acts as a hyperkinetic driving force for early sub-clinical vascular changes.[11,30] Dysregulation of the HPA axis may be a result of unmitigated increases in cortisol.[13] Increased activation of the HPA axis in response to stress has been associated with subclinical atherosclerosis.[12] However, little is known about glucocorticoids' molecular mechanisms involved in structural remodelling during chronic stress.[23]

A large response towards challenges in normotensive individuals increases the risk of developing hypertension.[31] Findings by Malan et al. support this notion as it was demonstrated that an individuals' coping style may increase the risk of hypertension as defensive coping responses demonstrated pathology in Black men.[27] In a Black male cohort with depressive symptoms, it was revealed that blunted neuroendocrine responses were associated with electro-cardiogram (ECG) left ventricular hypertrophy.[13]

2.3 Cortisol

Cortisol is associated with central abdominal obesity as cortisol increases central abdominal fat deposition. It was suggested that waist circumference may thus be a more effective predictor of CVD when psychological distress is present.[32] Cortisol may exert hypertensive effects in the cardiovascular system through various mechanisms. Cushing's syndrome is a disease characterized by a hypercorticoid state with hypertension as a distinguished feature of this syndrome.[22] The various pathophysiologic mechanisms of cortisol contribute to the increased prevalence of hypertension in Cushing's syndrome. According to Magiakou et al.[33] the corticosteroid mechanisms involved enhance the inotropic and pressor activity of

vasoactive substances as well as suppress the vasodilatory system.[33] Even though the mentioned features are part of Cushing's syndrome it highlights the role of excess mineralocorticoid and glucocorticoids in pathophysiologic conditions. Meyburg et al.[34] revealed that hypertensives have a more reactive cardiovascular system with enhanced HPA axis activity and enhanced salivary cortisol levels when stressed. Within the heart no specific glucocorticoid-mediated effects have been demonstrated even though corticosteroids are involved in cardiac remodelling.[21] Conversely during acute stress cortisol-induced hypertension has been associated with an increased cardiac output which further increases blood pressure. Large blood pressure changes in response to stress can predict hypertension.[35] Ultimately it may reflect increases in total peripheral resistance as a response to the increased cardiac output.[35] Additionally, mineralocorticoid-based hypertension increases extracellular fluid by increasing sodium and water retention which can ultimately lead to secondary hypertension.[23,36]

The mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) respectively are the two identified corticosteroid receptors. These receptors are sensitive to different levels of cortisol where GR appears to produce its effects during times of stress and MR functions mainly during the circadian cycle.[22] Corticosteroids critically impact vascular tone where depletion results in hypotension as observed in Addison's disease.[23] It was shown that glucocorticoids augment aortic contraction in response to catecholamines and angiotensin II but the role of the receptors are unknown. GR and MR receptors are also present within the heart. No specific effect on blood pressure regulation has been identified but inappropriate activation of the MR by aldosterone may lead to hypertrophy and fibrosis.[23]

It is clear that the glucocorticoids induce changes such as increases in cardiac output, total peripheral resistance and renovascular resistance.[37] The increase in blood pressure and heart rate may enhance ischemic events because of a decrease in coronary blood supply. This

happens during chronic activation of the HPA axis and emotional distress.[38] During chronic stress, downregulation of GR and MR may take place which reduces negative feedback to the HPA system. This in turn may result in increased cortisol levels as well as increased inflammatory effects of glucocorticoids. Both of these instances have been reported within patients suffering from depression.[39]

2.4 Depression

The aetiology of depression may involve the dysregulation of various biological systems. With this in mind depression is multifactorial in its origin and has been associated inflammation, hypo- and hypercortisolemia, dysregulation of the HPA axis as well as diabetes and CVD.[36] Melancholic depression has been associated with hypercortisolism whereas hypocortisolism has been associated with atypical depression.[39] When looking at stress-related psychopathology, depression can develop as a result of chronic stress.[39,40] Limited evidence suggests that GR down-regulation may predispose individuals to develop depression during chronic stress.[40] It has been stated that HPA axis dysregulation could act as a marker for stress-related psychiatric conditions.[36,39-40] Depression is a risk factor for cardiovascular events where it can predict higher mortality and morbidity within patients suffering from CVD. However, the causality between CVD and depression is still unclear.[40-41] Depressive patients often display increased inflammation levels, increased cortisol and higher sympathetic tone, since as all of the physiological changes increase CVD risk.[36,40-41] It is also apparent that CVD can lead to the development of depression which suggests that other underlying pathologies may contribute to the development of both pathologies.[41]

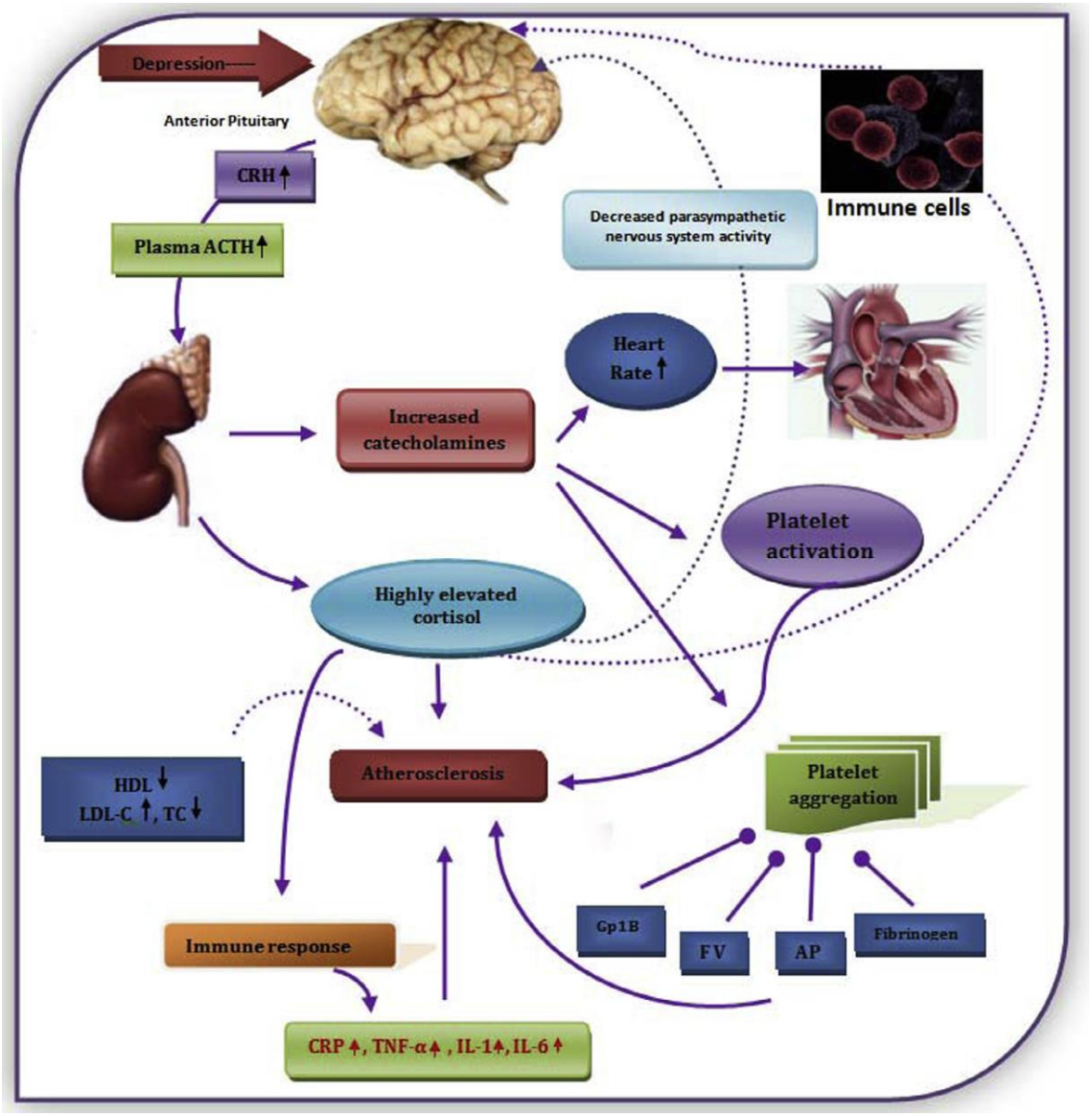

Figure 2. The pathway depicting the influence of depression on diabetes-CVD. Excerpt adapted from Suarez, Sundy & Alaattin Erkanli.[41]

When depression is present, the physiological stress response is activated to release catecholamines and cortisol.[41] The increased levels of stress hormones elevates the heart rate as well as influences the immune response, which has adverse side effects. The increased levels can thus lead to increased cardiometabolic risk.[39-41]

2.5 Cardiovascular risk: cortisol, double product and silent ischemia

Double product is the product of systolic blood pressure and heart rate which acts as an index of the oxygen consumption and work load of the heart.[31,43] An increased heart rate during sympathetic over-activity can therefore contribute to left ventricular hypertrophy.[43] Double product incorporating heart rate relates more broadly to metabolic factors and perhaps central nervous system influences.[19,43] The central influence may be exacerbated by the increased sympathetic activity during psychological distress.[20]

Cortisol is known as an anticipation stress marker and therefore as psychological distress marker may increase double product and the load on the heart through an increased heart rate which in turn may contribute to CVD progression.[43-44] An urban lifestyle is taxing and the high demands may increase progression of chronic psychosocial distress and hypertension.[2,34]

When looking at silent myocardial ischemia, otherwise known as ST-segment depression during ECG monitoring (ST), within CVD 70-80% of ST episodes are silent with very little symptoms such as angina or other associated ST symptoms.[45-50] ST occurs in about 25% to 50% of patients with coronary artery disease (CAD)[51] and has been associated with atherosclerosis, especially in Black men.[9,52] Thus ST, as an independent predictor, can possibly help to ultimately reduce the burden and mortality of CAD.[52-55] ST can also possibly be identified in early stage CAD through high sensitive troponin (Hs-Trop T) and NT-proBNP as biochemical markers for ST.[56] The importance of ST is that it has good predictive value for CVD risk.[45]

It has been observed that chronic distress can possibly increase ST.[57] Furthermore it has been stated that patients with depressive and anxiety symptoms more often had ST during daily life than non-depressive patients.[40] This can be supported, since the presence of depression and elevated NT-proBNP were identified as independent risk markers in patients with heart failure.[58]

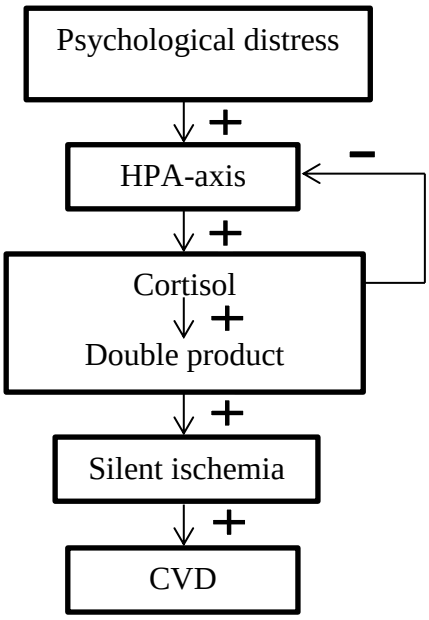

Figure 3: The proposed mechanism of downregulation and cortisol/double product's cardiovascular effects.

The relation between psychological distress (cortisol) and double product has not been investigated in a sub-Saharan Black cohort and investigating it may be beneficial as it contributes to the understanding of the high prevalence of hypertension and structural wall remodelling in a bi-ethnic sex cohort from South Africa.

Research questions

Is cortisol or ACTH associated with double product and silent ischemia in a bi-ethnic sex cohort?

Is double product associated with increased cortisol activity, ACTH and psychological distress in a bi-ethnic sex cohort?

Objectives

Our objective is to assess associations between double product (DP), silent myocardial ischemia (ST), cortisol and ACTH in different ethnic sex-groups, as well as to assess associations between DP, ST and cortisol during psychological distress.

Hypotheses

Positive associations will be present between DP, ST and cortisol in Black men and women.

Associations will be present between DP, ST and cortisol during psychological distress, especially in Black men and women.

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Chapter 3:

Double product and psychological distress in a bi-ethnic urban South African cohort: the SABPA study.

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Title: Double product and cortisol may induce lower myocardial oxygen supply when emotionally distressed: The SABPA Study

Running Title: Double product and psychological distress

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Abstract

Psychological or emotional distress has been associated with hypertension in urban-dwelling Blacks. Cortisol as marker of emotional distress may also increase hypertension risk. Our objectives were to assess associations between double product (DP), silent ischemia (ST), psychological distress (Patient Health Questionnaire-9, PHQ-9 ≥ 10), adrenocorticotropic hormone (ACTH) and cortisol. A cross sectional study within a bi-ethnic sex cohort (N=378), aged 44.7 ± 9.52 was conducted under well-controlled conditions. DP (systolic blood pressure x heart rate), -ECG, fasting ACTH, cortisol and other cardiometabolic risk markers were determined. The Black gender group, but mostly men, demonstrated higher DP, ST, more depressive symptoms (PHQ-9), decreased cortisol, pre-diabetes (glycated haemoglobin > 5.7 %) and low grade inflammation (C-reactive protein, CRP > 3 mg/l) as opposed to that of White gender groups. After stratification of participants into moderately to severely depressed groups (PHQ-9 ≥ 10), associations were found between dependent variables ST and DP [Adj. R^2 0.19; β 0.41 (0.40,0.42); P = 0.025] as well as cortisol [Adj. R^2 0.19; β 0.37 (0.25,0.48); P = 0.043] in Black men only. Central obesity was related to blood pressure (BP) in the total bi-ethnic sex cohort. However, in a Black male cohort only, a combination of cortisol and accompanying central obesity suggests possible dysregulation of the HPA axis indicative of emotional distress. Their cortisol values suggests lower myocardial oxygen when emotionally distressed and underscored the notion of compensatory increases in double product to increase oxygen supply to the heart.

Key words: Cortisol; Double product; Cardiovascular disease (CVD); Silent ischemia (ST)

Introduction

A significant contributing risk factor for cardiovascular disease (CVD), stroke and ischemic heart disease, is hypertension.[1] There are various factors that contribute to the risk of hypertension during chronic psychosocial stress including alcohol abuse, obesity, changes in dietary habits and acculturation during urbanisation.[2,3]

Psychological or emotional distress is associated with hypertension, coronary heart disease, left ventricular wall remodelling and stroke.[4,5] Batty 2014 stated that the presence of emotional distress may increase the risk of these conditions.[6] Long-term psychological distress may have a stronger association with atherosclerosis compared to short-term distress.[4] It is suggested that the increased risk is not only as a result of an unhealthy lifestyle but may also be attributed by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.[4]

A major pathway in regulating the stress response is the HPA axis. During the stress response, corticotrophin-releasing hormone (CRH) is secreted, which induces the release of corticotrophin. Corticotrophin stimulates the synthesis and secretion of glucocorticoids with cortisol as the end product.[7] Cortisol may exert hypertensive effects in the cardiovascular system through various mechanisms such as supressing the vasodilatory system or increasing the cardiac output.[3] Prolonged exposure to a taxing emotional stress environment, such as an urban-dwelling lifestyle, disrupts homeostasis, and the maintenance of normal cortisol levels becomes more difficult which may lead to the experience of chronic stress.[7] Chronic stress triggers sympathetic hyperactivity, which in turn increases the release of catecholamine and subsequently increases cardiometabolic risk.[5,9] Acute stress cortisol-induced hypertension has been associated with an increased cardiac output, which further increases blood pressure.[10] Furthermore, increased plasma levels of cortisol are positively associated with systolic blood pressure and may thus have an impact on double product.[11]

Double product (DP) is the product of systolic blood pressure and heart rate which acts as an index of the oxygen consumption and work load of the heart.[10,12] An increased heart rate during sympathetic over-activity or emotional distress can therefore contribute to left ventricular hypertrophy.[5,9] DP incorporating heart rate relates more broadly to metabolic factors and perhaps central nervous system influences.[13]

Cortisol is known as an anticipation stress marker[14] and may therefore, as psychological distress marker, increase DP and load on the heart through an increased heart rate which in turn may contribute to CVD progression. An urban lifestyle is taxing and higher demands may increase progression of chronic psychosocial distress and hypertension.[15] The relation between ambulatory DP, silent ischemia and psychological distress (cortisol and ACTH) has not been investigated in a sub-Saharan African cohort and such an investigation may be beneficial as it contributes to the understanding of the high prevalence of hypertension and structural wall remodelling in a bi-ethnic sex cohort from South Africa.

Methods

Our sub-study is nested in the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study (2008-2009), as described elsewhere.[16] A socio-economically similar population, despite cultural differences, were chosen with a total population consisting of 409 teachers from the Dr Kenneth Kaunda Education District, South Africa.

Exclusion criteria included tympanum temperature above 37.5 ◦C, the use of anti-depressants, α- and β-blockers and blood donors or individuals vaccinated 3 months prior to data collection. Additionally, we excluded cortisone users (n=3), participants diagnosed with atrial fibrillation (n=16) and clinically diagnosed diabetes (n=12). The final sample comprised 378 individuals. Participants were fully informed of the study procedure and signed an informed consent. The study was approved by the Ethics Review Board of the North-West University (NWU-00036-07-A6).

Cardiovascular measurements

Ambulatory blood pressure (ABPM)-, electrocardiogram- (Cardiotens CE120®, Meditech, Budapest, Hungary) and accelerometer measures were obtained (Actical®, Mini Mitter, Montreal, Quebec) during the 48 hour data clinical collection process. Participants were requested to record any abnormalities on a 24h diary card, for instance experiencing nausea, feeling stressed or having a headache. A blood pressure apparatus with an appropriately sized cuff was fitted on their non-dominant side before 09:00 in the morning at school. Blood pressure measures were obtained every 30 minutes during the day (08:00-22:00) and hourly during the night (22:00-06:00). Silent ischemia (ST) was assessed by two-channel ECG recordings (Cardiotens CE120®) for 20 seconds at 5 minute intervals. An ischemic event was recorded according to the following criteria: horizontal or descending ST-segment depression by 1 mm; duration of the ST-segment episode lasting 1 minute, and a 1-minute interval from the preceding episode. The ABPM data were analysed using the CardioVisions 1.19 Personal Edition software (Meditech).

At 16:30 on the first day, participants were transported to the North-West University's Metabolic Unit Research Facility where they were introduced to the experimental procedures. A registered clinical psychologist facilitated the process where participants completed psychosocial questionnaires in a comfortable and relaxing environment. Participants received a standardised dinner and were advised to go to bed at 22:00 and to fast overnight. Participants were woken at 05:45 the next morning and devices were removed after the last ABPM recording at 06:00. Anthropometric measurements and fasting blood samples followed.

Lifestyle confounders

The Actical® accelerometer measured physical activity for 24 hours considering resting metabolic rate. Gamma glutamyl transferase (γ-GT) and cotinine levels were used to assess alcohol and smoking habits. Anthropometric measurements were done in triplicate by level 2 accredited anthropometrists using calibrated instruments (Precision health scale, A & D Company, Tokyo, Japan; Invicta Stadiometer IP 1465, Invicta, London, UK). A mean of 3 waist circumferences were taken. The waist circumference was measured at the midpoint between the lower costal border and the iliac crest perpendicular to the long axis of the trunk. Intra- and inter-observer variability was less than 10%.

Depressive symptoms

Depressive symptoms were assessed using the 9-item self-administered Patient Health Questionnaire (PHQ-9)[17] which has been validated in various ethnic groups including sub-Saharan Africans.[18] The questionnaire is designed for use in primary health care settings adapting diagnostic criteria from the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). Each item of the PHQ-9 evaluates the presence of one of the nine DSM-IV criteria of major depression. In the current study, the Cronbach alpha-reliability index for the total PHQ-9 score was 0.81. Items on the questionnaire are scored to reflect the frequency of symptom occurrence during the prior two weeks on a scale of zero to three, with zero reflecting "not at all" and three "nearly every day". We used the recommended and established PHQ-9 cut-off point of >10 indicating the presence of moderate to severe depressive symptoms.[17-18]

Biochemical analyses

Fasting blood samples were obtained from the ante-brachial vein branches with a winged infusion set using standardised protocol and stored at -80°C until batch assay. Sequential

multiple analysers analysed serum gamma glutamyl transferase (GGT), high sensitivity C-reactive protein (CRP), cotinine and HbA1c (glycated haemoglobin) (Konelab 20i; Thermo Scientific, Vantaa, Finland; Unicel DXC 800- Beckman and Coulter®, Germany and the Integra 400, Roche, Switzerland respectively). To avoid the cortisol awakening response, (CAR) serum cortisol samples were obtained before 09:00 and analysed with ECLIA on Elecsys 2010, Roche. ACTH sampling analyses were obtained by Electrochemiluminescence immunoassay (ECLIA), e411 (Roche, Basel, Switzerland). Inter- and intra-batch variability was 5.4 % and 2.9% respectively.

Statistical analysis

Statsoft (Statistica V.12) was used to do data analysis. Normality of data was ascertained with Shapiro Wilks. Baseline characteristics were calculated with independent *t*-tests. Chi-square (X^2) tests computed proportions and prevalence. General linear models determined main effects interaction (ethnic x sex) for cardiometabolic risk markers, independent of *a priori* confounders (age, waist circumference, log physical activity, log cotinine and log γ-GT). General linear models compared bi-ethnic groups adjusted for *a priori* confounders. Multiple linear regression analyses determined associations between the dependent markers, double product, silent ischemia and independent markers (cortisol, ACTH, waist circumference, depressive symptoms and *a priori* confounders) in the separate ethnic groups. Similar linear regression analyses were repeated in ethnic groups after having been stratified into moderately and severely depressed (MDSD) and low depressed groups (PHQ-9 $\geq$ 10 and < 10).

Sensitivity analyses: Linear regression analyses were repeated after excluding HIV positive status and hypertensive participants. Significant values were noted as $p \leq 0.05$.

Results

In Table 1, the Blacks displayed more depressive symptoms, higher DP, BP and heart rate, HbA1c, silent ischemia and low grade inflammation (CRP > 3 mg/l) compared to White sex groups.

General linear models differences were observed for cortisol ($F_{1,377}$ = 7.20-6.25, p < 0·013) as well as ACTH ($F_{1,364}$ = 19.34-19.08, p <0.001) between ethnic and sex groups. Whereas differences for waist circumference ($F_{1,366}$ = 4.94, p <0.001) were only observed between sex groups.

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

Variables	**Black (N = 192)**	**White (N = 198)**	**P values**
Confounders			
Age, (years)	44.0 ± 8.13	45.15 ± 10.83	0.330
Waist circumference, (m^2)	93.15 ± 15.86	93.11 ± 16.29	0.982
Physical activity, (kcal/day)	2679.09 ± 800.03	3129.85 ± 1632.16	<0.001
Cotinine, (ng/ml)	27.95 ± 62.00	20.44 ± 72.15	0.273
γ-Gluthamyl transferase, (u/l)	66.70 ± 83.86	27.06 ± 34.77	<0.001
Potential stress markers			
Cortisol (nmol/l)	359.13 ± 151.53	385.77 ± 161.46	0.094
ACTH (pg/ml)	21.39 ± 14.09	15.92 ± 9.71	<0.001
Depressive symptoms	9.20 ± 5.40	5.58 ± 4.71	<0.001
Cardiovascular measures			
C-reactive protein, (mg/l)	8.47 ± 10.54	3.14 ± 3.94	<0.001
Cholesterol, (mmol/l)	4.60 ± 1.16	5.54 ± 1.26	<0.001
HbA1c (%)	6.08 ± 1.22	5.51 ± 0.42	<0.001
24h SBP, (mmHg)	133 ± 16.03	124 ± 12.09	<0.001
24h DBP, (mmHg)	83 ± 10.73	77 ± 8.15	<0.001
Heart Rate (bpm)	80 ± 10.70	74 ± 9.99	<0.001
Silent ischemic events (N)	6.12 ± 15.74	2.60 ± 6.08	0.003
Double product (mm Hg*b/min)	10596.6 ± 2083.5	9158.8 ± 1738.9	<0.001

Hypertension, N (%)	43 (22.4)	18 (9.1)	<0.001
Medications			
Hypertensive treatment, N (%)	69 (35.9)	27 (13.6)	<0.001
Statins, N (%)	2 (1.04)	9 (4.55)	0.05

Abbreviations: DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; 24h Hypertension (SBP ≥ 130 mm Hg and/or DBP ≥ 80 mm Hg; TEE, total energy expenditure. Values presented as arithmetic mean ± SD; *-values, presented as number of observations, n, and percentage of total group, (%).

In Figure 1 and 2, stratification into ethnic x sex groups showed low cortisol accompanied by higher ACTH and more ST events in Black men only. The Black women revealed a similar endocrine pattern as observed in Black men regarding ACTH.

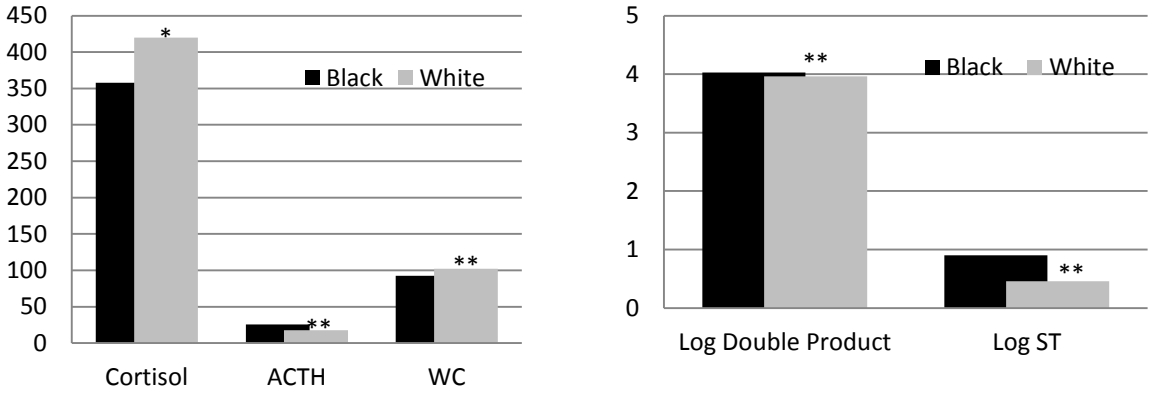

Figure 1: Cardiometabolic markers in ethnic x male status

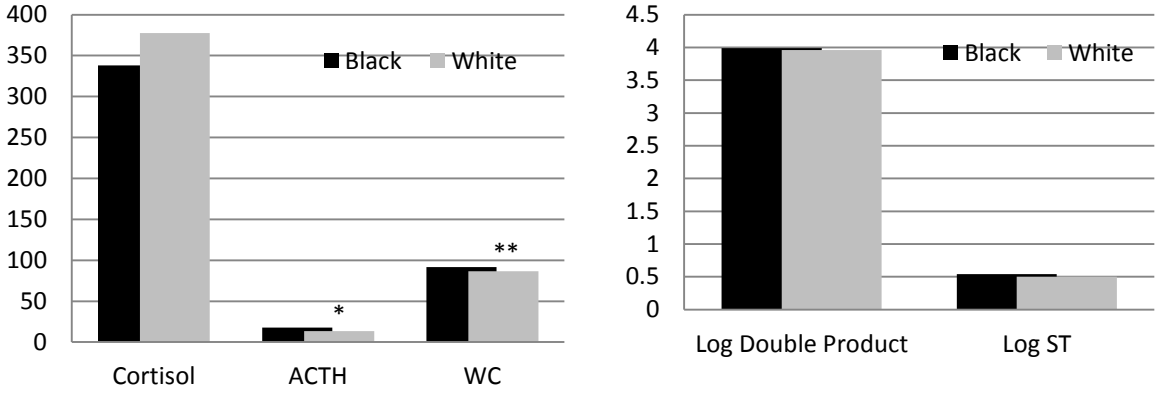

Figure 2: Cardiometabolic markers in ethnic x women status

Abbreviations: Adrenocorticotropic hormone (ACTH), silent ischemia (ST), waist circumference (WC)
Superscript symbol denotes significance for: *$p \leq 0.05$; **$p \leq 0.01$.

In Table 2, Black men revealed a poorer cardiometabolic profile with higher blood pressure values, more ST and higher DP values. Furthermore Black men displayed more depressive symptoms with higher ACTH levels accompanied by lower cortisol levels than their White counterparts. Black and White women displayed a similar profile when compared to their male counterparts.

Table 2: Cardiometabolic risk markers risk in Black vs. White sex groups.

	Black men (N = 92)	White men (N = 94)	Black women (N = 90)	White women (N = 102)
Unadjusted cardiometabolic markers				
γ-Glutamyl transferase (U/l)	84.83 (70.1,99.5)	34.83 (20.2,49.4)**	46.9 (35.9,57.9)	19.9 (9.6,30.2)**
Cholesterol (mmol/l)	4.55 (4.29,4.81)	5.66 (5.39,5.93)**	4.33 (4.04,4.62)	5.73 (5.47,6.0)**
C-reactive protein (mg/l)	5.93 (4.6,7.2)	1.71 (0.4,3)**	11.14 (9.4,12.8)	4.41 (2.8,6)**
HbA1c (%)	6.27 (6.05,6.5)	5.62 (5.39,5.8)**	5.86 (5.7,6.1)	5.39 (5.2,5.6)**
Adjusted cardiometabolic risk markers				
24h SBP (mmHg)	138 (136,142)	126 (123,129)**	128 (125,130)	121 (119,124)**
24h DBP (mmHg)	87 (86,90)	79 (77,81)**	78 (76,80)	74 (73,76)**
24h Heart rate (bpm)	78 (76,81)	73 (71,76)**	78 (76,80)	76 (74,78)**
Cornell product (mV.ms)	84.09 (74.06,94.1)	64.36 (54.54,74.2)*	56.79 (50.66,62.9)	35.95 (30.23,41.7)
Silent ischemic events, score	10 (6.24,13.53)	2 (0.0,5.27)**	3 (1.88,4.51)	3 (1.48,3.88)
Cortisol (nmol/l)	357.67 (325.79, 389.55)	419.67 (386.92, 452.42)*	338.01 (297.44,378.58)	377.39 (340.25,414.52)
ACTH (pg/ml)	25.85 (22.62,29.08)	17.74 (14.55,20.93)**	17.81 (15.55,20.07)	13.49 (11.44,15.54)*
Depressive symptoms	8.42 (7.25,9.59)	4.55 (3.39,5.70)**	9.51 (8.32,10.71)	7.03 (5.95,8.11)**
Double product (mmHg.b/min)	10894.47 (10475.61,11313.33)	9293.51 (8863.28,9723.74)**	9997.84 (9611.23,10384.45)	9303.06 (8949.19,9656.93)

Abbreviations: HbA1c, glycated haemoglobin. Adjusted for age, log cotinine, log gamma gluthamyl transferase, log physical activity and waist circumference. Values depicted as mean (95% confidence interval) and proportions as N (%). Superscript symbol denotes significance for: *$p \leq 0.05$; **$p \leq 0.01$.

In Table 3.1, multivariate linear regressions revealed a positive association between DP and cortisol, as well as between ST and cortisol, in Black men only. Positive associations were also found between DP and waist circumference in all ethnic sex groups, i.e. in Black men [Adj R^2 0.36; β 0.35 (0.17,0.51); P < 0.01], in Black women [Adj R^2 0.11; β 0.27 (0.06,0.48); P = 0.014], in White men [Adj R^2 0.33; β 0.52 (0.35,0.69); P < 0.01] and in White women [Adj R^2 0.37; β 0.35 (0.10,0.60); P = 0.007].

After stratification of participants into moderate to severely depressed (PHQ-9 ≥ 10) and (< 10 PHQ-9) we repeated our findings in Black men where associations between ST and double product [Adj R^2 0.19; β 0.41 (0.40,0.42); P = 0.025] as well as between ST and cortisol [Adj R^2 0.19; β 0.37 (0.25,0.48); P = 0.043] existed displayed in Table 3.2.

Sensitivity analyses after excluding HIV positive status and hypertensive participants and using body surface area instead of waist circumference did not change the main outcomes.

Table 3.1: Independent associations between double product, silent ischemia and cardiometabolic risk markers in Black and White sex groups (N = 378).

	Black Men		Black Women	
	Double Product	Silent ischemia	Double Product	Silent ischemia
Adjusted R^2	0.36	0.12	0.11	
β (95% CI)				
Cortisol	0.24 (0.07,0.41) P = 0.007	0.20 (0.01,0.39) P = 0.046	-	-
ACTH	-	-	-0.19 (-0.39,0.01) P = 0.074	-
Waist circumference	0.35 (0.17,0.51) P < 0.001	-	0.27 (0.06,0.48) P = 0.014	-

	White Men		White Women	
	Double Product	Silent ischemia	Double Product	Silent ischemia
Adjusted R^2	0.33	-	0.37	-
β (95% CI)		-		-
Waist circumference	0.52 (0.35,0.69) P < 0.001	-	0.35 (0.10,0.60) P = 0.007	-

F to enter=2.5. Co-variates included were: age, Total Energy Expenditure, Cotinine levels and Gamma glutamyl transferase.

Table 3.2 Independent associations between Silent Ischemia, double product and cortisol in moderately to severely depressed Black men (N = 29).

	Black men
	Silent Ischemia
Adjusted R^2	0.19
β (95% CI)	
Double Product	0.41 (0.40,0.42) P = 0.025
Cortisol	0.37 (0.25,0.48) P = 0.043

F to enter=2.5. Co-variates included were: age, waist circumference, log total energy expenditure, log cotinine levels and log gamma glutamyl transferase.

Discussion

We aimed at assessing associations between double product (DP), silent myocardial ischemia (ST), cortisol and ACTH in different ethnic sex-groups and at assessing associations between DP, ST and cortisol during psychological stress. Black men had attenuated cortisol and accompanying central obesity, exceeding ethnic-specific cut-off points which may suggest possible dysregulation of the HPA axis indicative of emotional distress.[19] Their cortisol values was associated with a lack of myocardial oxygen supply when emotionally distressed and underscores the notion of compensatory increases in double product to increase oxygen supply to the heart.

Chronic distress may be evident when viewing the lower cortisol levels and higher ACTH levels in the current Black cohort. Higher levels of cortisol would have been expected as elevated cortisol levels have been associated with psychological distress.[4,6] During chronic exposure to demanding situations, regulatory feedback down-regulation between the HPA-axis as well as inflammatory system, where cortisol is involved, is evident.[20] It might explain their lower cortisol levels than those of White men. However, it is an observational study and down-regulation has to be confirmed. The loss of downstream signalling may occur at receptor level which reduces negative feedback mechanisms; thus exacerbating the dysregulation of the HPA-axis.[20] This may indicate that the possibility of cortisol down-regulation has occurred as chronic psychological distress induces sympathetic hyperactivity which leads to increased catecholamine and cortisol secretion.[21-22] This may ultimately lead to induced down-regulation of cortisol and thus support the significantly lower levels in our Black men.[4,5,9]

It has been suggested that abdominal or central obesity acts as a stronger marker when cortisol or psychological distress is evident.[23] Our findings in both male and female cohorts support this notion, as waist circumference showed stronger associations with

cardiometabolic risk markers such as increased ST and DP than did body surface area. Cortisol as emotional distress marker may thus drive the higher DP in the Black men and culminate in central obesity in this bi-ethnic sex cohort. Indeed, in the depressed SABPA Black male cohort Mashele et al. revealed blunted cortisol and norepinephrine metabolite responses associated with structural wall remodelling.[5] This may support our findings as independent associations were shown between ST, cortisol and DP in the moderately severely depressed Black men. Increased DP responses may be compensatory to alleviate the vasoconstrictive effects of cortisol and prevalence of silent ischemia. It was also shown that DP values may be increased in chronic distress as sympathetic hyperactivity eliciting increased nor-epinephrine and cortisol responses stimulate vasoconstrictive responses.[5,24] Therefore elevated DP within depressed Black men may indicate progression of LVH via reduced coronary artery perfusion. The associations between silent ischemia and cortisol may thus impair autoregulation which can further support the compensatory increases in DP to maintain homeostasis.[3,25] Therefore the increased DP responses may alleviate the vasoconstrictive effects of cortisol and prevalence of silent ischemia. Other findings support a coping disability due to higher susceptibility to emotional distress which facilitated autonomic dysfunction or sympathetic hyperactivity in the current Black male cohort.[26] Thus, during chronic distress and dysregulation of the HPA-axis can lead to maladapted cortisol levels and more ST events. DP increases may act as a compensatory mechanism to upregulate myocardial oxygen supply in maintaining homeostasis. This suggests that higher emotional demands may impact on cardiometabolic health, as susceptibility to emotional distress may be an underlying factor for the observed differences in the bi-ethnic sex cohort.

Limitations

The nature of this study can be seen as a limitation seeing that the participants are from a specific environment and may not be fully representative of the entire Sub-Saharan African community.

Furthermore, obtaining serum cortisol can be experienced as a stressor, which can negatively impact the results. The Cardiotens ® ambulatory blood pressure measurement device can also be experienced as a stressor, which will impact ambulatory blood pressure readings.

To conclude, central obesity may impact on BP in a bi-ethnic sex cohort. However, a combination of attenuated cortisol and accompanying central obesity suggests possible dysregulation of the HPA axis indicative of emotional distress in a Black male cohort. Their lower cortisol values predicted lower myocardial oxygen when emotionally distressed and underscored the notion of compensatory increases in double product to increase oxygen supply to the heart.

What is known:	What is new:
• Cortisol plays a significant role in chronic distress. • Double product's prognostic value is unknown but acts as an index of myocardial oxygen consumption.	• Cortisol and accompanying central obesity suggest possible dysregulation of the HPA axis indicative of emotional distress in Black men. • Ambulatory double product was related to central obesity in a bi-ethnic sex cohort. • Both ambulatory double product and cortisol predicted lack of myocardial oxygen supply in emotional distressed Black men.

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Chapter 4:

Introduction

The following chapter is to summarize chapter 3 with a brief discussion of the aim, results and conclusion. Also in this chapter are the limitations and recommendations for future research regarding cortisol and double product.

Summary

We aimed at assessing associations between double product (DP), silent ischemia (ST) and cardiometabolic risk markers, specifically cortisol and adrenocorticotropic hormone (ACTH), in a bi-ethnic sex cohort. Blacks displayed a poorer cardiovascular profile than did White sex groups. Differences for cortisol ($F_{1,377}$ = 7.20-6.25, p < 0·013) as well as ACTH ($F_{1,364}$ = 19.34-19.08, p <0.001) were observed between ethnic and sex groups, whereas differences for waist circumference (WC) ($F_{1,366}$ = 4.94, p <0.001) were only observed between sex groups.

Multivariate linear regressions revealed a positive association between cortisol and DP [Adj R^2 0.36; β 0.24 (0.07,0.41); p<0.05] in Black men only. Positive associations were found between DP and WC in all sex groups, i.e. in Black men [Adj R^2 0.36; β 0.35 (0.17,0.51); P < 0.01], in Black women [Adj R^2 0.11; β 0.27 (0.06,0.48); P = 0.014], in White men [Adj R^2 0.33; β 0.52 (0.35,0.69); P < 0.01] and in White women [Adj R^2 0.37; β 0.35 (0.10,0.60); P = 0.007]. In mildly to severely depressed Black men associations were found between ST and DP [Adj R^2 0.19; β 0.41 (0.40,0.42); P = 0.025] as well as between ST and cortisol [Adj R^2 0.19; β 0.37 (0.25,0.48); P = 0.043].

We can thus partially accept both our hypotheses:

Positive associations will be present between DP, ST and cortisol in Black men and women.

Associations will be present between DP, ST and cortisol during psychological distress, especially in Black men and women

As positive associations were present between DP, ST and cortisol in Black men only and associations were present between DP, ST and cortisol after stratification of groups into moderately to severely depressed groups in Black men only.

A blunted cortisol response may support the lower cortisol levels found within our Black cohort. Both ambulatory DP and cortisol predicted a lack of myocardial oxygen supply in moderately to severely depressed African men. Central obesity may impact on BP in a bi-ethnic sex cohort. However, a combination of attenuated cortisol and accompanying central obesity suggests possible dysregulation of the HPA axis indicative of emotional distress in a Black male cohort. Their cortisol values suggested lower myocardial oxygen when emotionally distressed and underscores the notion of compensatory increases in DP to increase oxygen supply to the heart.

Limitations

The nature of this study can be seen as a limitation seeing that the participants are from a specific environment and may not be fully representative of the entire Sub-Saharan African community.

Furthermore, obtaining serum cortisol can be experienced as a stressor, which can negatively impact the results. The Cardiotens ® ambulatory blood pressure measurement device can also be experienced as a stressor, which will impact ambulatory blood pressure readings.

Recommendations

As this is the first for cortisol and double product to be reported within the cardiovascular system, further investigation might be necessary to support the significance of the findings.

As prospective data are available, it could be of interest to compare the baseline group with the follow-up data.

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10 November 2010

Prof L Malan
Physiology

Dear Prof Malan

HREC APPROVAL OF YOUR APPLICATION

Ethics number: NWU-00036-07-A6 SABPA Study

Kindly use the ethics reference number provided above in all correspondence or documents submitted to the Health Research Ethics Committee (HREC) secretariat.

Project title: Double Product and psychological distress in a bi-ethnic urban South African cohort: the SABPA Study

Project leader/supervisor: Prof L Malan

Student: CE Schutte

Application type: Sub-study

Risk level descriptor: Minimal

You are kindly informed that at the meeting held on 14/05/2015 of the HREC, Faculty of Health Sciences, the aforementioned was approved.

The period of approval for this project is from 10/11/2015 to 01/12/2016.

After ethical review:

Translation of the informed consent document to the languages applicable to the study participants should be submitted to the HREC (if applicable).

The HREC requires immediate reporting of any aspects that warrants a change of ethical approval. Any amendments, extensions or other modifications to the protocol or other associated documentation must be submitted to the HREC prior to implementing these changes. Any adverse/unexpected/unforeseen events or incidents must be reported on either an adverse event report form or incident report form.

A progress report should be submitted within one year of approval of this study and before the year has expired, to ensure timely renewal of the study. A final report must be provided at completion of the study or the HREC must be notified if the study is temporarily suspended or terminated. The progress report template is obtainable from Carolien van Zyl at

Carolien.VanZyl@nwu.ac.za. Annually a number of projects may be randomly selected for an external audit.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process.

Please note that for any research at governmental or private institutions, permission must still be obtained from relevant authorities and provided to the HREC. Ethics approval is required BEFORE approval can be obtained from these authorities.

The HREC complies with the South African National Health Act 61 (2003), the regulations on Research with Human Participants of 2014 of the Department of Health and Principles, the Declaration of Helsinki, 2013, the Belmont Report and the Ethics in Health Research: Principles, Structures and Processes (SANS document).

We wish you the best as you conduct your research. If you have any questions or need further assistance, please contact the Ethics Office at Carolien.VanZyl@nwu.ac.za or 018 299 2089.

Yours sincerely

Prof Minrie Greeff
HREC Chairperson

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I, **Ms Cecilia van der Walt,** hereby confirm that I took care of the **editing** of the **dissertation** of **CE Schutte** titled **Double product and psychological distress in a bi-ethnic urban South African cohort: the SABPA study.**

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