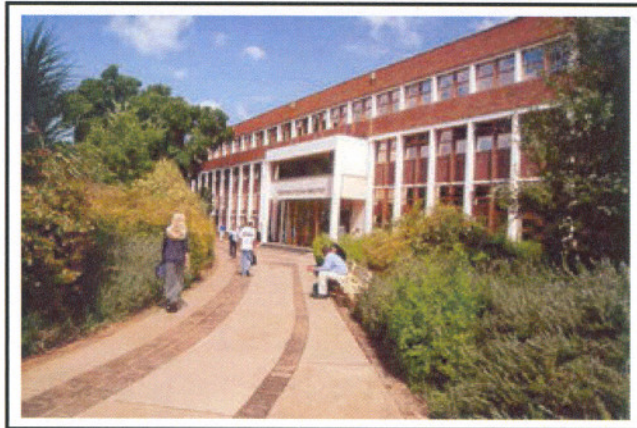




NORTH-WEST UNIVERSITY
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Psychological well-being and cardiovascular function in obese African women: The POWIRS study

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Dissertation submitted in fulfilment of the
requirements for the degree Magister Scientiae in
Physiology at the North-West University
(Potchefstroom Campus)

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November 2006



ACKNOWLEDGEMENTS

I would like to express my sincere gratitude towards the following persons who helped me to finally finish this dissertation:

- My Heavenly Father, without Whom none of this would have been possible.
- My mother, for her loving and caring support.
- Dr. Leoné Malan, for being the main driving force behind this study, and for providing me with guidance, support and encouragement.
- Drs. Rudolph Schutte and Johan Potgieter, as co-supervisors, for their invaluable input and advice, especially regarding their respective study fields.
- Misses Lanthé Palmer and Wilna Oosthuizen, for assistance with the writing and completion of this dissertation.
- Contributors to the POWIRS study: subjects, data sampling, analyses and interpretation of data.
- The sponsors of the POWIRS study: the South African National Research Foundation, the Medical Research Council and the Research Focus Area 9.1 of the North-West University (Potchefstroom Campus).

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DECLARATION BY AUTHORS


The contribution of each of the researchers involved in this study is given in the following table:

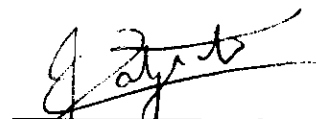
<u>Name</u>	<u>Role in this study</u>
Mr. H Malan (Physiologist)	Responsible for literature searches, statistical analyses, processing of data, design and planning of manuscript, interpretation of results and writing of the manuscript
Dr. L Malan (Physiologist)	Supervisor. Supervised the writing of the manuscript, initial planning and design of manuscript, technical advice regarding literature, statistical analyses and interpretation of results.
Dr. R Schutte (Physiologist)	Co-supervisor. Supervised the writing of the manuscript, technical advice regarding literature, statistical analyses, and interpretation of results.
Dr. JC Potgieter (Psychologist)	Co-supervisor. Supervised the writing of the manuscript, technical advice regarding literature, statistical analyses, and interpretation of results.

The following is a statement from the co-authors confirming their individual roles in the study and giving their permission that the article may form part of this dissertation.

I declare that I have approved the above-mentioned manuscript, that my role in the study, as indicated above, is representative of my actual contribution and that I hereby give consent that it may be published as part of the M.Sc. dissertation of Mr. H Malan.


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Dr. R Schutte


Dr. JC Potgieter

AFRIKAANSE TITEL: Psigologiese welstand en kardiovaskulêre funksie in obese Afrika vrouens: Die POWIRS-studie

OPSOMMING

Motivering: Abdominale obesiteit (verder na verwys as "obesiteit") is besig om die grootste "wêreldwye epidemie" van ons moderne tye te word. Dit word geassosieer met 'n verskeidenheid siektes, insluitende kardiovaskulêre siektes en hipertensie. Onlangse navorsing toon dat 'n verhoging in simpatiese aktiwiteit van kardinale belang is in die patogenese van obesiteit-gerelateerde siektes. Verhoogde leptiënvlakke en belemmerde barorefleks-sensitiwiteit is beide onafhanklik geassosieer met abdominale obesiteit en verhoogde simpatiese aktiwiteit. 'n Persepsie van swakker gesondheid mag dalk ook bydra tot die fisiologiese eienskappe van obesiteit-gerelateerde siektes. 'n Gebrek aan data in verband met simpatiese aktiwiteit, leptiënvlakke, barorefleks-sensitiwiteit en persepsie van gesondheid in Afrikaners, dien as motivering vir die uitvoer van hierdie studie.

Doelstelling: Om ondersoek in te stel na die bydraes van leptiënvlakke, barorefleks-sensitiwiteit en persepsie van gesondheid data tot verhoogde simpatiese aktiwiteit in maer en obese Afrika vrouens van Suid-Afrika.

Metodologie: Die manuskrip wat in Hoofstuk 2 vervat is, het gebruik gemaak van data wat versamel is tydens die POWIRS (Profiles of Obese Women with the Insulin Resistance Syndrome) studie. 'n Groep van 102 verstedelike

Afrika vrouens, woonagtig in die Noordwes Provinsie van Suid-Afrika, is gewerf volgens hul liggaamsmassa-indeks. Slegs 85 proefpersone is vir analyses ingesluit, as gevolg van onvolledige datastelle. Vir hierdie studie was proefpersone in maer en obese groepe ingedeel volgens hul middelomtrekke. Antropometriese metings volgens standaardmetodes is gedoen. Rustende kardiovaskulêre metings is verkry vanaf Finometerwaarnemings. Rustende vastende leptienvlakke is bereken na radioimmuunbepaling analyses. Subjektiewe persepsie van gesondheid is bepaal deur middel van die 28-item General Health Questionnaire. Vergelykings tussen die groepe is gedoen deur middel van analyses van kovariansie (ANCOVA) terwyl daar vir kardiovaskulêre risikofaktore (ouderdom, rook, alkoholverbruik en fisiese aktiwiteit) gekorrigeer is. Korrelasie-koëffisiënte is bepaal om enige assosiasies tussen leptien, barorefleks-sensitiwiteit en persepsie van gesondheid met simpatiese aktiwiteit (verteenwoordig deur harttempo) en ander kardiovaskulêre veranderlikes aan te toon.

Die studie is goedgekeur deur die Etiekkomitee van die Noordwes-Universiteit en al die proefpersone het skriftelike toestemming gegee. Die leser word verwys na die Metodes afdeling in Hoofstuk 2 vir 'n meer breedvoerige bespreking van die proefpersone, studie-ontwerp en analitiese prosedures wat gevolg is in hierdie verhandeling.

Resultate en gevolgtrekking: Resultate van hierdie studie dui aan dat obese Afrika vrouens in vergelyking met maer Afrika vrouens ouer was, hoër aktiwiteitsvlakke rapporteer het, en het hoër diastoliese - en gemiddelde

bloeddruk-, hartfrekwensie-, kardiaal omset-, arteriële meegewendheid-, leptien- en hipertensievoorkomswaardes openbaar. In maer Afrika vrouens was sosiale disfunksie positief geassosieerd met diastoliese – en gemiddelde bloeddruk en arteriële weerstand, en negatief geassosieerd met arteriële meegewendheid. In obese Afrika vrouens is barorefleks-sensitiwiteit negatief geassosieer met diastoliese bloeddruk wat 'n aanduiding kan wees van belemmerde barorefleks-sensitiwiteit. In hierdie obese groep is 'n persepsie van sosiale disfunksie geassosieer met verlaagde harttempo. Alhoewel leptien en harttempo betekenisvol verhoog was in die obese Afrikane, het geen betekenisvolle korrelasies tussen hierdie veranderlikes bestaan om leptien se versterking van simpatiese aktiwiteit te reflekteer nie. Leptin het egter 'n swak maar positiewe korrelasie getoon met kardiaal omset ($p = 0.054$, $r = 0.32$). In samevatting, blyk dit dat barorefleks sensitiwiteit (alhoewel dieselfde tussen groepe) en leptien bydra tot bloeddruk en gevolglik hipertensie in obese Afrika vrouens, moontlik deur verhoogde simpatiese aktiwiteit en volume belading. 'n Persepsie van swakker gesondheid, veral 'n persepsie van sosiale disfunksie, kan moontlik bydra tot hierdie beeld.

Sleutelwoorde: Simpatiese aktiwiteit; leptien; barorefleks-sensitiwiteit; persepsie van gesondheid; kardiovaskulêre funksie; middelomtrek; vrouens; Afrikane.

TITLE: Psychological well-being and cardiovascular function in obese African women: The POWIRS study

SUMMARY

Motivation: Abdominal obesity (hereafter referred to as “obesity”) is becoming the biggest “global epidemic” of our modern times. It is associated with a range of diseases, including cardiovascular diseases and hypertension. Recent research showed that an increase in sympathetic activity is of central importance in the pathogenesis of obesity-related diseases. Increased leptin levels and impaired baroreflex sensitivity have both been independently associated with abdominal obesity and increased sympathetic activity. A perception of poorer health may also contribute to the physiological characteristics of obesity-related diseases. A lack of data regarding sympathetic activity, leptin levels, baroreflex sensitivity and perception of health in Africans, serves as a motivation for conducting this study.

Objective: To investigate the contributions of leptin levels, baroreflex sensitivity and perception of health data to increased sympathetic activity in lean and obese African women from South Africa.

Methodology: The manuscript presented in Chapter 2 made use of the data obtained in the POWIRS (Profiles of Obese Women with the Insulin Resistance Syndrome) study. A group of 102 urbanized African women, living in the North-West Province of South Africa, was recruited according to body mass indexes. Only 85 subjects were included for analysis due to incomplete

datasets. For this study, subjects were divided into lean and obese groups according to their waist circumferences. Anthropometric measurements were done according to standardized methods. Resting cardiovascular measurements were obtained from Finometer observations. Resting, fasting levels of leptin were calculated after radioimmunoassay analyses. Subjective perception of health was determined by means of the 28-item General Health Questionnaire. Comparisons between the groups were done using analysis of covariance (ANCOVA) whilst adjusting for cardiovascular risk factors (age, smoking, alcohol consumption and physical activity). Correlation coefficients were determined to indicate any associations between leptin, baroreflex sensitivity and perception of health with sympathetic activity (represented by heart rate) and other cardiovascular variables.

The study was approved by the Ethics committee of the North-West University and all the subjects gave informed consent in writing. The reader is referred to the Methods section in Chapter 2 for a more detailed description of the subjects, study design and analytical procedures used in this dissertation.

Results and conclusion: Results from this study indicate that obese African women, compared to lean African women, were older, reported higher physical activity, and exhibited higher diastolic and mean blood pressure, heart rate, cardiac output, arterial compliance, leptin and hypertension prevalence rate values. In lean African women social dysfunction was positively associated with diastolic and mean blood pressure and arterial resistance, and negatively with arterial compliance. In obese African women

baroreflex sensitivity was negatively associated with diastolic blood pressure, which could be an indication of impaired baroreflex sensitivity. In this obese group a perception of social dysfunction was associated with decreased heart rate. Although leptin and heart rate were significantly higher in the obese Africans, no significant correlations existed between these variables to reflect leptin's enhancement of sympathetic activity. However, leptin correlated weakly but positively with cardiac output ($p = 0.054$, $r = 0.32$). In conclusion, baroreflex sensitivity (although similar between groups) and leptin seem to contribute to blood pressure and thus hypertension in obese African women, possibly through increased sympathetic activity and volume loading. A perception of poorer health, especially a perception of social dysfunction, could possibly contribute to this image.

Keywords: Sympathetic activity; leptin; baroreflex sensitivity; perception of health; cardiovascular function; waist circumference; women; Africans.

PREFACE

For the structure of this study it was decided to use the manuscript format. Chapter 1 serves as an introduction and provides the motivation, background and a brief summary of the knowledge necessary for meaningful interpretation of the data. At the beginning of Chapter 2 (the manuscript) is a brief summary of the Instructions for Authors of the peer reviewed journal aimed for publication (the *International Journal of Psychophysiology*). Chapter 3 provides a summary of the study results, as well as recommendations for future research. Relevant references are provided at the end of each chapter. The relevant references used in the unpublished Chapters 1 and 3 are provided according to the mandatory style stipulated by the North-West University, Potchefstroom Campus, Potchefstroom, South Africa. The technical style used in Chapters 1 and 3 is, therefore, uniform but differs in Chapter 2 according to the authors' instructions of the specific journal.

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LIST OF ABBREVIATIONS

ANCOVA:	Analysis of covariance
BMI:	Body mass index
BP:	Blood pressure
CO:	Cardiac output
CV:	Cardiovascular
CVD:	Cardiovascular diseases
C _w :	Arterial ("Windkessel") compliance
DBP:	Diastolic blood pressure
GHQ-28:	28-item version of the General Health Questionnaire
GHQ-AS:	Anxiety and Insomnia Symptoms
GHQ-DS:	Depressive Symptoms
GHQ-SD:	Social Dysfunction Symptoms
GHQ-SS:	Somatic Symptoms
GHQ-T:	General Health Questionnaire – Total Score
HPA:	Hypothalamus-pituitary-adrenal
HR:	Heart rate
HT%:	Hypertension prevalence rate (percentage)
IDF:	International Diabetes Foundation
MAP:	Mean arterial pressure
NO:	Nitric oxide
NPY:	Neuropeptide Y
POWIRS:	Profiles of Obese Women with the Insulin Resistance Syndrome
SBP:	Systolic blood pressure
SV:	Stroke volume
TPR:	Total peripheral resistance
WC:	Waist circumference
WHO:	World Health Organization
WHR:	Waist-hip ratio
WMA:	World Medical Association
xBRS:	Spontaneous baroreflex sensitivity

CHAPTER 1

INTRODUCTION AND LITERATURE STUDY

General Introduction

Abdominal obesity (hereafter referred to as "obesity") is the most prevalent metabolic condition worldwide, and the World Health Organization (WHO) refers to obesity as a "global epidemic" (Formiguera & Cantón, 2004; Isomaa, 2003; WHO, 2003). *New Scientist* (2006) quoted Paul Zimmet during his opening address at the 10th International Congress on Obesity as saying "This insidious, creeping pandemic of obesity is now engulfing the entire world. It's as big a threat as global warming and bird flu." Obesity is associated with a variety of components of the metabolic syndrome (Nammi *et al.*, 2004), perturbed neuroendocrine function (Njelekela *et al.*, 2004) as well as the development of cardiovascular diseases (CVD) (Sowers, 2003). It has been indicated that obesity and its progression are predictors of future hypertension (Chuang *et al.*, 2006). In recent years evidence has indicated that hypertension and CVD are becoming more prevalent in Sub-Saharan Africa (Seedat, 2004) and it is likely to be associated with the high prevalence of obesity in black Africans (Puoane *et al.*, 2002) (hereafter referred to as "Africans").

Recent hypotheses propose that increased activity of the sympathetic nervous system is a major component in the pathogenesis of obesity-related diseases (Hristova & Aloe, 2006). Obesity and elevated blood pressure (BP) are known to be characterized by increased sympathetic activity (Grassi & Seravalle, 2006) whilst increased sympathetic activity in itself is a risk factor for development of CVD such as hypertension (Kaaja *et al.*, 2006). Higher blood pressure, increased arterial resistance and decreased arterial compliance are all consequences of increased sympathetic stimulation (Guyton & Hall, 2006). These cardiovascular events, coupled with obesity in itself, and other factors (such as lipid abnormalities) may represent

increased risk for development of obesity-related diseases (IDF, 2005a). It has been found in African-Americans that obesity is associated with increased blood pressure, and that sympathetic activity may contribute to this increase in blood pressure (but only in women) (Mansour *et al.*, 1999). Hypertension has also been associated with obesity (Misra & Vikram, 2004) and Opie and Seedat (2005) found that obesity in African women was positively associated with urbanisation.

Hristova and Aloe (2006) propose a complicated etiological model for obesity-related diseases that leads, amongst others, to hyperleptinemia. This condition contributes to increased sympathetic nervous activity. Impaired baroreflex sensitivity (xBRS) is another condition that is associated with obesity (Lindgren *et al.*, 2006) and increased sympathetic activity (Schutte A.E. *et al.*, 2006). When studying obesity-related diseases, it may be necessary to also include leptin and xBRS, as these factors could contribute significantly to sympathetic activity.

Sympathetic activity is closely linked to diagnosable psychiatric disorders (Kaplan, 1996) (such as depression, anxiety disorders and eating disorders), as well as obesity and endocrinological disturbances (Antonijevic *et al.*, 1998; Brown *et al.*, 2003; Monteleone *et al.*, 2000; Nakai *et al.*, 1999). There is a limited amount of data available on psychological risk factors for coronary artery disease (Rozanski *et al.*, 1999) although Seedat (2004) found increases in hypertension prevalence rates in urbanised Africans. Additionally, Malan *et al.* (2006) found that Africans indicated a perception of poorer health when exposed to psychosocial stress or urbanisation. Psychological factors other than psychopathology, therefore, need consideration. Common emotional and cognitive states (not associated with diagnosable

psychopathology) also influence physical health (Salovey *et al.*, 2000). Subjective perception of health has for example been shown to be an accurate indicator of physical health (Farmer & Ferraro, 1997; Miilunpalo *et al.*, 1997). Katz *et al.* (2000) have indicated that overweight and obese individuals exhibit perception of poorer health. Additionally, Elliott (1995) argued that the relationship between perceived psychosocial stress and heart disease depends on the individual's perception of his / her life situation. This necessitates an investigation of so-called "sub-clinical" psychological factors (and more specifically, perception of health) alongside physiological variables when studying obesity-related diseases in Africans with regard to sympathetic activity.

Waist circumference as indicator of obesity

Defining obesity

The International Diabetes Foundation (IDF) recently released a new worldwide consensus definition for the diagnosis of the metabolic syndrome (IDF, 2005b). Central to this definition is the compulsory inclusion of abdominal obesity, defined by specific waist circumference (WC) cut-off measurements. Previous definitions and studies utilised body mass index (BMI) to determine overweight and obesity levels. Lately, evidence supports the notion that WC as a specific measurement of obesity is a stronger correlate to metabolic syndrome risk factors than BMI, which is a general measurement of obesity (ACE, 2003). Pihl *et al.* (2006) indicated that WC is a better correlate to certain cardiovascular risk factors (such as C-reactive protein, oxidative stress and triglycerides) as opposed to BMI and fat percentage. WC is also a stronger predictor for hypertension risk than BMI (Wittchen *et al.*, 2006). Using WC is, however, still a rather new approach, and some recent studies (Geleijnse *et al.*, 2005; Mobley *et al.*, 2006; Steptoe & Wardle, 2005) still used BMI and waist-hip ratio

(WHR) as measurements of obesity levels. WHR has also recently been shown to be a better indicator for obesity and CVD risk than BMI (Franzosi, 2006).

Causes of obesity

Possible causes of obesity include genetic mutations and syndromes, endocrine disturbances, nervous system lesions, medication, socio-demographic factors (such as socio-economic status, race, gender and ethnicity), lifestyle and diet, and eating disorders. It remains unclear however whether a causal relationship exists between obesity and psychological factors (Speiser *et al.*, 2005). Björntorp (2001) describes a possible etiological mechanism, wherein environmental factors, which are perceived as stress, disturb the hypothalamus-pituitary-adrenal (HPA) axis and the central sympathetic nervous system. Stress-related increases in cortisol secretion would lead to an imbalance in neuropeptide Y (NPY) and leptin levels (favouring the former). Increased NPY would stimulate food intake by creating a positive energy balance and increased cortisol levels will aid accumulation of fat in the visceral (i.e. central / abdominal) fat depots thereby blunting leptin action resulting in "leptin resistance" (Rahmouni & Haynes, 2005). It is, however, not entirely clear if central obesity is the result of inhibition of the leptin system (decreasing the inhibition of food intake), or of stimulation of the NPY system (increasing the stimulation of food intake). All of this leads to the description of the phenomenon called "stress-eating" (Björntorp, 2001), which is difficult to quantify due to the subjective nature of psychological stress (Rosengren *et al.*, 2004). Recent evidence also suggests some form of addiction could be responsible for constant food craving that would contribute to the maintenance of obesity (Wang G.-J. *et al.*, 2006).

In spite of the absence of a commonly accepted etiological mechanism, it remains important to bear in mind the possible role that psychological and environmental factors might play in not only the etiology, but also the maintenance of obesity-related diseases. Dietary and lifestyle factors such as obesity, physical inactivity, high salt intake and low potassium intake have already been identified as major contributors to the prevalence of hypertension in Western societies (Geleijnse *et al.*, 2005). Some of these factors are undoubtedly also connected to obesity itself, and require further study. The call for further studies is especially important, since evidence exists for a number of proposed models of childhood obesity that might prevail into adulthood (Braet, 2005).

Obesity in Africans

Puoane *et al.* (2002) recently investigated the anthropometric profile and determinants of obesity in the South African population. Results from their study indicated that the highest rates of abdominal obesity were found in urban African women. Dietary changes and urbanization could possibly contribute to this increased prevalence of obesity in Africans in general and African women specifically (Puoane *et al.*, 2002).

Baroreflex sensitivity (xBRS)

Function

An important mechanism in BP regulation is the arterial baroreflex (Guyton & Hall, 2006). The baroreceptor system consists of stretch receptors that are located in the carotid sinus and aortic arch. The stretch receptors monitor changes in BP and transmit impulses to the vasomotor regulatory centre in the brain stem. These impulses activate appropriate increases or decreases in autonomic nervous outflow

including appropriate changes in heart rate (HR) and vascular resistance to restore BP (Parmer *et al.*, 1992).

xBRS and cardiovascular health

Impaired xBRS has been associated with hypertension, heart failure and myocardial infarction (Lindgren *et al.*, 2006; Lucini *et al.*, 2006). It is generally accepted that an impaired xBRS is usually the result of lipid abnormalities (Gadegbeku *et al.*, 2002; Schutte A.E. *et al.*, 2006; Singh *et al.*, 2004). Evidence however, has also shown that impaired xBRS might be either a consequence of elevated arterial pressure or a genetic contributor to elevated arterial pressure in familial hypertension (Parmer *et al.*, 1992). Reduced xBRS exerts its pathological effects mainly by contributing to increased sympathetic activity (Zucker *et al.*, 1995). Endothelial dysfunction, in itself a major risk factor for CVD and the initial step in the atherosclerotic process (Avogaro *et al.*, 2006), could be caused by impaired xBRS, and possibly contributes to increased sympathetic outflow (Zucker *et al.*, 1995). The end results of increased sympathetic outflow include increases in BP and arterial resistance, and a decrease in arterial compliance – all of which are known risk factors for CVD (Guyton & Hall, 2006).

xBRS and obesity

Impaired xBRS is associated with obesity (Lindgren *et al.*, 2006). This might be attributed to obesity adversely affecting lipid levels and / or endothelial dysfunction caused by oxidative stress (Pihl *et al.*, 2006). An impaired endothelial-mediated vasodilatory response to increased blood flow and greater arterial stiffness has been observed in obese individuals (Singhal, 2005) and may also partly explain the xBRS-obesity association. Hypertension, heart failure and myocardial infarction are some of the cardiovascular conditions in which impaired xBRS has also been noted (Lindgren

et al., 2006). Insulin resistance is also negatively correlated to xBRS (Lucini *et al.*, 2006), which highlights the importance of xBRS in evaluating obesity and CVD.

xBRS in Africans

So far, little research has been done in Africans concerning xBRS. Zion *et al.* (2003) investigated arterial compliance and autonomic function in young African-American and non-African-American males. Results revealed that African-American males had lower arterial compliance, parasympathetic modulation, xBRS, and higher sympathovagal balance. South African researchers recently conducted an intervention study in a group of white Africans to determine the effects of dietary changes on xBRS (Schutte A.E. *et al.*, 2006). Their results suggested that xBRS could be sensitive to dietary changes, independent of obesity. However, this study did not include subjects of black African descent.

Leptin

Function

Leptin, the product of the *ob/ob* gene (Antonijevic *et al.*, 1998), is the major secretory product of white adipocytes and is mainly known for its effect as an energy balance regulator (Asakawa *et al.*, 2003; Matsumura *et al.*, 2003). Leptin binds with receptors in the hypothalamus to promote weight loss, by suppressing appetite and increasing energy expenditure (Rahmouni & Haynes, 2005). The appetite suppressing effect is thought to be achieved by inhibiting the release of NPY, a potent appetite stimulator (Matsumura *et al.*, 2003). Increased energy expenditure is achieved by increasing sympathetic nervous activity (Hristova & Aloe, 2006; Matsumura *et al.*, 2003).

Leptin and cardiovascular health

Leptin shows a positive association with BP (Molchanova *et al.*, 2003; Wang G. *et al.*, 1999), and has been indicated as an independent risk factor for coronary artery

disease (Sundell, 2005). Leptin receptors have been discovered on endothelial and vascular smooth muscle cells, and thus exerts a number of effects on the vascular system (Rahmouni & Haynes, 2005). Leptin enhances angiogenesis, mainly through the upregulation of vascular endothelial growth factor (Rahmouni & Haynes, 2005; Singhal, 2005). Leptin also has vasodilating effects, mainly through stimulation of endothelial nitric oxide production (Matsumura *et al.*, 2003). However, leptin also leads to vasoconstriction via increased oxidative stress, promotes vascular calcification and smooth muscle cell proliferation (Rahmouni & Haynes, 2005; Singhal, 2005). Sundell (2005) argues that in patients with endothelial dysfunction (such as obese individuals), leptin-induced vasodilation may be blunted. Matsumura *et al.* (2003) found that the effects of leptin on arterial pressure varies depending on chronic or acute exposure to leptin. Various studies have indicated that acute administration of leptin causes vasodilatation via nitric oxide mechanisms (thereby decreasing BP and arterial resistance, and increasing arterial compliance) (Frühbeck, 1999; Lembo *et al.*, 2000; Matsumura *et al.*, 2003; Nakagawa *et al.*, 2002). Chronically elevated leptin levels, on the other hand, may increase oxidative stress and thereby play a key role in atherosclerosis and hypertension associated with obesity (Rahmouni & Haynes, 2005; Singhal, 2005).

Leptin and obesity

Leptin varies directly with BMI and percentage body fat (Prolo *et al.*, 1998). Thus, it could be that obese individuals will have increased plasma leptin levels with subsequent weight loss occurring in these individuals. In leptin-deficient *ob/ob* obese mice (the genetic model for obesity and diabetes), treatment with leptin did lead to weight loss (Asakawa *et al.*, 2003). Unfortunately, this effect is not visible in humans, as most cases of human obesity are associated with elevated leptin levels (Prolo *et*

al., 1998). This has led to the hypothesis that human obesity represents a state of "leptin resistance" (Prolo *et al.*, 1998; Rahmouni & Haynes, 2005).

Leptin in Africans

So far little research has been done in Africans regarding leptin. Recent studies by Schutte R. *et al.* (2005a; 2005b) have explored the relationship of leptin with cardiovascular function. In a study comparing African and Caucasian females (Schutte R. *et al.*, 2005b), increased leptin was associated with lower diastolic blood pressure (DBP) and total peripheral resistance (TPR) in the obese Caucasians, but not in the obese Africans (despite leptin levels being similar in the respective groups). In a related study (Schutte R. *et al.*, 2005a), increased leptin was associated with increased systolic blood pressure (SBP) and decreased arterial compliance (C_w), but only in obese hypertensive African females.

Psychological influences

From psychopathology to psychological well-being

Although a wide array of psychological factors have definite and quantifiable effects on physical health (such as cardiovascular function), in the past most studies have focused only on psychopathology, and its influence on physiological functioning. In particular, depression and anxiety have enjoyed a lot of attention in this regard (Vieweg *et al.*, 1997; Vieweg *et al.*, 1998). Regarding CVD, xBRS and leptin, recent studies have found some relationships of these variables with psychopathology. Anxiety has for example been shown to be associated with decreased xBRS in patients after acute myocardial infarction (Watkins *et al.*, 2002), and leptin has been found to have anti-depressant (Lu *et al.*, 2006) and anxiolytic properties in *ob/ob* mouse studies (Asakawa *et al.*, 2003). In their exploration of the phenomenon of 'combined illness', Yates and Brooks (1998) found increasing evidence for

depression as an independent risk factor for hypertension. Depression increases the risk for CVD up to four times, and symptoms of depression predict future coronary events for healthy individuals and poorer prognosis for current CVD patients (Joynt *et al.*, 2003). Interestingly though, CVD and depressive symptoms seem to be related in a bi-directional manner (Dieguez *et al.*, 2004), meaning that CVD and depressive symptoms could both be causes and / or consequences of the other. These studies confirm the importance of psychological influences on physical health, and therefore attention should also be given to psychological factors when investigating CVD and obesity.

It should be noted however that recent studies indicate a need to shift focus from psychopathology to a more holistic representation of psychological functioning. This notion is suggested by studies such as those of Heo *et al.* (2006), which found a relationship between depressive mood – a rather common emotional state and gateway symptom for depression – and obesity (depending on gender, age, and race). Emotional states have also been found to impact directly on physiological health (Salovey *et al.*, 2000). These are not “psychopathological” factors *per se*, but could eventually lead to psychological disturbances which have been associated with physical illness. The possibility also exists that positive psychological function may ameliorate physical symptoms. Indeed, there is a growing body of evidence that happiness (thus a state of positive psychological functioning) may “influence our health via its effects on the immune system” (Carr, 2004). It may, therefore, be necessary to also investigate psychological factors other than psychopathological conditions, together with physiological factors when studying lifestyle related diseases such as obesity.

Certain indicators have been used to measure psychological well-being across the entire spectrum of psychological function – one of these is perception of health (Coyle, 1993). Even though perception of health is a subjective measurement, recent evidence indicates that self-reported psychological factors are risk factors for CVD (Rosengren *et al.*, 2004). Subjective ratings of personal health have in some instances shown a stronger correlation with positive psychological functioning than did objective health ratings made by physicians (Carr, 2004), and perception of health has also been shown to be an accurate indicator of physiological conditions (Farmer & Ferraro, 1997). Katz *et al.* (2000) found that obese subjects indicated a perception of poorer health. What is still unclear, though, is whether perception of poorer health is merely an indicator of physical illness, or if it could exert a positive feedback effect on the aforementioned illness (such as obesity). As CVD and depressive symptoms are related in a bi-directional manner (Dieguez *et al.*, 2004), it seems plausible to expect some form of feedback between the subjective perception that a person has of his / her health, and adverse physiological conditions such as obesity. This feedback could take the form of increases in psychological stress leading to stimulation of sympathetic activity (Björntorp, 2001). It seems more likely though, that perception of poorer health will merely indicate the presence of obesity-related pathological changes. Still, this may prove to be an important factor that could assist researchers in studies of obesity-related diseases and CVD.

Research Question

Although a number of studies have investigated xBRS, leptin and perception of health with regard to CVD, it seems that there is a need to investigate the above-mentioned factors in combination, especially in obese African women. This chapter

indicated that impaired xBRS, increased leptin levels and perception of poorer health could contribute to increased sympathetic activity and may therefore lead to CVD in obese African women.

Aim

The aim of this study is to investigate xBRS, leptin levels and perception of health as contributors to increased sympathetic activity in lean and obese African women from South Africa. The hypothesized associations between these variables are shown in Figure 1.

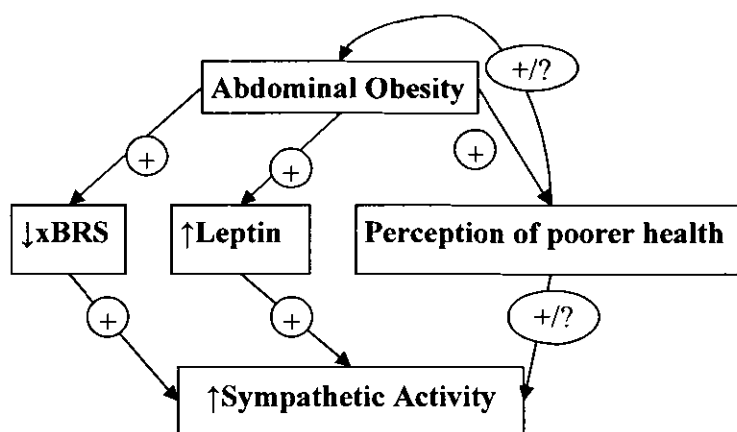


Figure 1: Possible associations of xBRS, leptin and perception of poorer health with abdominal obesity and sympathetic activity. Obesity contributes to impaired xBRS, higher levels of leptin, and perception of poorer health. Impaired xBRS and increased leptin contribute to enhanced sympathetic activity (measured through increased heart rate). It is unknown whether perception of poorer health will contribute to either sympathetic activity or obesity.

Hypotheses

1. Obese African women, compared to lean counterparts, would present with increased sympathetic activity, as indicated by increased HR.
2. The obese group with increased sympathetic activity will have higher BP, impaired xBRS, higher leptin levels and perception of poorer health.

3. Increased sympathetic activity would be reflected by positive associations between HR, leptin and perception of health, and a negative association between HR and xBRS.
4. Obese African women would present with increased prevalence rates of hypertension.

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CHAPTER 2

Psychological well-being and cardiovascular function in obese African women: The POWIRS study

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Abstract

Abdominal obesity, perception of poorer health and elevated blood pressure are known to be characterised by increased sympathetic activity. The aim of this study was to investigate baroreflex sensitivity (xBRS), leptin, and perception of health data as contributors to increased sympathetic activity in lean and obese subjects. African women (N = 85) were involved in a case-control survey and were divided according to low (< 80cm) and high (\geq 80cm) waist circumference measurements. Resting cardiovascular measurements were obtained with a Finometer device. Spontaneous xBRS was determined with pulse rate variability software. Resting, fasting leptin levels were determined with radioimmunoassay analyses, and perception of health was measured using the 28-item General Health Questionnaire (GHQ-28). Statistical analyses results were independent of CV risk factors (age, smoking, alcohol consumption and physical activity). Obese African women were older, reported higher physical activity, and exhibited higher diastolic (DBP) and mean blood pressure (MAP), heart rate (HR), cardiac output (CO), arterial compliance (C_w), leptin and hypertension prevalence rate values. In lean African women social dysfunction was positively associated with DBP, MAP and arterial resistance (TPR), and negatively with C_w . In obese African women xBRS was negatively associated with DBP, which could be an indication of impaired xBRS. In this obese group a perception of social dysfunction was associated with decreased HR. Although leptin and HR were significantly higher in the obese Africans, no significant correlations existed between these variables to reflect leptin's enhancement of sympathetic activity. However, leptin correlated weakly but positively with CO ($p = 0.054$, $r = 0.32$). In conclusion, xBRS (although similar between groups) and leptin seem to contribute to blood pressure and thus hypertension in obese African women, possibly

through increased sympathetic activity and volume loading. A perception of poorer health, especially a perception of social dysfunction, could possibly contribute to this image.

Keywords: Sympathetic activity; leptin; baroreflex sensitivity; perception of health; cardiovascular function; waist circumference; women; Africans.

Word count: 301

1. Introduction

Abdominal obesity (hereafter referred to as "obesity") is the most prevalent metabolic condition worldwide, and the World Health Organization (WHO) refers to obesity as a "global epidemic" (Formiguera and Cantón, 2004; Isomaa, 2003; WHO, 1997). Obesity is associated with a variety of components of the metabolic syndrome (Nammi et al., 2004), as well as the development of cardiovascular diseases (CVD) (Sowers, 2003) and perturbed neuroendocrine function (Njelekela et al., 2004).

Obesity and elevated blood pressure (BP) are known to be characterized by increased sympathetic activity (Grassi and Seravalle, 2006), which is a risk factor for the development of CVD such as hypertension (Kaaja et al., 2006). Higher BP and heart rate (HR) (Palatini and Julius, 1999), increased arterial resistance (TPR) and decreased arterial compliance (C_w) are all consequences of increased sympathetic stimulation (Guyton and Hall, 2006). Recent studies have shown that a number of variables could possibly contribute towards increased sympathetic activity, amongst them leptin and impaired baroreflex sensitivity (xBRS). Hristova and Aloe (2006) propose a model wherein elevated levels of leptin contribute to increased sympathetic nervous activity, especially in obesity. Impaired xBRS is another condition that is associated with obesity (Lindgren et al., 2006) and which contributes to increased sympathetic activity (Schutte A.E. et al., 2006).

Psychological factors, such as stress (Björntorp, 2001), are also known to increase sympathetic activity. Stress itself is an extremely subjective phenomenon, and as such it may possibly be elicited by factors such as a person's subjective perception of his / her physical and psychological health (Björntorp, 2001). In diabetic patients,

conflicting findings were made regarding the effect of psychological variables like depression, anxiety and health perception on metabolic control (Lustman and Clouse, 2005; Paschalides et al., 2004). Findings by Farmer and Ferraro (1997) did show however, that perception of health is an accurate indicator of physiological conditions. In line with this, Katz et al. (2000) confirmed that overweight and obese individuals exhibited a perception of poorer health. These findings suggest not only that perception of poorer health could be an accurate indicator of physiological disturbances, but that it could also exert a positive feedback effect on the progression of illness (Salovey et al, 2000).

To our knowledge, few studies exist that examined the effects of xBRS (Schutte A.E. et al., 2006), leptin (Schutte R. et al., 2005) and perception of health (Katz et al., 2000; Stover et al., 2001) on obesity-related diseases in black Africans (hereafter referred to as "Africans"). Malan et al. (2006) have indicated that urbanized black Africans in South Africa exhibit increased vascular reactivity to daily psychological stressors. It therefore seems necessary to investigate xBRS, leptin and perception of health as contributors to sympathetic activity in obesity-related diseases such as CVD in Africans. The aim of our study was to investigate the contributions of xBRS, leptin and perception of health data to increased sympathetic activity in lean and obese African women. The proposed hypotheses were, therefore, that (a) obese African women, compared to lean counterparts, would present with increased sympathetic activity, as indicated by increased HR (b) the obese group with increased sympathetic activity will have higher BP, impaired xBRS, higher leptin levels and perception of poorer health, (c) increased sympathetic activity would be reflected by positive associations between HR, leptin and perception of health, and a

negative association between HR and XBRS, and (d) obese African women would present with increased prevalence rates of hypertension.

2. Materials and Methods

The methods of this study have been adapted and truncated from the POWIRS (Profiles of Obese Women with Insulin Resistance Syndrome) study, as recently conducted and published by Schutte A.E. and co-workers (2005).

2.1 Study design and case selection

African women (N = 102) volunteers were recruited for participation in this study. All subjects were urbanized and employed in the Potchefstroom district in the North-West Province of South Africa. The women were recruited according to the initial study design with the help of a dietician and registered nurse. Inclusion criteria were apparently healthy women, between 20 and 55 years of age. Where possible, only HIV-negative subjects were recruited according to their status determined three months prior to this study, but the negative status could not be guaranteed for all subjects. Exclusion criteria were pregnancy, lactation, and oral temperatures above 37°C.

The subjects were divided into two groups according to waist circumference (WC). The "low WC" group consisted of subjects with WC < 80cm and the "high WC" group consisted of subjects with WC ≥ 80cm (IDF, 2005). Out of this total sample of 102 subjects, 85 were included in the analysis of this article. A total of 17 subjects were excluded due to incomplete datasets.

2.2 Ethical considerations

The Ethics Committee of North-West University, Potchefstroom campus approved the study. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki (WMA, 2005). Prior to the recruitment of subjects they were all fully informed about the objectives and procedures of the study and assistance was available to provide information in their home language.

2.3 Organizational procedures

Each afternoon for a period of about three weeks, 10 subjects were transported to a Metabolic Unit Facility (consisting of 10 single bedrooms, 2 bathrooms, a living room and kitchen). The women were introduced to the set-up and, after the experimental procedures were explained to them, signed informed consent forms. During the course of the evening, demographic, lifestyle, and psychological questionnaires were completed and all anthropometric measurements were taken, except for weight and height. All participants received an identical light supper, which excluded alcohol and caffeine, at 20:00 and went to sleep before 23:00.

After the overnight fast, weight, height and resting blood pressure measurements were taken from 06:00 in the morning. The subjects received breakfast after a fasting blood sample was taken. A personal information sheet was given to each subject regarding their blood pressure to refer them for further testing and treatment when deemed necessary.

2.4 Questionnaires

The questionnaires were designed or adapted for this study population and were validated with appropriate methods. Questionnaires were completed during individual

interviews conducted by the researchers and specially trained African fieldworkers in the language of the subjects' choice.

The *demographic questionnaire* included, amongst others, questions on smoking and alcohol consumption. Self-reporting smoking (Yes/No) and alcohol consumption status (Yes/No) were obtained and assessed. Alcohol consumption and smoking habits are sensitive indices and the responses obtained are, therefore, not reliable. *Physical activity levels* were evaluated using the Global Physical Activity Questionnaire (WHO, 2002). This questionnaire measures the total physical activity per day on information regarding participation in three settings / domains and sedentary behaviour. These domains are activity at work, travel to and from places and recreational activities. The sum of these domains was calculated in calories per week.

The *psychological questionnaire* utilised in this study was an adapted, translated and validated Setswana version (Stapelberg et al, 1999) of the 28-item General Health Questionnaire (GHQ-28) (Goldberg et al., 1997). It was administered by a registered psychologist with assistance from trained Setswana speaking fieldworkers and measured subjective perception of health. The Cronbach alpha-reliability values were 0.77 to 0.84 for subscales in this sample. The GHQ-28 consists of four (4) subscales with seven (7) items each. These subscales are: somatic symptoms (GHQ-SS), anxiety and insomnia (GHQ-AS), social dysfunction (GHQ-SD) and depressive symptoms (GHQ-DS). Subjects reported on their own perceived health pattern for the previous few weeks. Items were evaluated on a 0-0-1-1 scale (Goldberg et al., 1997). The values of response possibilities 1 and 2 are equal to 0, and those of response

possibilities 3 and 4 are equal to 1. This scoring method reduces the effects of “end users” (1 and 4) and “middle users” (2 and 3). Subscale totals are determined by summing the scored items on each subscale, and subscale totals are subsequently summated to determine the final total of the questionnaire. The range of the scores on the scale varies from 0 (for no symptoms) to 28 (where severe pathology is present) (Goldberg et al., 1997).

2.5 Anthropometric measurements

An anthropometrist measured height, weight and WC of subjects in their underwear with calibrated instruments (Invicta Stadiometer, IP 1465, U.K.; Precision Health Scale, A & D Company, Japan; Holtain unstretchable metal tape). Measurements were done using standard methods (Norton and Olds, 1996). The researchers' measurements were standardized and taken in triplicate.

2.6 Cardiovascular measurements

Cardiovascular physiologists took a 7-min continuous measurement of cardiovascular parameters using the Finometer™ device (FMS, Finapres Medical Systems, Amsterdam, The Netherlands) (Imholz et al., 1998). The Finometer™ device computed all cardiovascular variables online and stored the data in result files on a hard disk. The Beatscope 1.1 software program computed and stored systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), stroke volume (SV), heart rate (HR), cardiac output (CO), total peripheral resistance (TPR) and arterial compliance (C_w) values. Spontaneous baroreflex sensitivity (xBRS) was determined by the validated cross-correlation baroreflex sensitivity method. This method is used for the computation of time-domain baroreflex

sensitivity on spontaneous blood pressure and heart rate interval variability (Westerhof et al., 2004).

2.7 Blood samples

Fasting, resting blood samples were drawn from the antebrachial vein using a sterile winged infusion set and syringes. For preparation of serum, blood was allowed to clot in glass tubes, centrifuged at 3500 rpm for 10 min (Universal 16™, Hettich), and transferred to 1.5 ml Eppendorff tubes. All samples were immediately stored at -80°C in the laboratory.

2.8 Biochemical Analyses

Fasting, resting serum leptin levels were measured using a [¹²⁵I] IRMA kit (Diagnostic Systems Laboratories, Inc., Cat No. DSL-23100).

2.9 Statistical analyses

All processed data were statistically analysed by means of Statistica 7 (StatSoft Inc., 2005). Throughout the statistical analyses it was assumed that the underlined distribution of the population is normal. Data was adjusted for the following cardiovascular risk factors: age, smoking, alcohol consumption and physical activity. The analysis of covariance (ANCOVA) was used to show significant differences between groups. Partial correlations coefficients were used to show associations between various variables. The reliability of the General Health Questionnaire was determined by using Cronbach alpha (α) reliability coefficient. A p-value of ≤ 0.05 was considered as statistically significant and a p-value of ≤ 0.01 as statistically highly significant. Regarding the correlations, an r -value of $\geq \pm 0.35$ was considered

as statistically significant. Significance for smoking, alcohol consumption and hypertension prevalence rates were calculated with the Fischer exact method.

3. Results

Descriptive statistics for lean and obese groups are summarized in Table 1. Obese subjects were older, reported higher physical activity, and exhibited higher DBP, MAP, HR, CO, C_w and leptin values, as well as higher hypertension prevalence rates, when compared to their lean counterparts.

Table 1: Means ± standard errors [CI ± 95%] of cardiovascular variables, xBRS, leptin and perception of health data

	Lean (N = 44)	Obese (N = 41)	p values between lean and obese African women
Age (yrs)	27.8 ± 1.1 [25.5 - 30.1]	33.5 ± 1.19 [31.1 - 35.8]	0.00
Mass (kg)	59.6 ± 1.6 [56.4 - 62.7]	82.5 ± 1.6 [79.2 - 85.8]	0.00
WC (cm)	71.1 ± 1.1 [68.9 - 73.3]	93.2 ± 1.2 [90.9 - 95.5]	0.00
Smoking %	9.09 % (<i>F</i> (1,85) = 0.57)	4.88 % (<i>F</i> (1,85) = 0.57)	0.68
Alcohol consumption %	25.00 % (<i>F</i> (1,85) = 1.93)	39.02 % (<i>F</i> (1,85) = 1.93)	0.24
Physical Activity (cal/week)	4128.9 ± 481.0 [3172.1 - 5085.7]	5837.6 ± 498.3 [4846.5 - 6828.8]	0.02
SBP (mmHg)*	127 ± 2.3 [123 - 132]	132 ± 2.4 [127 - 137]	0.18
DBP (mmHg)*	75 ± 1.45 [72 - 78]	82 ± 1.50 [79 - 85]	0.00
MAP (mmHg)*	97 ± 1.73 [94 - 101]	104 ± 1.80 [100 - 107]	0.02
HR (bpm)*	65.7 ± 1.47 [62.8 - 68.7]	71.1 ± 1.53 [68.0 - 74.1]	0.02
SV (ml)*	81.5 ± 2.27 [77.0 - 86.1]	88.3 ± 2.36 [83.6 - 93.0]	0.06
CO (l/min)*	5.31 ± 0.18 [4.96 - 5.66]	6.19 ± 0.18 [5.83 - 6.56]	0.00
TPR (mmHg/ml/s)*	1.15 ± 0.04 [1.07 - 1.23]	1.04 ± 0.04 [0.96 - 1.12]	0.06
C _w (ml/mmHg)*	1.79 ± 0.04 [1.71 - 1.87]	1.93 ± 0.04 [1.85 - 2.02]	0.03
xBRS*	19.1 ± 1.71 [15.7 - 22.5]	15.7 ± 1.78 [12.1 - 19.2]	0.20
Leptin (ng/ml)*	39.5 ± 3.6 [32.4 - 46.7]	74.9 ± 3.75 [66.5 - 81.4]	0.00
GHQ-SS*	2.10 ± 0.34 [1.43 - 2.77]	2.26 ± 0.35 [1.56 - 2.96]	0.75
GHQ-AS*	2.01 ± 0.34 [1.32 - 2.69]	2.50 ± 0.36 [1.79 - 3.22]	0.35
GHQ-SD*	1.75 ± 0.30 [1.15 - 2.35]	2.07 ± 0.31 [1.45 - 2.70]	0.48
GHQ-DS*	1.29 ± 0.32 [0.66 - 1.92]	1.83 ± 0.33 [1.18 - 2.49]	0.26
GHQ-T*	7.15 ± 0.98 [5.19 - 9.10]	8.67 ± 1.02 [6.64 - 10.70]	0.31
HT %	2.27% (<i>F</i> (1,85) = 6.66)	19.51% (<i>F</i> (1,85) = 6.66)	0.01

CI, Confidence interval; xBRS, spontaneous baroreflex sensitivity; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; C_w, arterial compliance; GHQ-SS, somatic symptoms; GHQ-AS, anxiety and insomnia symptoms; GHQ-SD, social dysfunction symptoms; GHQ-DS, depressive symptoms; GHQ-T, total GHQ score; HT %, Hypertension prevalence rate (percentage) – determined by Fischer exact two-tailed test for small sample sizes.

Significant differences are highlighted in **bold**.

* Data adjusted for age, smoking, alcohol consumption and physical activity.

Table 2: Partial correlations in lean African women: WC and CV variables with xBRS, Leptin, and perception of health data

	xBRS	Leptin	GHQ-SS	GHQ-AS	GHQ-SD	GHQ-DS	GHQ-T
WC	$p = 0.434; r = -0.13$	$p = 0.084; r = 0.28$	$p = 0.062; r = -0.30$	$p = 0.200; r = -0.21$	$p = 0.878; r = 0.03$	$p = 0.498; r = -0.11$	$p = 0.180; r = -0.22$
SBP	$p = 0.428; r = -0.13$	$p = 0.891; r = 0.02$	$p = 0.434; r = 0.13$	$p = 0.995; r = -0.00$	$p = 0.101; r = 0.26$	$p = 0.608; r = -0.08$	$p = 0.579; r = 0.09$
DBP	$p = 0.395; r = 0.14$	$p = 0.988; r = 0.00$	$p = 0.886; r = 0.02$	$p = 0.650; r = 0.07$	$p = 0.017; r = 0.38$	$p = 0.685; r = -0.07$	$p = 0.468; r = 0.12$
MAP	$p = 0.860; r = 0.03$	$p = 0.974; r = -0.01$	$p = 0.573; r = 0.09$	$p = 0.717; r = 0.06$	$p = 0.025; r = 0.36$	$p = 0.755; r = -0.05$	$p = 0.400; r = 0.14$
HR	$p = 0.000; r = -0.54$	$p = 0.914; r = 0.02$	$p = 0.443; r = -0.12$	$p = 0.829; r = 0.04$	$p = 0.915; r = 0.02$	$p = 0.176; r = 0.22$	$p = 0.778; r = 0.05$
SV	$p = 0.70; r = -0.29$	$p = 0.604; r = -0.08$	$p = 0.327; r = -0.16$	$p = 0.134; r = -0.24$	$p = 0.031; r = -0.34$	$p = 0.415; r = -0.13$	$p = 0.072; r = -0.29$
CO	$p = 0.000; r = -0.59$	$p = 0.749; r = -0.05$	$p = 0.204; r = -0.21$	$p = 0.232; r = -0.19$	$p = 0.115; r = -0.25$	$p = 0.946; r = 0.01$	$p = 0.185; r = -0.21$
TPR	$p = 0.000; r = 0.54$	$p = 0.941; r = -0.01$	$p = 0.158; r = 0.23$	$p = 0.346; r = 0.15$	$p = 0.014; r = 0.38$	$p = 0.570; r = -0.09$	$p = 0.180; r = 0.22$
C _w	$p = 0.432; r = -0.13$	$p = 0.845; r = 0.03$	$p = 0.177; r = -0.25$	$p = 0.427; r = -0.13$	$p = 0.008; r = -0.41$	$p = 0.378; r = -0.14$	$p = 0.058; r = -0.30$

WC, waist circumference; CV, cardiovascular; xBRS, spontaneous baroreflex sensitivity; GHQ, General Health Questionnaire; GHQ-SS, somatic symptoms; GHQ-AS, anxiety and insomnia; GHQ-SD, social dysfunction; GHQ-DS, depressive symptoms; GHQ-T, total GHQ score; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; C_w, arterial compliance. All data were adjusted for age, smoking, alcohol consumption and physical activity. Significant correlations are highlighted in **bold**.

Table 3: Partial correlations in obese African women: WC and CV variables with xBRS, Leptin, and perception of health data

	xBRS	Leptin	GHQ-SS	GHQ-AS	GHQ-SD	GHQ-DS	GHQ-T
WC	$p = 0.161; r = -0.24$	$p = 0.064; r = 0.31$	$p = 0.102; r = 0.27$	$p = 0.230; r = 0.20$	$p = 0.680; r = -0.07$	$p = 0.911; r = -0.19$	$p = 0.443; r = 0.13$
SBP	$p = 0.244; r = -0.20$	$p = 0.869; r = 0.03$	$p = 0.445; r = -0.13$	$p = 0.452; r = -0.13$	$p = 0.482; r = 0.12$	$p = 0.833; r = 0.04$	$p = 0.823; r = -0.04$
DBP	$p = 0.026; r = -0.37$	$p = 0.913; r = 0.02$	$p = 0.657; r = -0.08$	$p = 0.181; r = -0.22$	$p = 0.819; r = -0.04$	$p = 0.407; r = -0.14$	$p = 0.362; r = -0.15$
MAP	$p = 0.058; r = -0.31$	$p = 0.868; r = 0.03$	$p = 0.569; r = -0.10$	$p = 0.377; r = -0.15$	$p = 0.762; r = 0.05$	$p = 0.884; r = -0.02$	$p = 0.666; r = -0.07$
HR	$p = 0.196; r = -0.22$	$p = 0.140; r = 0.25$	$p = 0.361; r = 0.15$	$p = 0.748; r = -0.05$	$p = 0.017; r = -0.39$	$p = 0.209; r = -0.21$	$p = 0.378; r = -0.15$
SV	$p = 0.735; r = 0.06$	$p = 0.301; r = 0.17$	$p = 0.316; r = 0.17$	$p = 0.046; r = 0.33$	$p = 0.108; r = 0.27$	$p = 0.056; r = 0.32$	$p = 0.037; r = 0.34$
CO	$p = 0.375; r = -0.15$	$p = 0.054; r = 0.32$	$p = 0.134; r = 0.25$	$p = 0.094; r = 0.28$	$p = 0.942; r = 0.01$	$p = 0.286; r = 0.18$	$p = 0.162; r = 0.23$
TPR	$p = 0.798; r = -0.04$	$p = 0.132; r = -0.25$	$p = -0.062; r = -0.31$	$p = 0.059; r = -0.31$	$p = 0.725; r = 0.06$	$p = 0.623; r = -0.08$	$p = 0.204; r = -0.21$
C _w	$p = 0.507; r = 0.11$	$p = 0.240; r = 0.20$	$p = 0.048; r = 0.33$	$p = 0.066; r = 0.31$	$p = 0.681; r = 0.07$	$p = 0.375; r = 0.15$	$p = 0.097; r = 0.28$

WC, waist circumference; CV, cardiovascular; xBRS, spontaneous baroreflex sensitivity; GHQ, General Health Questionnaire; GHQ-SS, somatic symptoms; GHQ-AS, anxiety and insomnia; GHQ-SD, social dysfunction; GHQ-DS, depressive symptoms; GHQ-T, total GHQ score; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; C_w, arterial compliance. All data were adjusted for age, smoking, alcohol consumption and physical activity. Significant correlations are highlighted in **bold**.

Tables 2 and 3 show partial correlation results when comparing WC and cardiovascular variables with xBRS, leptin and perception of health data. In lean subjects (Table 2) perceived social dysfunction correlated positively with DBP, MAP and TPR, and negatively with C_W .

In obese subjects (Table 3) xBRS correlated negatively with DBP, leptin correlated weakly but positively with CO ($p = 0.054$, $r = 0.32$) (Figure 1), and social dysfunction correlated negatively with HR.

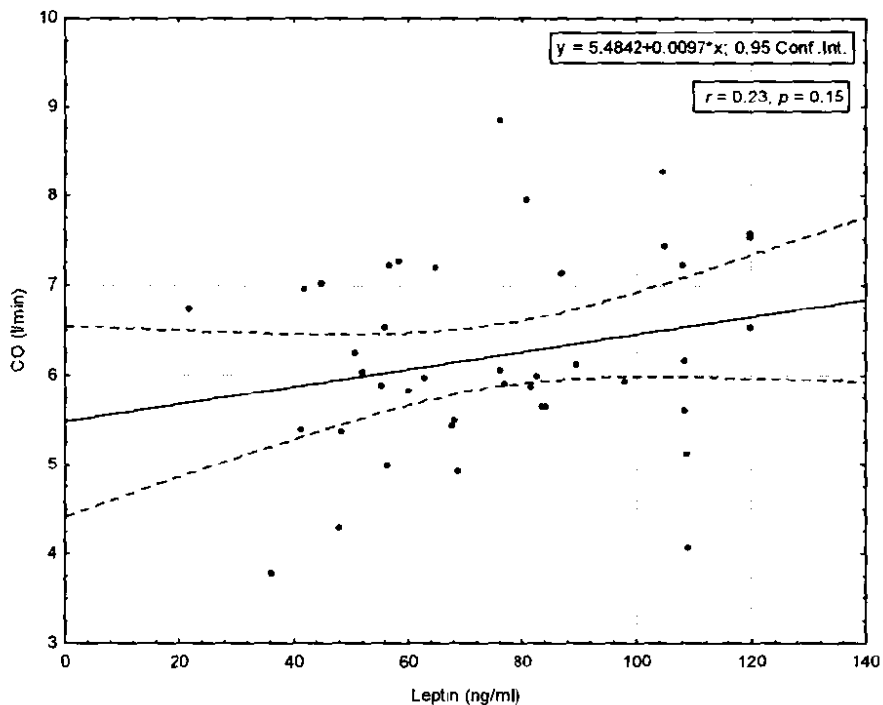


Figure 1: Correlation between leptin and cardiac output. Data unadjusted for age, smoking, alcohol consumption and physical activity. Regression and confidence interval ($\pm 95\%$) lines shown.

4. Discussion

The aim of our study was to investigate the contributions of xBRS, leptin and perception of health to increased sympathetic activity in lean and obese African women. It seems that the obese group showed higher central cardiac activity, judging by the CO (Table 1), which was significantly higher in the obese group compared to

the lean group. Overall, this would indicate increased sympathetic activity (as reflected by the increased HR) as well as a volume-loading effect (as indicated by the increased SV ($p = 0.06$) and / or increased contractile activity) (Dagenais et al., 2005). Additionally, this profile is accompanied by increased leptin levels, which could directly contribute to increased sympathetic activity and volume loading (Rahmouni and Haynes, 2005). Although no correlations were observed between leptin, HR and SV, a weak but positive correlation was obtained between leptin and CO ($p = 0.054$, $r = 0.32$).

Although no significant differences existed for xBRS, a positive correlation existed in the lean group between xBRS and TPR. This correlation was absent in the obese group, however xBRS showed a negative correlation with DBP. This may indicate not only impairment and / or desensitization of xBRS, but also a shortening of the DBP phase (Palatini and Julius, 1999). It is possibly indicative of a shift towards increased sympathetic activity, accompanied by increased leptin levels. These findings are further supported by the increased hypertension prevalence rates in the obese Africans.

Arterial compliance (C_w) was shown to be higher in the obese group. This may be attributable to the proposed direct effect of leptin on the vascular system (Rahmouni and Haynes, 2005) – where leptin is thought to have a potent vasodilatory effect (by inducing endothelial nitric oxide (NO) synthesis). Leptin also exerts angiogenic characteristics (Friedman and Halaas, 1998; Rahmouni and Haynes, 2005). Both these effects of leptin may have contributed to our findings – by increasing C_w and

decreasing TPR (via NO synthesis). However, as there were no significant correlations between leptin and these CV variables, this idea remains speculative.

The perception of health data is inconclusive. In the lean group, perception of social dysfunction had adverse associations with CV variables (positively with DBP, MAP and TPR, and negatively with SV and C_w). In the obese group, only weak correlations existed between CV variables and perception of health data, except for perceived social dysfunction which was negatively associated with HR. Although the subscales showed seemingly contradictory associations, the total GHQ-score was weakly but positively associated with SV. This suggests that in obese African women an overall perception of poorer health could be associated with a volume-loading effect and increased sympathetic activity. The precise mechanisms are still under scrutiny, but it is possible that a perception of poorer health could contribute to subjective stress, in turn being associated with increased sympathetic activity (Björntorp, 2001) and hence hypertension.

It seems that social dysfunction could contribute negatively towards cardiovascular variables in the lean group. This may indicate that African women will perceive themselves or their situation as socially unacceptable if they are not obese, since most African cultures still see obesity as a symbol of high social status, wealth, fertility and beauty (Fezeu et al., 2005; Mokhtar et al., 2002). Consequently, lean African women may undergo behavioural and dietary changes in order to become obese, and thus reach higher social status. Social dysfunction may therefore be an initial contributor towards sympathetic activity and hypertension in lean women who are in a process of becoming obese. However, if the women do reach a socially

acceptable level of obesity, their perceived social dysfunction would decrease as they would experience increased social support. Due to the cross-sectional nature of our study, however, this hypothesis could not be tested.

However, social dysfunction should not merely be viewed as a lack of receiving social support. Although the benefit of receiving social support has been acknowledged by Piferi and Lawler (2006), their own study also indicated that giving informal social support is associated with decreased ambulatory blood pressure. The authors hypothesized that this effect may be achieved through increased self-esteem and self-efficacy, influencing perceptions of stress, and ultimately improving physical health. Social dysfunction, therefore, is an indication of integration into the social network, both in giving and receiving social support (Piferi and Lawler, 2006). This may be particularly important in collectivistic cultures, from which all the participants of the current study came, and should be kept in mind for future research into social dysfunction and obesity-related diseases.

In conclusion, xBRS (although similar between groups) and leptin seem to contribute to blood pressure and thus hypertension in obese African women, possibly through increased sympathetic activity and volume loading. A perception of poorer health, especially a perception of social dysfunction, could possibly contribute to this image.

There were a number of limitations to this study. It has for instance been shown that xBRS can be influenced by the current phase of menstruation (Saeki et al., 1997). There were no adjustments for this in the analyses, which was an oversight of our study. It is likely that adjusting for these factors may have improved statistical

significance for xBRS. The role of the renin-angiotensin system subcutaneous abdominal adipocytes and its relationship towards obesity and hypertension has not been addressed (Sharma et al., 2002).

Future research on perception of health should incorporate either additional or other questionnaires besides the GHQ-28. Although the GHQ-28 was used to examine subjective perception of health, which provided an estimate of participants' levels of psychological well-being, it is more suited towards identifying psychopathology. In our study we expected perception of poorer health to be present in the obese subjects, and the GHQ-28 indicated such a trend. However, other questionnaires might be better suited to evaluate psychological functioning across the entire spectrum.

5. Acknowledgements

The authors are grateful to those funding this project, namely the South African National Research Foundation (NRF GUN number 2054068), the Medical Research Council and the Research Focus Area 9.1 of the North-West University (Potchefstroom Campus). The authors also wish to express their gratitude towards Proff. Marié Wissing and Alta Schutte for their contributions regarding the POWIRS study.

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CHAPTER 3

GENERAL FINDINGS AND CONCLUSIONS

INTRODUCTION

This chapter will present the *main findings* that were reported in this dissertation. Results will be discussed, interpreted, elucidated and compared to the relevant literature in Chapter 1. Conclusions will be drawn and recommendations will be made regarding further research into sympathetic activity in Africans, supported by baroreflex sensitivity, leptin and perception of health in Africans.

SUMMARY OF MAIN FINDINGS

The significant findings of this article reported in this dissertation were:

Psychological well-being and cardiovascular function in obese African women: the POWIRS study (Chapter 2)

The aim of the study was to investigate the contributions of baroreflex sensitivity (xBRS), leptin and perception of health data to increased sympathetic activity in lean and obese African women. It was hypothesized that (a) obese African women, compared to lean counterparts, would present with increased sympathetic activity, as indicated by increased HR, (b) the obese group with increased sympathetic activity will have higher BP, impaired xBRS, higher leptin levels and perception of poorer health, (c) increased sympathetic activity would be reflected by positive associations between HR, leptin and perception of health, and a negative association between HR and XBRS, and (d) obese African women would present with increased prevalence rates of hypertension.

Results of obese individuals indicated increased sympathetic activity as reflected by the increased heart rate (HR), and the first hypothesis was therefore accepted. The obese group had a higher diastolic blood pressure (DBP) and leptin levels, however xBRS and perception of health data were similar between the lean and obese groups. The second hypothesis was, therefore, partially accepted. HR showed no positive associations with leptin or perception of health data, nor a negative association with xBRS. The third hypothesis was, therefore, rejected. Finally, the obese subjects showed higher hypertension prevalence rates, and the fourth hypothesis was therefore accepted.

COMPARISON TO RELEVANT LITERATURE

When comparing the results of this study with existing literature, it is evident that certain findings confirmed that of previous research. It was found that, in African women, obesity is associated with increased sympathetic activity (Grassi & Seravalle, 2006), increased prevalence of hypertension rates (Sowers, 2003) and increased leptin levels (Hristova & Aloe, 2006). Social dysfunction has also been associated with increased vascular sympathetic activity in Africans (Malan *et al.*, 2006).

Contradictory findings of this study were that impaired xBRS was not directly associated with increased sympathetic activity (Zucker *et al.*, 1995); and increased leptin levels were only weakly associated with increased sympathetic activity (Hristova & Aloe, 2006). Leptin also showed no correlation with obesity (indicated by increased waist circumference) within the obese group (Prolo *et al.*, 1998).

CHANCE AND CONFOUNDING

Chance: Before the main findings of the study are discussed, some important factors need to be taken into consideration. A number of methodological issues may have caused weaknesses in the study and may therefore have influenced the outcomes of the research.

The number of subjects (N=85) in the study sample may have been inadequate to correctly identify etiological trends in the greater population. The South African population is a diverse mixture of different cultures and ethnicities, and since this group was recruited from the Potchefstroom district in the North West Province of South Africa, it is not representative of the entire South African population.

Concerning the results, the possibility of chance should be taken into account. By using partial correlations and forward stepwise regression analyses, statistics indicate that one out of twenty significant correlations may be because of chance.

Confounding factors: Although an inclusion criteria for this study was that the subjects should be "apparently healthy", the health status of the subjects is not a certainty. Other confounding factors such as diet, HIV status and socio-economic status may have influenced the results. Age, smoking, alcohol consumption and physical activity level, as possible confounders, were addressed by adjusting statistically.

WEAKNESSES OF STUDY

Weaknesses of the study included:

1. Duration of obesity was not known, which could influence adaptation / habituation of physiological resources;
2. The exclusion of 17 subjects (due to incomplete datasets) could have affected the statistical significance of the various analyses;
3. No adjustments were incorporated for either menstrual cycle phase or oral contraceptive usage, both which could have impacted on the statistical significance of xBRS;
4. The General Health Questionnaire (GHQ) does not measure the complete spectrum of health perception, but merely the perceived absence or presence of symptoms indicative of pathological conditions. Other questionnaires, which could provide a more holistic view of psychological functioning, should therefore be considered in future.

DISCUSSION OF MAIN FINDINGS

Abdominal obesity is associated with hypertension (Chuang *et al.*, 2006) and the development of CVD (Sowers, 2003). Both obesity and hypertension are becoming more prevalent in Sub-Saharan Africa (Puoane *et al.*, 2002; Seedat, 2004), but the role of increased sympathetic activity in obesity-related diseases (Hristova & Aloe, 2006) has not yet been investigated in Africans.

The main focus of this study was to investigate the contributions of xBRS, leptin and perception of health to increased sympathetic activity in lean and obese African women. Although the findings cannot be generalized to the whole African female population of South Africa, they serve as a foundation for future in-depth studies.

Increased sympathetic activity (as reflected by increased HR) and increased leptin levels were observed in the obese group, however, no differences existed for xBRS and perception of health between the lean and obese groups. However, a negative correlation existed between xBRS and DBP, indicating a possible shortening of the diastolic phase (Palatini & Julius, 1999). Additionally leptin correlated weakly but positively with cardiac output ($p = 0.054$, $r = 0.32$). In the lean group, social dysfunction was adversely associated with cardiovascular variables (positively with DBP, MAP and TPR, and negatively with C_w). However, in the obese group social dysfunction was negatively associated with HR. In obese women with higher BP and increased HR a perception of poorer health may represent a novel contributor to high blood pressure and subsequently cardiovascular diseases.

CONCLUSION

In conclusion, xBRS (although similar between groups) and leptin seem to contribute to blood pressure and thus hypertension in obese African women, possibly through increased sympathetic activity and volume loading. A perception of poorer health, especially a perception of social dysfunction, could possibly contribute to this image.

RECOMMENDATIONS

The following recommendations are proposed for future studies:

1. The subjects in the study group were relatively young. Follow-up studies are, therefore, recommended to determine the long-term effects that xBRS, perception of health, and especially leptin, may have on sympathetic activity and cardiovascular function.

2. Duration of obesity is a factor that needs to be considered. As some of leptin's effects seem to differ depending on acute or chronic exposure (Matsumura *et al.*, 2003), it would be valuable to assess the influence (if any) that duration of obesity may have on both physiological and psychological parameters.
3. Additional psychological questionnaires should be included to evaluate perception of health and / or psychological well-being.