



# **Metabolic syndrome marker cut-off points and target organ damage revisited in an urban South African cohort: The SABPA Study**

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**Lord, it's my joy to honor You.**

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The Author

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## DECLARATION

The co-authors of the article which form part of this dissertation, Prof J Hans de Ridder (promoter), and Prof L Malan (co-promoter) hereby give permission to the candidate, Ms Svelka Hoebel, to include three articles as part of a Doctoral dissertation. The contribution, both supervisory and supportive, of these co-authors was kept within limits, thereby enabling the candidate to submit this dissertation for examining purposes. This thesis serves as fulfillment of the requirements for the Ph.D. degree within the School of Biokinetics, Recreation and Sport Science in the faculty of Health Sciences at the North-West University, Potchefstroom Campus.

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## SUMMARY

**Objectives:** The aim of this study was to determine the prevalence of MetS among different African populations using the new Joint Statement Criteria. Hereafter we aimed to determine whether waist or neck circumference is the best predictor of MetS risk after ethnic, gender and age-specific cut-points were developed. Lastly, we aimed to determine whether afore-mentioned cut-point can predict albumin:creatinine ratio as a marker of target organ damage. **Methods:** The study sample (N=409) comprised of urban African (men, N=101; women, N=99) and Caucasian (men, N=101; women, N=108) teachers from the Dr. Kenneth Kaunda Education district in the North-West Province, South Africa. Participants were aged between 25 and 65 years. Anthropometric measurements, albumin:creatinine ratio and other markers of the metabolic syndrome (MetS) (systolic and diastolic blood pressure [SBP and DBP], glucose, triglycerides [TG] and high density lipoprotein [HDL]) were determined. **Results:** Africans (65 and 63 % for men and women) and Caucasian men (73%) showed high prevalence of MetS; ROC analysis determined neck circumference (NC) cut-points of 39 and 35 cm for young and older African men, 32 and 35 cm for young and older African women, 40 and 41 cm for Caucasian men and 34 and 33 cm for Caucasian women. This NC cut-point can be used to determine metabolic syndrome risk in all groups, except in African women; ROC developed waist circumference (WC) cut-points were 91 cm for all African male groups, 84, 81 and 84 cm for young, older and total group of African women. Suggested WC cut-points for Caucasian men were 93 cm for the young group and 97 cm for older as well as total Caucasian male groups, while cut-points for Caucasian women were 87 cm, 79 cm and 84 cm for young, older and total Caucasian women. These WC cut-points were good measures of metabolic syndrome risk in all groups; neither cut-point of WC nor NC could increase the risk of albumin:creatinine ratio. **Conclusion:** African women as a group present with few MetS risk factors and glucose is associated with renal function risk in Africans; NC cut-points may be used as an additional anthropometric marker to predict the metabolic syndrome in a South African cohort, but not in African women; WC cut-points demonstrated to be good predictors of the metabolic syndrome in the same

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South African cohort, especially among men; WC would seem to be the best measure of MetS risk in all African populations, although NC can also be used for this purpose in all African populations, except in African women.

**Key Words:** Metabolic syndrome, neck circumference (NC), waist circumference (WC), target organ damage (TOD), microalbuminuria, African, Caucasian

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## OPSOMMING

**Doel:** Die doel van hierdie studie was om die voorkoms van metaboliese sindroom in verskillende Afrika-populasies te bepaal wanneer die nuwe metaboliese sindroom-kriteria gebruik word. Hierna is etnies-, geslag- en ouderdomspesifieke afsnypunte vir die nek- en middelomtrekke ontwikkel om sodoende te bepaal watter een van hierdie metings die beste sal wees om die risiko vir die metaboliese sindroom aan te dui. Ten slotte het ons gepoog om te bepaal of die voorgenoemde metings gebruik kan word om die risiko van albumien:kreatinien-verhouding te voorspel. **Metode:** 'n Teikenpopulasie-studie het 409 onderwysers uit die Dr. Kenneth Kaunda Onderwysstreek van die Noordwes Provinsie, Suid-Afrika, ingesluit. Deelnemers het in die ouderdomsgroep tussen 25 en 65 jaar geval en het Afrikane (mans, N=101; vroue, N=99) en Kaukasiërs (mans, N=101; vroue, N=108) ingesluit. Data is verkry aangaande die antropometriese merkers, albumien:kreatinien-verhouding en die merkers van die metaboliese sindroom, naamlik sistoliese en diastoliese bloeddruk, glukose, trigliseriede en hoëdigtheidslipoproteïene. **Resultate:** Afrikane (65 en 63 % vir mans en vroue) en blanke mans (73%) het 'n hoë voorkoms van die metaboliese sindroom getoon; afsnypunte vir die nekomtrek is gevind by 39 en 35 cm vir jong en ou Afrikane-mans, 32 en 35 cm vir jong en ou Afrikane-vroue, 40 en 41 cm vir Kaukasiese mans en 34 en 33 cm vir Kaukasiese vroue. Hierdie nekomtrek-afsnypunte kan in alle groepe, behalwe die Afrikane-vrouegroep, gebruik word om die risiko vir die metaboliese sindroom te bepaal; voorgestelde afsnypunte vir die middel is 91 cm vir alle Afrikane-mans, 84, 81 en 84 cm vir die jong, ou en totale Afrikane-vrouegroep. Die afsnypunt vir Kaukasiese mans word gestel op 93 cm vir die jong groep, terwyl die afsnypunt vir ouer mans sowel as die totale groep gestel word op 97 cm, Die afsnypunt vir die Kaukasiese vroue word gestel op 87, 79 en 84 cm vir die jong, ou en totale vrouegroep. Die afsnypunte vir die middelomtrek kan gebruik word om die metaboliese sindroom-risiko in alle groepe te bepaal; Geeneen van die antropometriese metings kon die risiko vir die teenwoordigheid van 'n hoë albumien:kreatinien-verhouding bepaal nie. **Gevolgtrekking:** Afrikane-vroue presenteer met min metaboliese sindroom-risikofaktore, en glukose word geassosieer met renale risiko by Afrikane. Nekomtrek-afsnypunte kan gebruik word

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as 'n bykomstige meting om die metabooliese sindroom-risiko by alle groepe te bepaal, behalwe by die Afrikane-vroue; middel omtrek is 'n goeie voorspeller van die metabooliese sindroom by al die groepe in dieselfde populasie, veral vir mans; middelomtrek blyk dus die beste meting vir die metabooliese sindroom te wees, al kan die nekomtrek ook vir hierdie doel gebruik word, net nie by die Afrikane-vrouegroep nie.

Middelomtrek is die beste meting om metabooliese sindroom-risiko te bepaal. Die nekomtrek kan ook vir hierdie doel gebruik word by al die getoetste groepe, behalwe by Afrikane-vroue

**Sleutelwoorde:** Metabooliese sindroom, nekomtrek, middelomtrek, teikenorgaan-skade, mikroalbuminurie, Afrikane, Kaukasiërs

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## LIST OF ABBREVIATIONS

SABPA: Sympathetic activity and Ambulatory Blood Pressure in Africans.

### Anthropometry

BMI:	Body Mass Index
NC:	Neck Circumference
WC:	Waist Circumference

### Physiological

BP:	Blood Pressure
DBP:	Diastolic Blood Pressure
GGT	Gamma Glutamyl Transferase
HdL:	High Density Lipoprotein
LdL	Low Density Lipoprotein
MetS:	Metabolic Syndrome
SBP:	Systolic Blood Pressure
TG:	Triglycerides
PA	Physical Activity
ACR	Albumin : creatinine ratio

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## Organizations

ACSM:	American College of Sports Medicine
ADA:	American Diabetes Association
AHA:	American Heart Association
IDF:	International Diabetes Federation
JSC	Joint Statement Criteria
NCEP ATP III:	National Cholesterol Education Program's Third Adult Treatment Panel
WHO:	World Health Organization

## Statistics

CI:	Confidence Interval
N:	Number of participants
ROC	Receiver Operating Characteristic
SE:	Standard error
OR	Odds Ratios
%:	Percentage

## Chapter 1

*Problem Statement and Aim of the Study***1.1 PROBLEM STATEMENT**

Metabolic Syndrome (MetS) or Syndrome X affects 20-25% of the world's adult population (IDF, 2006:4). MetS patients are twice as likely to die from cardiac disease and are at a greater risk of developing type 2 diabetes than persons without this metabolic cluster (International Diabetes Federation [IDF], 2006:4). Type 2 diabetes accounts for 90% of the diabetic population (ACSM, 2006:207; IDF, 2006:5; Mahan & Escott-Stump, 2004:797; Ehrman *et al.*, 2003:131) and increases the risk of the development of cardiovascular disease. Subsequently these conditions can cause premature death (IDF, 2006:5).

The MetS is a cluster of cardiovascular risk factors in an individual (IDF, 2006:4; Mahan & Escott-Stump, 2004:568; Whitney & Rolfes, 2002:607). In the past, different expert groups have put forward different cardiovascular risk factors. These risk factors include high waist circumference, increased levels of triglycerides and fasting glucose, hypertension, decreased levels of high density lipoprotein, and some criteria include microalbuminuria (IDF, 2006:10; NCEP ATP III, 2002:3189). However, recently consensus was reached by these expert groups (Alberti *et al.*, 2009:1642).

This recently reached consensus (here after referred to as the Joint Statement Criteria or JCS) lessens the confusion with regard to identifying the MetS, as was the case when several clinical definitions were presented (Alberti *et al.*, 2009:1641). According to Alberti *et al.* (2009:1642), a diagnosis can be made when 3 of the 5 following risk factors are present:

- Elevated waist circumference (WC) (population and country specific values)
- Elevated triglycerides ( $\geq 1.7$  mmol/L) or drug treatment for elevated triglycerides

- Reduced high density lipoprotein (HdL) Cholesterol ( $<1.0$  mmol/L for males and  $1.3$  mmol/L for females) or drug treatment for reduced HdL
- High fasting glucose ( $\geq 5.6$  mmol/L) or treatment thereof
- Increased blood pressure (systolic  $\geq 130$  mm Hg and/or diastolic  $\geq 85$  mm Hg) or antihypertensive treatment

These new Joint Statement Criteria, are the sum of previously presented definitions that have not been developed within an African population. In fact Fezeu *et al.* (2007:70, 75) found that many of the earlier definitions cannot be applied to African populations. They found that application of a diagnostic tool developed in one population may not be as effective when applied to another population or ethnic group (Fezeu *et al.*, 2007:75). Hence it is imperative to define the criteria for different ethnic groups.

In terms of WC, the JSC does not suggest that this measure be a prerequisite for the syndrome as previously recommended (Alberti *et al.*, 2009:1642). However, anthropometric measurement can be very useful in impoverished communities in order to determine risk for the development of the MetS or other chronic diseases (Shultze *et al.*, 2006:1922; Mensink *et al.*, 2003:556; Sargeant *et al.*, 2002:795). It is recommended that the International Diabetes Federation (IDF) cut-off points for WC (94 cm for males and 80 cm for females) be used for sub-Saharan Africans until more data is available for this ethnic group (Alberti *et al.*, 2009:1642 and IDF, 2006:11). In terms of Africans, Fezeu *et al.* (2007:75) found that WC had a stronger association with MetS markers in this population than insulin resistance as seen with high glucose levels.

Together with WC, the neck circumference (NC) is a promising easy measurement that can also be used as part of the screening tool for MetS (Savas *et al.*, 2009:s69). NC is associated with metabolic disorders related to insulin resistance and it is easier to measure than WC, since it does not change during the day (Laakso *et al.*, 2002:875). The last 2 mentioned measurements have also been found to be associated with target organ damage (TOD), specifically microalbuminuria, in urban Africans (Hoebel *et al.*, 2010:177). Although microalbuminuria is not part of the new

criteria, it has been found the MetS increases this risk twofold (Leoncini *et al.*, 2005:458). In non-diabetic hypertensive persons, MetS has also been associated with TOD as measured by urine albumin concentrations (Leoncini *et al.*, 2005:459). Leoncini and co-workers (2005:459) concluded that MetS subjects showed a greater risk for TOD than either of the MetS components on their own (Leoncini *et al.*, 2005:459). Since it has been found that MetS predispose to TOD, it is prudent to investigate this phenomenon in the African population.

As mentioned previously, the MetS criteria have not been developed for an African population, and it is well known that disease prevalences (Thom *et al.*, 2006:e128-129) and physical appearances (Kruger *et al.*, 2001:738; Croft *et al.* 1995:61) differ between different ethnic groups and populations. These differences in disease prevalence among different ethnic groups can be ascribed to differences in education, socio-economic status, culture linguistics, differences in compliance with medical treatment and lifestyle (Homedes & Ugalde, 1993:294,300).

MetS can be brought on by poor lifestyle choices such as unhealthy dietary habits and physical inactivity, obesity or overweight, some genetic factors and aging (IDF, 2006:7; National Cholesterol Education Program (NCEP ATP III), 2002:3188; Whitney & Rolfes, 2002:607). It has also been found that MetS can be inherited since risk factors cluster in families (Groop & Orho-Melander, 2001:106).

Poor lifestyle choices (i.e. smoking, alcohol usage and low physical activity) have been associated with urbanization. Urbanization has been associated with increased health risk because of the transformation in lifestyle due to environmental and social changes (McMicheal, 2000:1119). These changes to society include different diet and physical activity patterns and a more stressful environment (Malan *et al.*, 2012: 546; Popkin, 1999:1905; Mutatkar, 1995:980). Alcohol and tobacco use are in some instances a coping mechanism for stress, which can lead to the deposit of fat in visceral depots (Björntorp, 1997:802). Urban Africans are more prone to being overweight or obese, their diet and physical activity are less favourable, and stress is more prevalent (Wild *et al.*, 2004:1049; Mutatkar, 1995:980). This could lead to the increased prevalence of chronic diseases such as diabetes, hypertension and other

cardiovascular complications (Seedat, 2009:39; Malan *et al.*, 2006:309; American Diabetes Association (ADA), 2005:S38; Ehrman *et al.*, 2003:283; Popkin, 1999:1913; Mutatkar, 1995:980). Physical activity, be it leisure time activities have proven to reduce this risk for developing MetS (Cho *et al.*, 2009:786,791).

With the rising epidemic of MetS, there is a moral medical and economic imperative to identify persons at risk to prevent progression of disease (IDF, 2006:8). Early detection of any disease is important for both the individual and the community for health and financial reasons. The risk to the health of adults should be identified early and treated, because this group is responsible for the economic support of the community (De Onis & Habicht, 1996:654). Early detection is essential for the community in order for strategic planning to take place and for the development of health policies (Fields *et al.*, 2004:401).

For early detection, easy and more economic methods for screening should be implemented in impoverished communities. Anthropometric measurements are portable and inexpensive and therefore convenient to use for screening (De Onis & Habicht, 1996:657) and known for their value as predictors of health risk (Mensink *et al.* 2003:556; Sargeant *et al.* 2002:795). However, African-specific, as well as age specific cut-off values are non-existing, and as mentioned earlier, ethnicity has an effect on physical appearance and disease prevalence and age is also a factor that needs to be taken into account when developing anthropometric references (De Onis & Habicht, 1996:655, 657). When accurate anthropometric cut-off values have been developed for screening it would lessen the need for expensive tests in a clinical setting. These measurements should, however, only be used for screening and referral, and not as self-sufficient diagnostic tools (De Onis & Habicht, 1996:657).

Second to screening, prevention and management strategies are important and include lifestyle modification such as weight loss through diet and physical activity (Alberti *et al.*, 2009:1641; IDF, 2006:15; NCEP ATP III, 2002:3271) and when this course of treatment is inadequate, drug therapies should be introduced. At a clinical level, the identification of a MetS patient is important to reduce or manage other risk factors (Alberti *et al.*, 2009:1641).

Information with regards to MetS of Africans and differences between the African and Caucasian population in Sub-Saharan Africa proved difficult to obtain. In this regard Alberti *et al.* (2009:1643) suggested that more studies are needed in order to develop more reliable WC cut-off points for the different ethnic groups (Alberti *et al.*, 2009:1642). Fezeu *et al.* (2007:76) also suggested that WC cut-off values that are specific to the African population must be developed through further research and that preventive strategies must be implemented in this population.

With the above in mind, this research aimed to answer the following questions: Firstly, how do the MetS markers in Black Africans compare to Caucasians, when using the new Joint Statement Criteria? Secondly, can we develop specific anthropometric cut-off points for NC amongst the African and Caucasian populations in South Africa? And thirdly, can we determine a WC specific to African and Caucasian populations with which to screen for metabolic syndrome and target organ damage?

Benefits include addressing the lack of ethnic specific cut-off points for Africans, so that more effective screening can be done amongst this group. This could also lead to the development of more cost effective screening tools that could be used among impoverished areas, lessening the need for initial clinical tests.

## 1.2 OBJECTIVES

The objectives of this study are to:

- 1 Compare the prevalence of MetS markers in Africans and Caucasians using the new joint statement criteria set forward by Alberti *et al.* (2009).
- 2 Determine ethnic-, gender- and age specific cut-points for NC as possible MetS marker in South Africans using Receiver Operating Characteristic curves (ROC).
- 3 Determine ethnic-, gender- and age specific WC cut-points for WC in order to develop ethnic specific cut-point for the MetS in South Africans using Receiver Operating Characteristic curves (ROC).

## 1.3 HYPOTHESES

The study is based on the following hypotheses:

1. The MetS prevalence is high amongst Africans when using the new joint statement criteria.
2. NC cut-off points would be higher in African than Caucasian South Africans and can successfully be used as a MetS screening tool.
3. WC cut-points would be higher in African than Caucasian South Africans and these newly developed cut-points will be effective as a screening tool for determining the presence of MetS.

## 1.4 STRUCTURE OF THE THESIS

The thesis is presented in six main parts namely, an introduction (Chapter 1), a literature review (Chapter 2) and three research articles (Chapter 3-5). Thereafter a summary with conclusions and recommendations will follow (Chapter 6).

**Chapter 1** consists of the problem statement together with the objectives and the hypotheses of this study.

**Chapter 2** contains the literature review focussing on the metabolic syndrome, anthropometry and target organ damage in different ethnicities. The third to fifth chapters take the form of articles.

### Chapter 3

Article 1: Differences in MetS marker prevalence between Black and Caucasian

Africans: The SABPA Study (2011. *Journal of Endocrinology, Metabolism and Diabetes of South Africa*, 16(1):49-56.)

### Chapter 4

Article 2: Determining cut-off values for neck circumference as a measure of the metabolic syndrome amongst a South African cohort: the SABPA Study. (2012. *Endocrine*, DOI: 10.1007/s12020-012-9642-y)

### Chapter 5

Article 3: Developing ethnic-,gender- and age appropriate cut-points to predict the metabolic syndrome: The SABPA study (**prepared for Obesity**).

The summary, the conclusions and the recommendations are posed in **Chapter 6** which will be followed by a list of appendices.

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*Metabolic syndrome: An epidemic of our time***2.1 INTRODUCTION**

X marks the metabolic syndrome (MetS), an epidemic that has reached Africa and it would seem that more Africans than Caucasians present with this syndrome (Hoebel *et al.*, 2011:52). The metabolic syndrome (MetS) manifests in the clustering of hypertension, hyperglycemia, dislipidemia and central obesity (Alberti *et al.*, 2009:1642; IDF, 2006:10) and ultimately leads to target organ damage (Schillaci *et al.*, 2006; Leoncini *et al.*, 2005; Mulè *et al.*, 2005). The epicentre seems to be in an urban environment with the western lifestyle it entails (IDF, 2006:4). Although this cluster of risk factors presents serious complications to health, it can successfully be controlled with lifestyle modification if detected early (IDF, 2006:8, 15). Early detection, and thus control is, however, hampered by lack of awareness, easy screening methods and different health needs competing for limited resources (Bradshaw *et al.*, 2007:700).

As resources are limited, it would be of great importance to develop early and cost-effective methods of screening for MetS that can routinely be implemented. For this purpose, anthropometry is vital, as this method is portable, inexpensive and convenient. Despite anthropometric measures being a suitable method, it should only be used for screening and referral purposes and not as a self-sufficient diagnostic tool (De Onis & Habicht, 1996:657). For optimal results in the screening process it is necessary to develop ethnic-specific cut-points (IDF, 2006:11). Routine screening can be done by registered anthropometrist (Biokineticists), who can incorporate extra screening measures into an existing protocol. As a profession that is concerned with preventative and rehabilitative treatment, namely Biokinetics, new

and effective and specific cut-points could greatly improve health and quality of life through early detection (Biokinetics Association of South Africa [BASA], 2011).

Developing quick and easily integrateable screening methods could ultimately reduce prevalence of health risk factors and target organ damage and improve the overall health of impoverished communities.

## **2.2 URBANIZATION, INSTIGATOR OF THE MetS**

In Africa, urbanization is a more recent (Seedat, 2009:39; Seedat 1990:s67) and rapid occurrence (McMicheal, 2000:1117). Urbanization is the process in which a growing percentage of a population migrates to city areas (Mutatkar 1995:977) and is associated with acculturation which is the process by means of which one cultural group adopts behaviours of another (De Klerk, 2007:3). Urbanization is an imminent process, due to the promise of better education and job availability (Moore *et al.*, 2003:274; McMicheal, 2000:1117). However, this so-called economic stability promised in urban areas has a negative effect on health due to a more Westernized lifestyle with accompanying poor lifestyle choices concerning diet, physical activity and increased stress (Popkin, 1999:1905; Mutatkar, 1995:980). Poor behaviours such as alcohol consumption and smoking have been found to be utilized as coping strategies and the stress of coping with urbanisation could consequently cause hypertension prevalence (Malan *et al.*, 2012: *in press*; Malan *et al.*, 2008:327) and waist circumferences to escalate (Björntorp, 2001:80), both of which are risk factors of MetS.

The effect of a modern industrial lifestyle can be seen in the lowering of some communicable diseases (Strydom, 2005:5) and an increase in non-communicable diseases (diabetes, cardiovascular disease) (Mutatkar, 1995:980 Strydom, 2005:5).

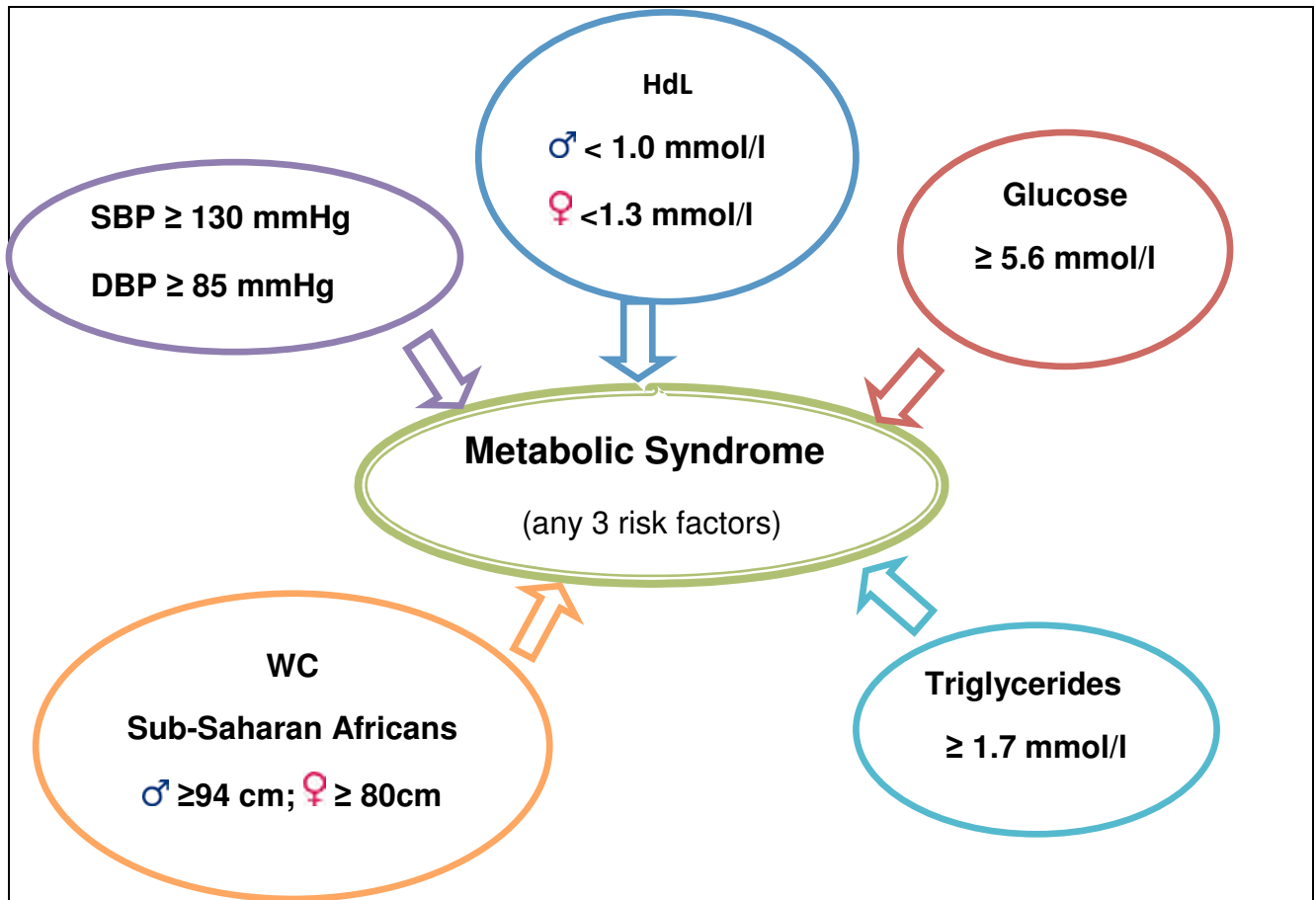
Urbanization can thus be said to set off the development of MetS and as such can be a central starting point from which the MetS will be discussed.

### 2.3 THE METABOLIC SYNDROME

It has been found that the metabolic syndrome (MetS) is an increasing epidemic worldwide and that it is largely related to the increasing prevalence of obesity and sedentary lifestyle (Alberti *et al.*, 2009:1641) in an urban environment (Popkin, 1999:1905; Mutatkar, 1995:980).

Risk factors of the metabolic syndrome have long been established. However, different definitions and cut-points for these risk factors have been put forward by various organizations, for instance the International Diabetes Federation (IDF), the American Heart Association (AHA), the third National Cholesterol Education Program (NCEP III), and the World Health Organization (WHO) (IDF, 2006; Grundy *et al.*, 2005; NCEP III, 2002; WHO, 1999). These different definitions have led to confusion in respect of diagnosing and identifying persons at risk of developing MetS (Alberti *et al.*, 2009:1641). The dilemma resulted in the development of one new definition by all the organizations concerned (Alberti *et al.*, 2009:1642). The 2009 Joint Statement Criteria (JSC) risk factors (figure 2.1) include elevated levels of systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (Trig), fasting glucose and central obesity and lowered levels of high-density lipoprotein cholesterol (HDL) (Alberti *et al.*, 2009:1642). The only component that needs further refinement through research is the waist circumference (WC), which has yet to have ethnic- and gender-specific cut-points developed for Africans (Alberti *et al.*, 2009:1643).

## Components of the metabolic syndrome



**Figure 2.1** Components of the metabolic syndrome (Alberti *et al.*, 2009:1643).

### 2.3.1 Anthropometry

Anthropometry, the measurement of size, weight and proportions of the body, is the most inexpensive and portable method for determining body composition with the intention to identify health status (De Onis & Habicht, 1996:650). These measurements can thus be used for the purpose of monitoring and screening health (De Onis & Habicht, 1996:650).

It is suggested that anthropometry be used together with traditional diagnostic methods to improve prediction of MetS risk factors such as Type 2 diabetes

(Mensink *et al.*, 2003:552,555). Anthropometric reference data can successfully be used to screen for the presence of health risk factors but should, however, not be used as independent means of diagnosis. Age, race, socioeconomic and lifestyle factors should be taken in account when developing anthropometric references (De Onis & Habicht, 1996:655, 657).

### 2.3.1.1 Obesity and Overweight

Obesity is a visible sign of the possible presence of the MetS and is more prevalent in the female African community (Puoane *et al.*, 2002:1041). Obesity is defined as an accumulation of excess fat, regardless of the localization of this fat (Björntorp, 2001:78). With an increase in adipose tissue and consequently body mass index (BMI), body composition will change. A greater abdominal, or central fat distribution, has been associated with increased risk for insulin resistance, hyperinsulinemia and lipids abnormalities (Raji *et al.*, 2001:5370). Peripheral fat accumulation does not have the same adverse effect on health as does the accumulation of central fat (Cnop *et al.*, 2002:1005). Fat accumulation around visceral organs has metabolic characteristics, which implicate insulin resistance and glucose intolerance, which are major risk factors for MetS (Menke *et al.*, 2007:793; Ehrman *et al.*, 2003:156).

Furthermore, for every 5 kg weight gain, regardless of central or peripheral fat distribution, Cicero *et al.* (2005:1264-1266) found that health risk increases. This risk is further increased with duration of being overweight or obese (Wannamethee & Shaper, 1999:1271). Although BMI values theoretically reflect overweight and obesity (ACSM, 2006:58) and are associated with diabetes incidence (Cicero *et al.*, 2005:1264-1266; Almdal *et al.*, 2008:40-45), this measure should not be used without other methods because it does not give an account of the body composition (ACSM, 2006:58). It is also not clear whether BMI values can be applied to populations in which the incidence of overweight and obesity is high (Sargeant *et al.*, 2002:792) as is the case among African women (Puoane *et al.*, 2002:1041), suggesting that other, more effective screening methods should be developed.

### 2.3.1.2 Waist Circumference

Obesity defines excess fat accumulation while waist circumference (WC) shows central or abdominal fat accumulation (Björntorp, 2001:78). Obesity and circumferences are related and as such can be used to determine health risk (ACSM, 2006:58, 59; Ehrman, 2003:154). Perry *et al.* (2000:642) found that WC can be used successfully to determine the risk as an alternative for the use of visceral fat (intra-abdominal fat) which is the more accurate measure but requires more technical equipment. The reason why WC is an accurate measure is that it includes the amount of visceral fat and subcutaneous adipose tissue (adipose tissue between the skin and muscle). WC is influenced, amongst others, by gender and age. Males tend to have an android or apple-shaped build while women tend to show a gynoid or pear-shaped build (Mahan & Escott-Stump, 2004:568). This would have the effect of men theoretically having smaller hip circumferences and larger WC than women. Ageing has the effect of muscle mass lessening and a fat redistribution from the periphery to central adipose depots and the health risk of individuals increase with an increase in WC as well as with ageing (Janssen, 2009: 164, 168). It has been suggested that more age-specific cut-points need to be developed for WC to be a more accurate determinant of health risk, this could however lessen the simplicity of this measure (Stevens *et al.*, 2010:13).

The need exists for ethnic-specific cut-points to be developed for sub-Saharan Africans (Alberti *et al.*, 2009:1642; IDF, 2006:11). Currently, all sub-Saharan Africans are advised to be classified into WC groups according to European reference values (Alberti *et al.*, 2009:1642; IDF, 2006:11). Prinsloo *et al.* (2011:601,602) has started the process of developing more accurate ethnic-specific cut-off values for Africans. Although advanced research in larger datasets is needed, Prinsloo *et al.* (2011:601,602) suggested a cut-off value of 90 cm for African men (n=81) and 98 cm for African women (n=90). These cut-points were developed for blood pressure as a risk factor for MetS because participants with WC's at these cut-points revealed the greatest probability to present as hypertensive (Prinsloo *et al.*, 2011:601). The cut-points developed by Prinsloo *et al.* (2011) differ greatly from

the suggested JSC values of  $\geq 94$  cm for men and  $\geq 80$  cm for women (Alberti *et al.*, 2009:1642; IDF, 2006:11). This could suggest that hypertension or MetS as a whole occurs at different WC cut-points and that using the suggested European cut-off values could over or underestimate health risk in African populations.

### 2.3.1.3. Neck Circumference

Furthermore, neck circumference (NC) might be an independent screening tool for metabolic risk factors (Laakso *et al.*, 2002:875; Ben-Noun *et al.*, 2001:476-477). This possible new measure of MetS was found to be related to other anthropometric parameters such as BMI and WC and indicated central obesity (Onat *et al.*, 2009:48, 49; Laakso *et al.*, 2002). As NC is related to BMI and WC, which increase with ageing (Janssen, 2009: 164), it would stand to reason that NC could possibly also increase with age. Research to this regard has however not been found. Furthermore it has been recommended that when determining anthropometric reference data that age also be taken into account (De Onis & Habicht, 1996:655, 657).

Associations have been found between NC and metabolic disorders such as insulin resistance (Laakso *et al.*, 2002; Dixon & O'Brien, 2002:774; Ben-Noun *et al.*, 2001:476-477). Additionally, NC has been found to be related to microalbuminuria, which was previously a risk factor for MetS (Hoebel *et al.*, 2010:177). It would seem that NC does not correlate with total or low-density ILDLipoprotein (LDL) cholesterol but is associated with most other cardiometabolic risk factors (Preis *et al.*, 2010:3703, 3703). Controversy exists, since another study suggested that associations between NC and physiological factors differ between genders. Onat *et al.* (2009:48,49) demonstrated more profound results for men than for women, while Preis *et al.* (2010:3708) concluded that NC is associated more with adverse health risk factors in women. This could possibly be ascribed to the differences in the storage of free fatty acids between men and women (Preis *et al.*, 2010:3709). It would seem that there is a stronger relationship between upper body fat and free fatty acids in women than in men (Nielsen *et al.*, 2004:1587).

NC is recommended as a screening tool because it is easy and affordable and related to other anthropometric parameters (Onat *et al.*, 2009:48, 49; Laakso *et al.*, 2002:875; Ben-Noun *et al.*, 2001:476-477). NC has been found to be a superior measurement above WC, due to the fact that NC does not change during the day as is the case with WC (Laakso *et al.*, 2002:875). However, it is recommended that NC should not be independently used to assess MetS risk and should be used together with WC to provide additional information on MetS prevalence (Onat *et al.*, 2009:49, 51).

NC cut-points that have been suggested are  $\geq 39$ cm for men and  $\geq 35$ cm for women (Onat *et al.*, 2009:50). A cut-point of  $\geq 42$ cm for women has been found to reveal insulin resistance and excess androgen levels which increase type 2 diabetes risk in women (Dixon & O'Brien, 2002:776). Again, further research is needed to determine African-specific cut-points. Hoebel *et al.* (2012) has taken on this challenge to investigate NC as a MetS predictor. This investigation revealed that NC cannot be used to determine MetS risk for African women, which could strengthen the notion of healthy obesity as first mentioned by Walker *et al.* (1989). NC was, however, found to be a predictor of MetS risk in African men, as well as in Caucasian men and women (Hoebel *et al.*, 2012).

### 2.3.2 Blood Glucose

Glucose is an important source of energy, especially for the brain, which depends on a regular supply (Mahan & Escott-Stump, 2004:38, 41) but when target cells become insulin resistant, there is a diminished response to the available insulin (Powers & Howley, 2007:85). This can occur with obesity as excess adipose tissue releases fatty acids and because visceral fat is metabolically active (Beckman *et al.*, 2008:1096; Menke *et al.*, 2007:793; ADA, 2005:S39). When insulin resistant, blood glucose levels elevate and glucose is not utilized for its intended purpose even if insulin levels are adequate (Ehrman *et al.*, 2003:131).

Glucose abnormality is a component of MetS (Alberti *et al.*, 2006:1641, 1642; IDF,

2006:5). Abnormal glucose levels exceed 11.1 mmol/l at any time, or exceed 7.0 mmol/l after fasting (ACSM, 2006:208; Ehrman *et al*, 2003:135; Mahan & Escott-Stump, 2004:799; WHO, 1999:52). Higher than normal glucose can either be identified as impaired fasting glucose (6.1- 7.0 mmol/l) or impaired glucose tolerance (7.8- 11.1 mmol/l) (WHO, 1999:52). The new MetS definition classifies glucose as a health risk when levels exceed 5.6 mmol/l (Alberti *et al.*, 2009:1642).

Monitoring glucose levels is of great importance to the health of individuals. With prolonged increases in blood glucose macro and microvascular complications can occur (ACSM, 2006:211; Ehrman *et al.*, 2003:133-135). Prolonged high glucose levels alter the function of vascular endothelial cell in such a manner as to promote atherogenesis (Beckman *et al.*, 2008:1096). These macrovascular complications occur in the larger vessels of the body and include an increase in cerebrovascular disease and atherosclerosis (ADA, 2005:S37). Damage to the small vessels results in organ damage that includes neuropathy, retinopathy and nephropathy (Greenstein *et al.*, 2007:164; ADA, 2005:S37).

### **2.3.3 Hypertension**

Hypertension is described as ‘a blood pressure (BP) at which a person has an increased risk for developing a morbid cardiovascular event (Ehrman *et al.*, 2003:281). As with diabetes, it can lead to cardiovascular and end-stage renal disease and can be aggravated by obesity (Thom *et al.*, 2006:110; Ehrman *et al.*, 2003:281). Furthermore physical inactivity, salt and alcohol usage have been known to contribute to the development of systemic or secondary hypertension which can be improved or cured with lifestyle modification and/or medical intervention (Opie & Seedat, 2005:3566) and as such has been identified as a modifiable risk factor.

Hypertension is defined by the European Society of Hypertension as having a systolic blood pressure (SBP) of more than 140 mmHg and/or a diastolic blood pressure (DBP) of more than 90 mmHg (Mancia *et al.*, 2007:1465). In terms of the new MetS definition, BP constitutes a risk factor when SBP is 130 mmHg or more and/or when DBP is 85 mmHg or more (Alberti *et al.*, 2009:1642). This classification

has also been known as pre-hypertension/high-normal (SBP 130-139 mmHg and DBP 85-89 mmHg) (Mancia *et al.*, 2007:1465). The American Heart Association (AHA) has, however, defined pre-hypertension as being SBP of 120-139 mmHg and DBP of 80-89 mmHg (Thom *et al.*, 2006:109). It has however been suggested that the word 'hypertension' should not be used to classify blood pressure as the word may cause anxiety among laymen. Blood pressure should be monitored over time as increased BP could lead to the development of ischemic heart disease (Jensen *et al.*, 2000:899). When hypertension remains controlled, myocardial infarction and stroke can be prevented (Seshadri *et al.*, 2006:345,349; Yusuf *et al.*, 2004:945,951). This may be possible as hypertension has been identified as being a modifiable risk factor for both males and females (Yusuf *et al.*, 2004:945,951).

### 2.3.3 Triglycerides

Triglycerides are the form in which fatty acids are stored in the body and it is formed with three molecules of fatty acids and glycerol and can be consumed through diet or synthesized in the liver (Powers & Howley, 2007:32; Ehrman *et al.*, 2003:173; Whitney & Rolfes, 2002:132,144). Triglycerides are stored in fat and muscle tissue to be used as energy when broken down into its components (Powers & Howley, 2007:32). Elevated cholesterol and triglycerides are two of the factors that have been found to predispose to atherosclerosis which in turn is associated with cardiovascular disease and stroke (Powers & Howley, 2007:372).

Hypertriglyceridemia will mostly be present in MetS patients (Ehrman *et al.*, 2003:172). The new definition of MetS classifies triglycerides as being a risk when levels exceed 1.7 mmol/l (Alberti *et al.*, 2009:1642) When triglycerides are high, the HDL is usually low (Ehrman *et al.*, 2003:173), as these two factors are inversely associated (Mahan & Escott-Stump, 2004:876). Interestingly it has been found that these levels are low in women compared to those in men and lower in women of African descent than in Caucasians (Hoebel *et al.*, 2011:53; Schutte *et al.*, 2008:531; Schutte & Olckers 2007:653). These low levels of triglycerides in Africans cannot be used to determine insulin sensitivity, as is the case with Caucasians, and can lead to the under diagnosis of insulin resistance or MetS (Summer *et al.*, 2005:1396, 1397).

Hypertriglyceridemia can be treated with lifestyle modification such as weight loss through physical activity, smoking cessation and a decrease in alcohol consumption.

### 2.3.4 High-density lipoprotein (HDL)

HDL is known as the 'healthy' cholesterol. HDL precursors are produced in the liver and consist of cholesterol and phospholipids (Riccardi *et al.*, 2003:226). HDL is known for its cardio-protective effect through reverse cholesterol transport (Mahan & Escott-Stump, 2004:874; Riccardi *et al.*, 2003:227). Circulating cholesterol from peripheral tissue is transported back to the liver for oxidation via HDL (Riccardi *et al.*, 2003:227). With reduced levels of HDL, excess cholesterol will not be removed from peripheral tissues, leading to an accumulation of cholesterol in these cells. This will result in a down-regulation of LDL receptors resulting in less LDL being removed from the circulation (Riccardi *et al.*, 2003:235); thus increasing atherosclerotic risk through oxidative modification of LDL (Mahan & Escott-Stump, 2004:865,876; Riccardi *et al.*, 2003:235). In order for this mechanism to function, HDL is classified as being adequate when levels exceed 1.0 mmol/l for males and 1.3 mmol/l for females (Alberti *et al.*, 2009:1642).

Although knowledge of HDL levels is important, it should not be seen as an isolated value. The LDL:HDL ratio is a better (improved) predictor of cardiovascular risk than either measurement alone (Riccardi *et al.*, 2003:235). For example, if LDL values are high, but HDL levels are also high, the ratio between these two variables should be to such an extent that HDL could remove LDL. The higher the HDL values, the more LDL can be transported back to the liver, whilst the opposite is true for low HDL values. Thus the importance of the LDL:HDL ratio is evident. An LDL:HDL ratio greater than 5 indicates health risk in men while women are at risk with a ratio greater than 4.5 (Whitney & Rolfes, 2002:608)

## 2.4 LIFESTYLE RISK FACTORS OF THE METABOLIC SYNDROME.

The IDF has identified physical inactivity as a lifestyle risk factor that influences the MetS (IDF, 2006:7). Other modifiable lifestyle factors that could aggravate the severity or presence of MetS risk factors have been identified and include alcohol consumption and smoking (Yusuf *et al.*, 2004:941,945-946). The above-mentioned risk factors can all easily be found among people living in urban areas. It has been mentioned elsewhere that an urban environment is associated with a negative lifestyle consisting of physical inactivity, poor diet, and increased cigarette and alcohol consumption due to increased stress (Hamer *et al.*, 2011:239, 240; Malan *et al.*, 2008:327; Wild *et al.*, 2004:1049; Popkin, 1999:1905). It would seem that MetS is mostly a result of lifestyle choices as occurring during urbanization and therefore a summary will be given of the effect of poor lifestyle choices on health factors.

### 2.4.1 Physical inactivity

With modernization, physical activity declines, lifestyles become more sedentary and herewith there is a rise in weight gain and health problems (Whitney & Rolfes, 2002:275). Inactivity causes an imbalance between energy consumption and energy expenditure. This positive energy balance is converted into fat that is stored in the adipose tissue (Whitney & Rolfes, 2002:269-276) and, as mentioned, this excess adipose tissue is metabolically active (Menke *et al.*, 2007:793). Inactivity has been found to independently predict cardiovascular risk (Powers & Howley, 2007:393), and inactive persons have two times higher risk of developing cardiovascular diseases than their active counterparts (Powers & Howley, 2007:292). With inactivity, physical adaptations to improve or maintain health do not occur. Health benefits are prevalent even without weight loss because of the improvements in cardiovascular function (Ehrman *et al.*, 2003:161).

Physical activity positively affects all components of the MetS. Exercise shows a dose response relationship in terms of progression to diabetes as opposed to inactivity (Engberg *et al.*, 2010:73) because with regular endurance exercise glucose

and fatty acids can be more easily utilized for energy due to increased capillary density and mitochondria which increase the oxidation of glucose and fatty acids (Powers & Howley 2007:272). Progression to diabetes can also be slowed by leisure time activities (Engberg *et al.*, 2010:74). In terms of hypertension, endurance exercise lowers peripheral resistance due to an increase in capillary density and elasticity of blood vessels (Powers & Howley, 2007:367) which lower SBP (Frag *et al.*, 2010:7). Furthermore, enzymatic changes occur with exercise increasing lipoprotein lipase activity which favourably changes the lipid profile (Frag *et al.*, 2010:7; Monda *et al.*, 2009:1687). In order to facilitate healthy levels of HDL, the BMI should preferably be below 28 kg/m<sup>2</sup> (Kodama *et al.*, 2007:1006); thus obese individuals should first have to lose weight in order to benefit the HDL levels. The degree to which these changes occur are inter-individual (Monda *et al.*, 2009:1687) but physical activity, even leisure-time activities, have proven to reduce the risk of developing MetS (Cho *et al.*, 2009:786,791).

#### **2.4.2 Dietary Changes**

A western diet which can accompany urbanization and/or acculturation, consists of food high in fat, salt and refined sugars (Popkin, 1999:1908). It would appear that Africans living in rural areas consume less fat-dense foods than their urban counterparts (Kruger *et al.*, 2002:425,426 & Popkin, 1999:1908, 1911). Contrasts between urban and rural diets are more profound in low income countries (Popkin, 1999:1908).

Furthermore, a westernized diet with its processed foods that are high in sodium and low in potassium (Whitney & Rolfes, 2002:399), will more negatively affect the health of black Africans (Seedat, 2009:40; Lindhorst *et al.*, 2007:241; Opie & Seedat, 2005:3565). The reason being that Africans are prone to poor sodium handling through their renal system and an accompanying water retention and increased blood pressure (Lindhorst *et al.*, 2007:243). Africans prefer diets low in potassium, calcium and magnesium which may also elevate blood pressure (Lindhorst *et al.*, 2007:243). Findings of the DASH-study revealed that a diet rich in potassium and

low in sodium has a protective effect against hypertension and thus preventing cardiovascular and renal disease (Harsha *et al.*, 1999:s39).

### 2.4.3 Alcohol

Alcohol abuse has been found to be a coping strategy for increased stress in an urban environment (Malan *et al.*, 2012:546; Malan *et al.* 2008:327; Björntorp, 1997:802; Mutatkar, 1995:980). It would seem that Africans, especially men in urban areas, show high levels of alcohol consumption (Hoebel *et al.*, 2011:52; Vorster *et al.*, 2000:510). Alcohol abuse is known to increase BP, blood glucose and the risk of kidney failure, all which are risk factors for the MetS (Whitney & Rolfes, 2002:237). Alcohol consumption, through its increase in energy intake and effect on endocrine system (Björntorp, 1997:801,802), is associated with higher BP, triglycerides (Lee *et al.*, 2010:198) and WC (Whitney & Rolfes, 2002:237), thus, it can be said that the prevalence of MetS may increase with alcohol consumption (Lee *et al.*, 2010:198). An objective method of determining alcohol consumption is with the use of GGT (gamma-glutamyl transferase). This is a liver enzyme which has been recommended for use in prediction of the MetS and cardiovascular disease, since it can be a marker of oxidative stress and inflammation (Kasapoglu *et al.*, 2010:60). Hamer *et al.* (2011) showed that the odds of early structural vascular changes ( $\geq 0.9$  mm carotid intima media thickness) based on high GGT levels were 3.1 (95% CI; 0.6 - 15.5) in the African men, independent of other confounders. It is possible that alcohol abuse is utilized as a coping strategy in the African male.

Worthy of note is the decreased risk of developing type 2 diabetes when alcohol is being used in moderation. Koppes *et al.* (2005) has pooled the data of many studies pertaining to the effect of alcohol and health. The collective data suggests a U-shaped relationship between alcohol use and risk for developing type 2 diabetes. Persons using alcohol in moderation have a 30% reduced risk of developing type 2 diabetes as compared to abstainers and heavy drinkers. These findings were regardless of accompanying BMIs (Koppes *et al.*, 2005:722)

#### 2.4.4 Smoking

Smokers present with a cluster of metabolic abnormalities such as insulin resistance, and lipid disorders (Berlin, 2008:310). According to Berlin (2008:310), smoking affects lipids through impaired lipoprotein metabolism and increases total cholesterol and triglycerides while lowering HDL. Furthermore, it affects glucose metabolism by causing increased blood glucose due to decrease in peripheral glucose uptake or insulin resistance (Berlin, 2008:309), all of which are risk factors of MetS (Alberti *et al.*, 2009:1642). Smoking is also associated with increases in WHR and WC because smokers tend to present with abdominal obesity, known as cardiovascular risk factors (Berlin, 2008:310) and thus an increased risk for MetS.

As with cigarette smoking, the use of snuff is also associated with the different components of MetS (Sundbeck *et al.*, 2009:487), especially with abdominal obesity (Sundbeck *et al.*, 2009:491,492). Of possible importance is the finding that the more urbanized a group becomes, the more smoking percentages decrease. It would seem that persons in more urban areas present with lower usage of cigarettes and snuff than do more urban populations (Vorster *et al.*, 2000:510).

### 2.5 TARGET ORGAN DAMAGE AND METS

Several studies have determined that MetS is associated with target organ damage (TOD) (Schillaci *et al.*, 2006; Leoncini *et al.*, 2005; Mulè *et al.*, 2005). Left ventricular hypertrophy, microalbuminuria and carotid atherosclerosis are frequently researched as markers of target organ damage (Schillaci *et al.*, 2006; Mulè *et al.*, 2005; Leoncini *et al.*, 2005; El-Gharbaway *et al.*, 2001). Ventricular hypertrophy and renal damage are common results of hypertension which is a prominent risk factor for MetS (Alberti *et al.*, 2009:1642; IDF, 2006:10). The presence of left ventricular hypertrophy has been found to be increased by the presence of MetS, especially in women (Schillaci *et al.*, 2006:884) and BP variability has been suggested as an early measure to identify risk of ventricular hypertrophy in Africans (Schutte *et al.*, 2011a:1133). Africans furthermore are more inclined to have higher albumin levels. Ethnicity plays a predictive role in microalbuminuria excretion in persons of African descent (El-

Gharbaway *et al.*, 2001:765). In high-risk ethnic groups, albumin excretion below the diagnostic threshold for microalbuminuria is associated with glomerular endothelial dysfunction and can be used as a marker of blood pressure progression. (Schutte *et al.*, 2011b:867). Microalbuminuria will be further explained as a marker of TOD.

### 2.5.1 MICROALBUMINURIA

Microalbuminuria as an indicator of organ damage has previously been considered to be a risk factor for MetS by the WHO (WHO, 1999:33) indicating that this marker can lead to cardiovascular disease (Volpe, 2008:97) and is an independent cardiovascular disease risk factor for all persons (McCullough, 2008:2157). Microalbuminuria can be a complication of diabetes, hypertension and subsequently of MetS (Greenstein *et al.*, 2007:166; Thom *et al.*, 2006:110). The WHO defines microalbuminuria as either a urinary albumin:excretion rate  $\geq 20 \mu\text{g}/\text{min}$ , or as an albumin:creatinine ratio (ACR)  $\geq 30 \text{ mg}/\text{g}$  (0 - 2.9 mg/micromole) (WHO, 1999:33). Spot ACR tests for determining microalbuminuria can be routinely be done as a part of a cardiovascular risk assessment (McCullough, 2008:2157). Microalbuminuria, also a marker of an inflammatory process (Volpe, 2007:97) which is implicated in the MetS (IDF, 2006:13), results from functional and structural changes in the kidneys resulting in impaired renal function and is categorized by means of the glomerular filtration and the presence of albumin in the urine (Thom *et al.*, 2006:110). As kidneys age, the glomerular filtration rate decreases with creatinine has been found to be the best predictor of this rate (Douville *et al.*, 2009:99, 101). Furthermore, it would seem that women had a slower decline in the filtration rate (Eriksen & Ingebretsen, 2006:378). Considering the above mentioned, further research in ethnic-, gender- and age specific groups for this marker of TOD would be beneficial, especially in African populations.

Early detection of renal disease can be done with the use of urine albumin levels (Harwell *et al.*, 2003:245, 247; Pylypchuk & Beaubien; 2000:637-639). A high level of this protein is associated with increases in cardiac disease (Asselbergs *et al.*,

2005:73-77; Araki *et al.*, 2005:2983-2987; Jensen *et al.*, 2000:898-903). Increases in albumin secretion in the kidney or the albumin: creatinine ratio further increases health risk, regardless of diabetic status (Gerstein *et al.*, 2001:421,425). The risk for ischemic heart disease increases when microalbuminuria is accompanied by high systolic blood pressure (SBP) (Jensen *et al.*, 2000:899). By controlling glucose, HbA1C (glycated hemoglobin), BP and BMI, microalbuminuria levels can in turn be controlled alleviating progression of renal and cardiac diseases (Araki *et al.*, 2005:2986-2987; Cederholm *et al.*, 2005:264). In an African population it has been found that the development of microalbuminuria can be explained by BP, triglycerides and WC, all of which are risk factors of the MetS (Hoebel *et al.*, 2010:151). In the same population, Du Plessis *et al.* (2010:273) has come to the conclusion that African men with an active coping style revealed positive associations between the different MetS risk factors and target organ damage as portrayed by microalbuminuria.

## **2.6. BATTLE OF THE SEXES: DIFFERENCES IN HEALTH RISK FOR MEN AND WOMEN**

Gender-specific differences in some MetS risk factors differ between men and women. Physiologically, hormones play an important role in health and physical appearance for males and females respectively.

Differences in body build between men and women were first categorized by Jean Vague (1956:24) by whom women were labelled as gynoid (excess gluteofemoral fat), while men are said to be android (excess subcutaneous truncal fat). Men have a more muscular build due to the male hormone testosterone which is responsible for the high muscle-mass to fat-mass ratio through protein synthesis and inversely associated with adiposity (Powers & Howely, 2007:86; Oh *et al.*, 2002:55). With ageing, however, testosterone levels decrease and the male build changes from high muscle and lean mass to a more adipose mass (Kupelian *et al.*, 2008:3403). This change is accompanied by an increase in health risk factors such as insulin resistance and lipid abnormalities; thus low testosterone levels could be inversely

associated with MetS (Kupelian *et al.*, 2008:3403, 3404, 3407). Lower levels of testosterone are best associated with dislipidemia and abdominal or visceral obesity which increases the WC (Kupelian *et al.*, 2008:3408, 3409; Björntorp, 2001:73, 77). Furthermore, low testosterone levels are associated with increased risk of developing impaired fasting glucose, impaired glucose tolerance or type 2 diabetes (Zitzmann *et al.*, 2006:4342; Goodman-Gruen & Barrett-Connor, 2000:915). High levels of testosterone, however, are inversely related to the development of type 2 diabetes (Ding *et al.*, 2006:1294, 1297).

Women's health is also affected by testosterone levels, but here high levels of testosterone present with impaired glucose tolerance or type 2 diabetes, contrary to the findings for men (Ding *et al.*, 2006:1294,1297; Oh *et al.*, 2002:59; Goodman-Gruen & Barrett-Connor, 2000:915). Furthermore, increased free androgens in women are related to an increased visceral obesity (Anders & Hampson, 2005:248-249). The same can be said for men with high levels of estradiol, which increases central obesity (Ding *et al.*, 2006:1294; Goodman-Gruen & Barrett-Connor, 2000:916).

Women are known to benefit from estrogens which protect against cardiovascular diseases and osteoporosis (Vander *et al.*, 1998:268,661). These hormones are responsible, amongst others, for female fat distribution and thus the higher fat-mass of women than that of men (Powers & Howely, 2007:86). As with men, ageing in women, or menopause, changes body build. Women tend to develop a more android shape with increased visceral obesity and thus have an increased risk for developing glucose intolerance, lipid and BP irregularities because of the metabolically active nature of visceral fat (Mahan & Escott-Stump, 2004:569). High estradiol levels in post-menopausal women are associated with increased prevalence of type 2 diabetes and this same trend is presented in men (Ding *et al.*, 2006:1294; Goodman-Gruen & Barrett-Connor, 2000:915). However, it should be noted that it has not yet been determined whether diabetes influences the sex steroid hormones or whether

this occurrence is the result of a change in these hormone levels. It is thus recommended that further studies be done (Goodman-Gruen & Barrett-Connor, 2000:916).

Another point of interest is that along with differences in fat distribution, insulin sensitivity differs between genders. Visceral fat is a better predictor of insulin sensitivity in women while both visceral and subcutaneous fat should be considered when screening for insulin sensitivity in men (Rattarasarn *et al.* 2004:6268-6289). Taking all differences into account it would seem that when comparing men to women, men would seem to reveal a less favourable metabolic profile, mostly due to a poor lipid profile (Després *et al.*, 2000:1934).

## **2.7. ETHNIC DIVERSITY AND DISEASE**

Disease outcomes may differ due to differences in physiological factors and differences in behaviour and culture of different ethnic groups. This is of special importance in developing or third-world countries where the cycle of poverty, and the resulting illiteracy, further hampers the compliance with required treatment in order to manage and prevent diseases (Homedes & Ugalde, 1993:293,300). This situation is further exaggerated in areas where urbanization or acculturation is rapidly occurring (Homedes & Ugalde, 1993:293,300; Seedat, 1990:s67).

Physically, where anthropometry is concerned, it is suggested that different categorizations be made (He *et al.*, 2002:2169) because persons of African descent, especially women, have elevated anthropometric measurements compared to those of Caucasians (Faber & Kruger, 2005:238; Kruger *et al.*, 2001:738; Després *et al.*, 2000:1934; Croft *et al.*, 1995:61). A health survey done during 2003 showed that African women tend to be obese (SADHS, 2003:277) and women of African descent have been found to present with higher indices of overall adiposity (Després *et al.*, 2000:1934). Contrary to this finding, African men are less likely to be obese than

their Caucasian counterparts (SADHS, 2003:277). Although African women tend to be obese, they do not perceive themselves as being overweight, while Caucasian women perceive themselves to be overweight even when they are not (Faber & Kruger, 2005:242-243; Puoane *et al.*, 2005a:92; Puoane *et al.*, 2005b:10; SADHS, 2003:277).

This perception of African women could possibly promote physiological well-being, which in turn could be a possible reason for the phenomenon of 'healthy obesity', where overweight African women tend to be in good health. Healthy obesity was first labelled by Walker *et al.* (1989). Africans perceive themselves as not being overweight, which could stem from the belief that 'big is beautiful' and healthy. Possible reasons for this perception include the belief among Africans that being thin reflects a positive HIV status and thus thinness relates to disease (Puoane *et al.*, 2005a:92; Puoane *et al.*, 2005b:10). It has also been found that weight loss can be perceived as an indicator of poor health among Africans (Faber & Kruger, 2005:243; Puoane *et al.*, 2005b:10). Furthermore, African culture dictates that women should be overweight in order to reflect the husband's financial capability as well as the women's ability to perform her duties and to be viewed as being dignified and strong (Puoane *et al.*, 2005a:92; Puoane *et al.*, 2005b:10). These perceptions are starting to change as the media portrays thin as being attractive and African women stand confused (Puoane *et al.*, 2005b:14).

A further explanation could be attributed to the activation of the inflammatory cascade. Inflammation does not depend on the level of expansion of the adipose tissue and thus the insulin resistance that accompanies obesity depends on the activation of the inflammation cascade and not only the obese state (Barbarroja *et al.*, 2010: 145, 148). Insulin resistance that accompanies obesity may be caused by adipose tissue dysfunction which contributes to the afore mentioned inflammatory state (Klötting *et al.*, 2010: E513)

Physiologically, Africans possess factors that protect or predispose them to certain health risks. Physiological differences that make Africans more prone to develop certain conditions such as hypertension include the renin-angiotensin-aldosterone system (RAAS) which predispose Africans to hypertension (Lindhorst *et al.*, 2007:241,245; Opie & Seedat, 2005:3564-3565). Africans tend to have a lower ability to excrete sodium than Caucasians, and this is termed sodium sensitivity. Although Africans have higher sodium sensitivity than Caucasians, it has been found that they do not consume more sodium than Caucasians. (Lindhorst *et al.*, 2007:243; Charlton *et al.*, 2005:41). When, however, observing sodium chloride, or table salt intake, Africans add more salt to their food for a salty taste than do Caucasians (Charlton *et al.*, 2005:42).

In addition to high salt intake, Africans have a low intake of calcium and potassium and this may contribute to the hypertension prevalence in this population (Lindhorst *et al.*, 2007:243; Charlton *et al.*, 2005 :42, 43; Lytle *et al.*, 2002:323; 30 37). The American Heart Association's (AHA) statistics committee has indeed found that African American populations show greater prevalence of hypertension as well as diabetes (Thom *et al.*, 2006:129e) than Caucasians. Furthermore, the statistics committee found that African Americans tend to develop hypertension earlier than Caucasians and have higher mean values for BP. In the presence of high BP, Africans have a 4.2 times greater prevalence of end stage renal disease than do their Caucasian counterparts (Thom *et al.*, 2006:111e). In terms of kidney disease, Africans tend to have higher albumin levels than Caucasians (Xu *et al.*, 2004:1222), which could predispose this group to endothelial dysfunction and renal impairment.

A favourable lipid profile can also be seen in Africans since they tend to have less visceral fat than Caucasians of the same weight (Després *et al.*, 2000:1936, 1937). African women tend to have low triglyceride (Hoebel *et al.*, 2010:150; Schutte & Olckers, 2007:656) and HDL levels (Hoebel *et al.*, 2010:150) although findings have differed for HDL levels (Schutte & Olckers, 2007:656). The low HDL levels could possibly be ascribed to the high level of obesity. Normal HDL levels are more easily obtained when BMI is below 28 kg/m<sup>2</sup> (Kodama *et al.*, 2007:1006). It should be

mentioned that lipoprotein lipase (LPL) levels, that should clear triglycerides from circulation, are higher in persons of African descent and more so in women; hence the low levels of triglycerides amongst Africans (Després *et al.*, 2000:1398). Because of the low triglyceride levels in Africans, and because this factor could lead to the under-diagnosis of MetS as mentioned, cut-off values for this MetS component should be adjusted for Africans (Schutte & Olckers, 2007:656; Summer *et al.*, 2005:1396,1397). Lastly, it has been found that, together with obesity, African Americans present with vitamin D deficiency. This could be ascribed to adiposity which leads to poor bio-availability of vitamin D, their darker skin pigmentation and low exposure to sun due to a sedentary lifestyle (Ashraf *et al.*, 2009:3200, 3203). This deficiency has also been implicated in abnormal glucose metabolism due to low insulin sensitivity (Ashraf *et al.*, 2009 3204).

Environmental factors can also affect health outcomes of different ethnicities. Opie and Seedat (2005:3567) found that health risk factors, such as high BP, are common among black urban Africans, regardless of income group. They found that environmental factors contributing to health risk in low income urbanized groups consist of economic stress, poor access to health facilities and poor nutrition. Environmental factors that affect higher income urbanized Africans include dietary excess, alcohol abuse and a physically inactive lifestyle (Hamer *et al.*, 2010:240; Opie & Seedat, 2005:3567). Taking dietary restrictions into account, intrauterine malnutrition can cause low birth weight (Groop & Orho-Melander, 2001:108) which is more prevalent in Africans than in Caucasians (Bachmann *et al.*, 1996:970). Low birth weight is associated with the development of disease later in life, especially if a person is genetically predisposed to develop the risk factors for the metabolic syndrome (Groop & Orho-Melander, 2001:108; Levitt *et al.*, 2000:4615; Barker *et al.*, 1989:565).

All aspects taken into account, it would seem that environmental factors contribute greatly to the prevalence of health-risk factors, especially among Africans.

## 2.8 SUMMARY

The global epidemic MetS is also reflected in African populations (Hoebel *et al.*, 2011:52). Most components of the metabolic syndrome can be controlled with lifestyle modification when early identification has occurred (IDF, 2006:15). Effective anthropometric screening for MetS is easy and cost effective and can be routinely implemented in any evaluation to assist in identifying health risk early. This will be of great importance, especially in impoverished African communities. WC is known as a screening tool for MetS, but ethnic-, gender- and age-specific cut-points are yet to be developed for African populations (Alberti *et al.*, 2009:1642; De Onis & Habicht, 1996:655, 657). NC as an additional screening tool should be further investigated in the same groups as WC. Ultimately, further research into easy screening for health purposes could help in developing improved health strategies and assist in improving the health of a nation.

The research that follows aimed to determine the prevalence of MetS as well as its risk factors in Africans and Caucasians, while using the new Joint Statement Criteria. Furthermore, NC was examined to determine cut-points and to establish this measure's value as an indicator of MetS risk. Lastly, specific WC cut-points was defined in order to address the issue of ethnic-specific cut-points. Ultimately, these cut-points can be compared in order to determine the best anthropometric measure to be used as a screening tool for MetS and TOD. This research could help to cost-effectively screen for MetS.

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Chapter 3

*Differences in MetS marker prevalence between Black and  
Caucasian teachers from the North-West province, South Africa:  
The SABA Study*

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## ABSTRACT

**Background:** The aim of this study was to compare metabolic syndrome (MetS) prevalence between Black and Caucasian Africans using different definitions and secondly, to determine the association between MetS, anthropometric markers and the albumin : creatinine ratio using the Joint Statement Criteria (JSC). This was a target population study including 409 urban African and Caucasian men and women (aged 25-65years) from the North-West Province, South Africa were stratified into gender and ethnic groups. **Method:** We obtained anthropometric measurements, levels of microalbuminuria and other markers of the metabolic syndrome (MetS) (systolic and diastolic blood pressure, glucose, triglycerides and high density lipoprotein). **Results:** JSC included more persons with MetS than the other definitions and African women and Caucasian men presented with more cases of MetS. Risk factors most prevalent were blood pressure among men and waist circumference (WC) and glucose among women. African men as a group presented with more risk factors than the other groups. African women, although obese, seem to have few cardiovascular risk factors while all groups presented with an unhealthy WC according to European cut-off values. Multiple linear regression analysis independent of co-variables, showed that the albumin : creatinine ratio is explained only by glucose in Africans. **Conclusion:** African women as a group present with few MetS risk factors, and glucose is associated with renal function risk in Africans.

**Key Words:** Metabolic Syndrome (MetS), neck circumference (NC), microalbuminuria, ethnic

## **Differences in MetS marker prevalence between Black and Caucasian teachers from the North-West province, South Africa: The SABPA Study**

### **3.1 INTRODUCTION**

The metabolic syndrome (MetS) consists of a variety of health risk components. Many definitions for diagnosis have been put forward and this has led to confusion concerning which should be used. Recently expert panels have come to a consensus regarding a new definition.<sup>1</sup> This new Joint Statement defines MetS as having any 3 or more metabolic abnormalities that include high glucose, triglycerides, blood pressure (BP), waist circumference (WC) and low high-density lipoproteins (HDL).

This new definition does not have WC as a prerequisite for the syndrome as did the previous IDF guidelines. It is, however, known that WC is a predictor of health risk<sup>2</sup> and it can therefore be used as an easy screening tool. Together with WC, the neck circumference (NC) is a promising easy measurement that can also be used as part of the screening tool for MetS.<sup>3</sup> NC is associated with metabolic disorders and may be an easier screening tool than WC.<sup>4</sup> Both these measurements have been found to be associated with microalbuminuria in urban Africans.<sup>5</sup> In terms of screening it would prove useful to determine which of these anthropometric measures could best be used to determine the presence of the different risk factors of the MetS. The new definition could lessen the inconsistencies with the diagnosis of persons presenting with MetS because a standardized definition can now be used. Although standardization is necessary, anthropometric cut-off values can, however, not easily be standardized because anthropometric profiles differ between ethnic groups<sup>6</sup> and differences in relation to risk factors.<sup>1</sup> Physiological differences also have been known to make Africans more prone to developing certain conditions such as hypertension, including the renin-angiotensin-aldosterone system which predisposes Africans to hypertension.<sup>7,8</sup> Urbanization could also be a health risk factor.<sup>9</sup> Urbanized Africans seem more prone to being overweight and obese,<sup>10,11</sup> possibly due to increased intake of saturated fat and low levels of physical activity.<sup>10</sup> Thus a

Western lifestyle amongst Africans can lead to the increased prevalence of chronic diseases such as diabetes, hypertension and other cardiovascular complications.<sup>11-14</sup>

Microalbuminuria, as a marker of target organ damage (TOD), is no longer a part of this new definition as was the case with previous definitions of the metabolic syndrome.<sup>15</sup> Since persons presenting with MetS are two times more likely to develop microalbuminuria,<sup>16</sup> a marker of endothelial dysfunction, it still necessitates determination of the association between microalbuminuria and the components of the MetS in Africans.<sup>17</sup> Microalbuminuria expressed as urinary albumin : creatinine ratio, is an indicator of endothelial dysfunction and renal impairment and needs early identification.

The aim of this study was firstly, to compare MetS prevalence between urban Black and Caucasian Africans utilizing different definitions of the MetS. Secondly, to determine the association between MetS, anthropometric markers and microalbuminuria in these groups using the Joint Statement Criteria (JSC). We hypothesized that the MetS prevalence will be high amongst Africans when using the new Joint Statement Criteria

## **3.2 METHODS**

### **3.2.1 Ethical Aspects**

The North-West Department of Education and the South African Democratic Teachers Union gave the necessary authorization for this study to be conducted. Participants signed an informed consent form which has been approved by the Ethics Committee of the North-West University (NWU) (NWU-00036-07S6) and the study conformed to the ethical guidelines for human participants of the World Medical Association Declaration of Helsinki.<sup>18</sup>

### **3.2.2 Participants**

Teachers (N=409) from the Dr. Kenneth Kaunda District in the North-West Province of South Africa included African (men, N=101; women, N=99) and Caucasian (men

N=101; women, N=108) aged 25-65 years. Exclusion criteria for participation included pregnancy, lactation, temperature  $>37^{\circ}\text{C}$  and the users of alpha and beta blockers. Blood donors and persons who had been vaccinated in the 3 months prior to participation were also excluded. For the purpose of this study further exclusions were made for cases of diabetes (n=12), HIV positive (n=19) and hypercholesterolemic (n=11) persons.

### 3.2.3 Design

Avoiding seasonal changes, collection of data for each participant continued over a 48-hour period in the working week from February – May 2008 as well as in the same timeframe during 2009. Participants had to overnight at the Metabolic Unit Research Facility on the NWU campus. The Metabolic Unit consists of bedrooms for each participant, bathrooms, a kitchen and a dining room as well as a living room with a television. Participants were welcomed and introduced to the experimental setup to lessen anticipation,<sup>19</sup> where after participants fasted from 22h00. The following day, at 06h00, the urine samples were collected followed by anthropometric measurements taken in triplicate by registered Biokineticists. Subsequently BP and blood sampling followed, obtained by a registered nurse and medical doctor.

### 3.2.4 Classification of MetS

Diagnosis of MetS was based on the definitions of the new Joint Statement, the International Diabetes Federation (IDF) and the National Cholesterol Education Program's Third Adult Treatment Panel (NCEP ATP III). The new Joint Statement requires any three of the following:

- Elevated waist circumference (WC) (population and country specific values)
- Elevated triglycerides ( $\geq 1.7$  mmol/L) or drug treatment for elevated triglycerides
- Reduced HDL Cholesterol ( $< 1.0$  mmol/L for males and  $1.3$  mmol/L for females) or drug treatment for reduced HDL

- High-fasting glucose ( $\geq 5.6$  mmol/L) or treatment thereof
- Increased blood pressure (systolic  $\geq 130$  mm Hg and/or diastolic  $\geq 85$  mm Hg) or antihypertensive treatment

IDF and NCEP ATP III guidelines correspond, except for WC, which is a prerequisite in the case of the IDF, and the cut-off values differ, namely the IDF WC for MetS is  $\geq 94$ cm and  $\geq 80$ cm for men and women respectively while the NCEP ATP III values are defined as being a health risk at  $>102$ cm and 88cm in men and women respectively.

### **3.2.5 Lifestyle Factors**

Physical activity was measured by means of the Actical® physical activity monitor, which was water resistant, lightweight and small, using 1-min recording epochs. The monitors were initialized and the results downloaded using a serial port computer interface, with the resulting data exportable as text files.<sup>20</sup> Acticals were fitted to participants' waists and were worn for 24 hours and removed after their overnight stay at NWU.

Cotinine, a metabolite of nicotine, was determined to evaluate exposure to first- and second-hand smoke. A widely used cutpoint for determining smoking is  $>14$  ng/mL.<sup>21</sup>

Gamma glutamyl transferase (GGT) determined alcohol consumption. GGT has also been recommended for early diagnosis of the MetS since it can be a marker of oxidative stress and inflammation.<sup>22</sup> Cutt-points for this measure are 65 u/l for men and 45 u/l for women.<sup>23</sup>

HIV positive status was determined by an antibody test provided by the Department of Health of the North-West Province.

### 3.2.6 Anthropometric Variables

Mass was measured to the nearest 0.1 kg on a KRUPS scale with the participant wearing minimal clothes and with the weight evenly distributed. The above-mentioned measurements were used to calculate body mass index (BMI) by dividing weight (kg) by length (m)<sup>2</sup>.<sup>24</sup>

Maximum stature was measured with a stadiometer to the nearest 0.1cm whilst the participant's head was in the Frankfort plane, the heels together and the buttocks and upper back touching the stadiometer.<sup>25</sup>

The circumferences were measured with the participant in a standing position using a non-extensible and flexible anthropometric tape. Firstly, the neck circumference (NC) was taken immediately superior to the thyroid cartilage perpendicular to the long axis of the neck.<sup>25</sup> Secondly, the WC was taken at the midpoint between the lower costal rib and the iliac crest, perpendicular to the long axis of the trunk.<sup>25</sup> The hip circumference (HC) was taken at the greatest posterior protuberance of the buttocks perpendicular to the long axis of the trunk.<sup>25</sup>

### 3.2.7 Urine Samples

An overnight (8hr) collected fasting urine sample as measure of microalbuminuria was obtained after waking at 06h00. Urine was stored at 4° after collection and frozen at -80°. Analysis involved a measurement of immunoprecipitation enhanced by polyethylene glycol at 450 nm with Konelab™ 20i Sequential Multiple Analyzer Computer (ThermoScientific, Vantaa, Finland) and the timed-end-point method, (Unicel DXC 800 - Beckman and Coulter, Germany) at independent accredited laboratories. Microalbuminuria is expressed as the urinary albumin : creatinine ratio (exceeding 2.9 mg/micromole).

### 3.2.8 Blood Pressure

Participants rested for 5 minutes in a semi-recumbent position before the first measurement was taken. BP was measured with a sphygmomanometer using the

Riva-Rocci/Korotkoff method<sup>26</sup> on the non-dominant arm using an appropriate cuff size for obese and normal persons. Two duplicate measures were taken with a 3-5 minute resting period between each measurement and the last measurement was used for screening for MetS prevalence.

### **3.2.9 Blood Samples**

A fasting resting blood sample was obtained with a winged infusion set from the brachial vein branches from the dominant arm by a registered nurse. Sodium fluoride glucose and serum samples for MetS markers were handled according to standardized procedures and stored at -80°. Analysis was done using Sequential Multiple Analyzer Computer, Konelab™ 20i Sequential Multiple Analyzer Computer (ThermoScientific, Vantaa, Finland) and the timed-end-point method (Unicel DXC 800 - Beckman and Coulter, Germany) at independent accredited laboratories.

### **3.2.10 Statistical Analysis**

Statistical analysis was performed using Statistica 9.<sup>27</sup> A single 2x2 ANCOVA determined interaction between gender (male and female) and ethnicity (African and Caucasian). Participants were stratified into ethnic and gender groups. Proportions were determined with Chi-square statistics. For comparison between variables, t-test and analysis of covariance were performed, including co-variables body mass index (BMI), gamma glutamyl transferase (GGT) and physical activity (PA). Single and multiple regression models determined associations between the albumin : creatinine ratio as a dependent variable whilst MetS indicators and anthropometric measures were independent variables for each ethnic and gender group. Differences were regarded as statistically significant when  $p \leq 0.05$ .

### 3.3 RESULTS

Significant 2-way interaction effects of gender (male x female) and ethnicity (Africans x Caucasians) were found for systolic blood pressure (SBP) ( $F(1,400) = 6.90$ ,  $p=0.01$ ) and diastolic blood pressure (DBP) ( $F(1,400)=12.96$ ,  $P=0.00$ ).

Participant characteristics are shown in **Table 3.1**. Lifestyle factors showed significant values for alcohol consumption or GGT. Both African groups had high levels of this enzyme, revealing high alcohol consumption although not reflected in the mean triglyceride levels. Although the GGT levels were low in both Caucasian groups, the high standard deviation may show that some of the Caucasian men and women also showed high alcohol consumption. Caucasian men had the highest energy output ( $3674.35 \pm 2059$ ) as measured with the Actical activity meter.

Both male groups demonstrated a mean BMI indicating overweight ( $\geq 25 \text{ kg/m}^2$ ) as well as a WC that presents a health risk.<sup>28</sup> NC was increased in Caucasian compared to African men. African men demonstrated higher BP compared to their Caucasian counterparts. Both male groups had glucose levels above the recommended cut-off point<sup>1</sup> with the Caucasian males presenting with the highest glucose levels. The African women demonstrated a mean BMI indicating obesity ( $> 30 \text{ kg/m}^2$ ) and have a WC above the recommended cut-point.<sup>28</sup> The only other risk factor present in the African women was their low HDL levels. Caucasian women were found to be overweight with high waist circumferences.

No significant differences were evident between either gender ethnic groups for the albumin:creatinine ratio. The urinary albumin:creatinine ratio showed levels indicating a health risk in the African men whilst not present in any of the other groups.

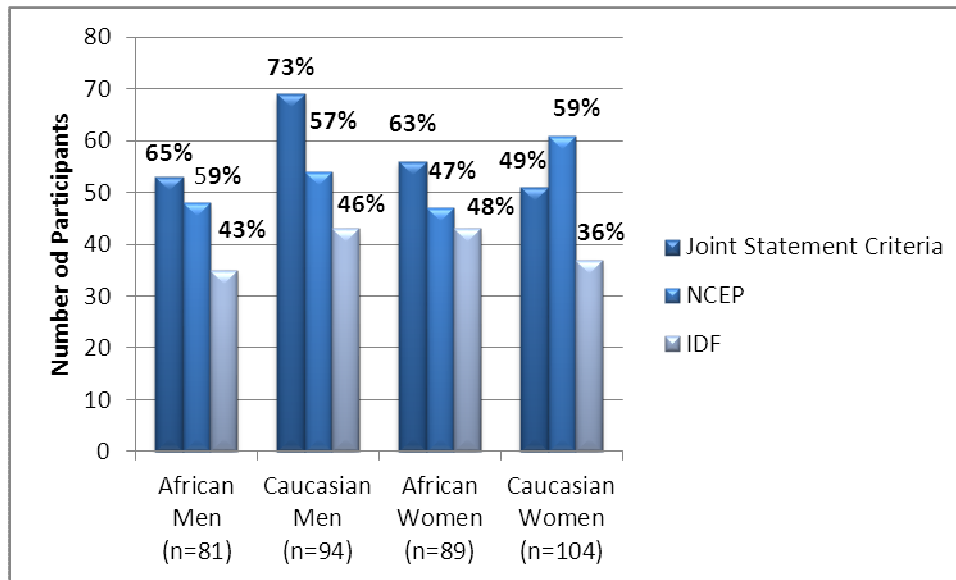
**Table 3.1:** Baseline characteristics of Africans and Caucasians, ANCOVAS (95% CI).

Participant Variables		African Men N=80	Caucasian Men N=94	P	African Women N=89	Caucasian Women N=104	P
<b>Lifestyle Factors</b>							
*Age (years)		43.18 ±8.05	44.96±11.08	0.19	45.39±7.86	44.89±10.7	0.70
*BMI (kg/m <sup>2</sup> )		27.57± 5.77	29.03 ±5.20	0.06	<b>32.73±7.22</b>	<b>26.26±6.29</b>	<b>0.00</b>
*Cotinine (ng/ml)		35.46±65.01	30.89±96.69	0.69	18.68±55.43	15.07±52.99	0.63
*GGT (u/L)		<b>84.84±91.70</b>	<b>34.72±29.51</b>	<b>0.00</b>	<b>47.06±66.60</b>	<b>19.61±36.20</b>	<b>0.00</b>
*PA (kcal)		<b>2714.85±800.12</b>	<b>3674.35±2059.15</b>	<b>0.00</b>	2646.20±789.63	2587.36±644.92	0.56
<b>Physiological Factors</b>							
WC (cm)		<b>95.10 (93.96, 96.25)</b>	<b>99.99 (98.84, 101.13)</b>	<b>0.00</b>	88.17 (86.54, 89.81)	90.16 (88.63, 91.69)	0.11
NC (cm)		<b>37.99 (37.59, 38.39)</b>	<b>40.55 (40.15, 40.95)</b>	<b>0.00</b>	33.83 (32.21, 35.44)	34.71 (33.19, 36.22)	0.48
Glucose (mmol/L)		5.94 (5.63,6.26)	6.02 (5.70, 6.34)	0.75	5.11 (4.77, 5.45)	5.54 (5.23, 5.85)	0.10
Albumin : creatine ratio (mg/micromole)		3.27(0.96, 5.58)	0.38(-1.93, 2.69)	0.098	1.63(1.02, 2.24)	0.92(0.35, 1.5)	0.13
SBP (mmHg)		<b>140.32 (136.88, 143.76)</b>	<b>129.57 (126.13, 133.01)</b>	<b>0.00</b>	126.50 (123.08, 129.93)	125.85 (122.65, 129.06)	0.80
DBP (mmHg)		<b>94.28 (91.92, 96.63)</b>	<b>84.96 (82.60, 87.32)</b>	<b>0.00</b>	83.00 (80.89, 85.11)	80.87 (78.89, 82.84)	0.19
Triglycerides (mmol/L)		1.68 (1.43, 1.93)	1.65 (1.40, 1.90)	0.88	0.99 (0.86, 1.11)	0.95 (0.83, 1.06)	0.66
HDL (mmol/L)		1.04 (0.97, 1.10)	1.01 (0.95, 1.07)	0.55	<b>1.22 (1.14, 1.30)</b>	<b>1.38 (1.30, 1.46)</b>	0.01
<b>Clinically Diagnosed (excluded in all analyses)</b>							

HIV and AIDS	<b>13(12.87)</b>	<b>0(0)</b>	<b>0.00</b>	<b>6(6.06)</b>	<b>0(0)</b>	<b>0.01</b>
Diabetic medication	<b>7(6.93)</b>	<b>1(0.50)</b>	0.03	3(3.03)	1(0.93)	0.27
Statin use	<b>1(0.99)</b>	<b>6(5.94)</b>	0.05	1(1.01)	3(2.78)	0.36

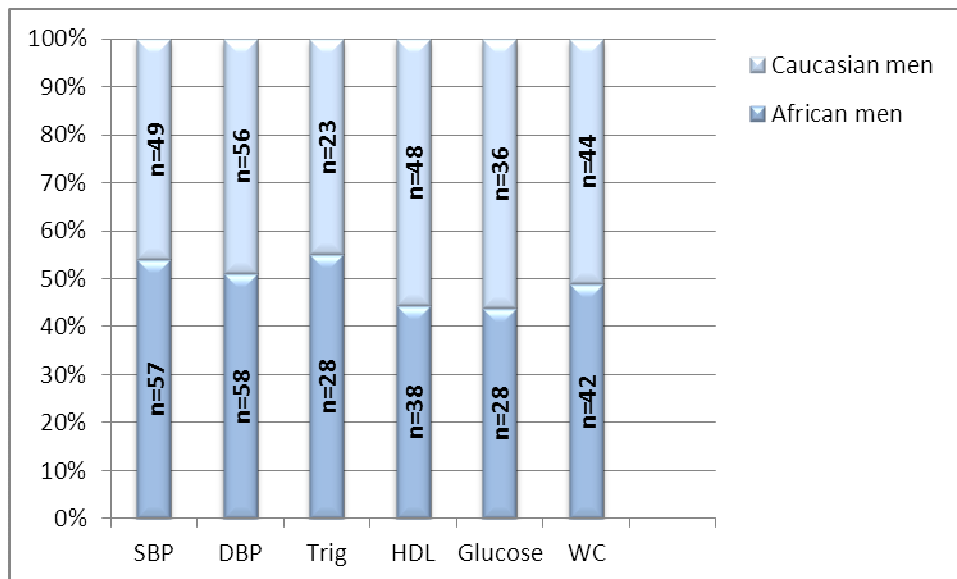
\*Not adjusted; Adjusting for confounders (BMI, PA, GGT) \*, Mean  $\pm$  SD; 95%CI , confidence interval; GGT, Gamma-glutamyl transferase; PA, physical activity;  
 Values in bold differ significantly, significance,  $p \leq 0.05$ . All other values are non-significant.

**Figure 3.1** shows the differences in prevalence of MetS in our population according to 3 different definitions. The new Joint Statement definition included more people with the syndrome, whereas the IDF has the lowest prevalence of MetS. Africans and Caucasian men presented with high prevalence of MetS and differences between Caucasian and Africans were statistically significant.

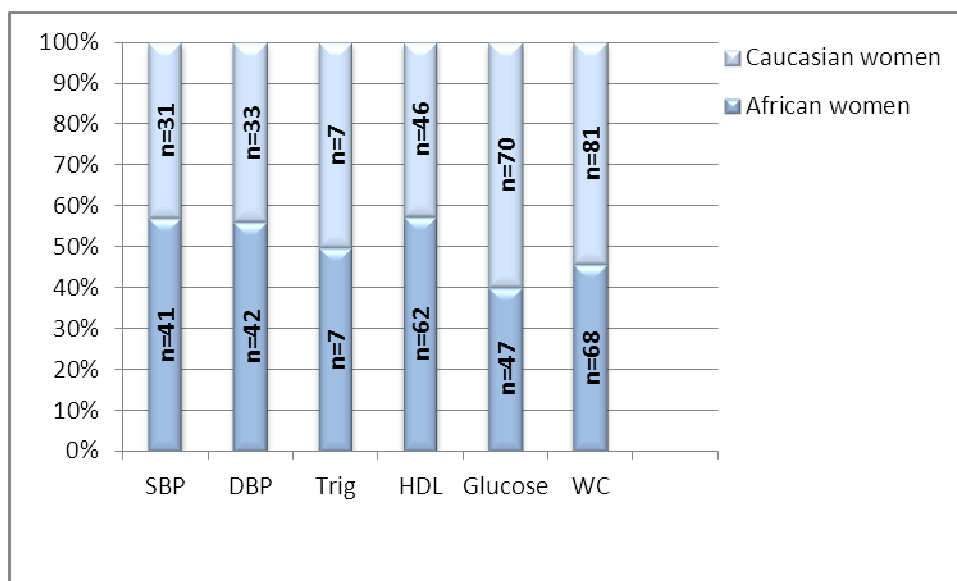


**Figure 3.1:** Prevalence of metabolic syndrome based on the new Joint Statement, IDF and NCEP: ATP III definitions among Black and Caucasian Africans. Where Joint Statement 3>risk factors, IDF WC + 2 or more, NCEP 3or more.

Frequencies of the different risk factors using the new Joint Statement values are shown in **Figures 3.2** and **3.3** for men and women respectively. High blood pressure was most evident among men and more so among the Africans (SBP, 70.37%; DBP, 71.60%). The risk factors most prevalent among women were high WC (n=68, 75.56%; n=81, 77.88%) and glucose levels (n=47, 52.22%; n=70, 67.31%), with the highest prevalence occurring among Caucasian women. Low HDL was highly prevalent among the African women (n=62, 70.45). Worth mentioning is the very low prevalence of high triglycerides among all the women (n=14).



**Figure 3.2:** Prevalence's of the different MetS risk factors for men using the new JSC



**Figure 3.3:** Prevalence's of the different MetS risk factors for women using the new JSC

Forward stepwise linear regression analysis (**Table 3.2**) demonstrated that the urinary albumin : creatinine ratio was explained in African men and women by glucose levels only.

**Table 3.2:** Forward stepwise regression analysis in ethnic groups between measures of urinary albumin : creatine ratio, MetS indicators and anthropometric measures

African men (N=80)			African women (N=89)		
Urinary albumin : creatine ratio (mg/micromol)			Urinary albumin : creatine ratio (mg/micromol)		
Adjusted R <sup>2</sup>	0.17		Adjusted R <sup>2</sup>	0.54	
	<b>β coefficient (95% CI)</b>	<b>P values</b>		<b>β coefficient (95% CI)</b>	<b>P values</b>
<b>Glucose (mmol/L)</b>	0.49 (0.69, 0.29)	0.00	<b>Glucose (mmol/L)</b>	0.76 (0.90, 0.62)	0.00

### 3.4 DISCUSSION

The main aim of this study was to determine the presence of MetS indicators using the new Joint Statement definition for African and Caucasian South Africans and to determine which of the MetS indicators predicted microalbuminuria.

Our data clearly showed that the new definition included more participants with MetS than previously set definitions. This could be due to the lack of any prerequisite measures such as WC. Furthermore, blood pressure levels are lower compared to some of the previous definitions' values, which would mean that pre-hypertensive persons are already eligible to develop MetS. According to the new JSC, after excluding diabetics, Africans have a high prevalence of MetS. This contradicts the findings of Kalk and Joffe<sup>29</sup> which found that Africans demonstrated a lower prevalence of MetS. This difference could possibly be ascribed to a different definition of the MetS being used as well as the fact that their study included diabetics.

Lifestyle factors could have contributed to the higher MetS prevalence. Low to medium physically active levels were evident, which could in part explain the increased body weight that we have seen amongst our participants. Alcohol consumption as a lifestyle risk factor was measured objectively with the use of the liver enzyme GGT. GGT was high amongst all Africans, especially concerning the men. The triglyceride and glucose levels however did not support these GGT

findings suggesting other possible underlying mechanisms such as hepatic steatosis, insulin resistance and increased oxidative stress<sup>30</sup>. Both Caucasian groups had GGT levels below the cut-point,<sup>23</sup> although the standard deviation (SD) was high, implying possible higher alcohol consumption for some participants. Substance abuse such as alcohol and smoking has been found to be utilized as coping strategies when challenged with increased stress in urban environments.<sup>9,11,31</sup> Furthermore, increased alcohol intake is known to increase visceral obesity through an increased energy intake<sup>31</sup> as well as the risk of developing MetS components such as BP and impaired glucose tolerance (IGT)<sup>32</sup> through endocrine disorders.<sup>31</sup> Alcohol sensitizes the arterial wall, increasing BP.<sup>33</sup> The above could explain in part the high prevalence of both the elevated SBP and the DBP among the African men.

The apparent high prevalence of MetS for African women (63%) in our study could be ascribed to the suggested European WC cut-off points (men, 94cm and women, 80cm)<sup>1,28</sup> which are possibly too low, especially for African women. This could mean that the pathology of MetS will occur at a higher WC cut-off than the suggested 80cm. If more accurate cut-off points are developed, it is possible that a lower occurrence of MetS will be prevalent among the African women. Rural<sup>34</sup> and urban<sup>35</sup> African women have been found to be healthy obese because obesity in women showed weak associations with cardiovascular risk.<sup>35,36</sup> Recently contradictory results were demonstrated by Van der Merwe<sup>37</sup> in diabetic participants. Our data excluded clinically confirmed diabetics, users of statins as well as HIV infected participants whilst including participants from all BMI groups. A lower cardiovascular risk was revealed albeit an increased metabolic risk. Clearly no conclusive evidence exists on this matter and further research is needed in controlled homogenous sample groups

Conversely the risk of developing MetS further increases if taken into account all groups' overweight status. The African women run the highest risk with a mean value indicating obesity. These findings are consistent with previous studies that have also found that BMI is high among women of African descent.<sup>38-40</sup> African women tend to be overweight and obese because they believe 'fatness' indicates wealthy spouses and good health, such as the absence of HIV/AIDS.<sup>41</sup> Faber and Kruger<sup>42</sup> found that African women may think that weight loss rather than 'thinness' indicates sickness and financial problems. These women also do not perceive themselves as being

overweight and this, coupled with diabetes prevalence, has been found to relate to the level of education.<sup>33,41</sup> Obesity has been found to be high amongst African women, regardless of economic status.<sup>41</sup> A recent study also revealed that a BMI of more than 29.9kg/m<sup>2</sup> and less than 25.7kg/m<sup>2</sup> showed higher levels of microalbuminuria compared to normal weight.<sup>42</sup> Our data support this as the women demonstrated overweight-obese status with glucose levels predicting microalbuminuria. This would lead us to believe that although African women are obese, their cardiovascular health tends to be healthy but metabolically that is not the case. Unfortunately duration of obesity is not known and should be addressed in the progression of metabolic disease. All the above lifestyle factors have been related to a Westernized society which is also associated with an increased prevalence of obesity.<sup>39,44</sup> Furthermore, although African women are obese, it is known that increases of visceral fat and adipose tissue dysfunction are associated with insulin resistance independently of total body mass which proposes that the type of fat depots are important in developing of pathology.<sup>45</sup>

Regarding anthropometric measures, waist circumference has been found to be a better predictor of health risk<sup>2</sup> than other measures of adiposity. WC is an indicator of central fat distribution rather than overall fatness such as in the case of BMI<sup>2</sup> and WHR.<sup>46</sup> Central fat, or adipose fat, is known for its metabolically active nature<sup>2,13</sup> which results in increased blood lipids and glucose.<sup>2</sup> The men with their overweight BMI, revealed a WC below the level, which constitutes health risk (>102cm) according to the ACSM.<sup>24</sup> In both female groups WC revealed a health risk (>88cm) although African women with their increased BMI demonstrated a lower WC than their overweight Caucasian counterparts.

Additionally, in order to improve the prediction of health risks, NC was measured as a possible new measurement criterion. Although cut-off values do not yet exist for this measurement, it has been found that NC shows promise as a health risk indicator.<sup>3,5</sup> Furthermore, it has been found that NC relates to other measures of health risk such as BMI, fat distribution and insulin resistance which in turn is associated with MetS.<sup>4,47</sup> In our study, NC did not predict microalbuminuria in the African women as was the case with previous findings<sup>5</sup> where diabetics were not excluded.

In terms of ethnicity and urine albumin levels, it has been found that albumin levels are higher amongst African Americans than among their Caucasian counterparts.<sup>48</sup> Findings also showed that microalbuminuria as a measure of renal impairment and endothelial dysfunction is more prevalent amongst Africans, regardless of blood pressure.<sup>7</sup> In the presence of hypertension, such as is the case with our African male group, they could be more prone to renal impairment.<sup>49,50</sup> In our current study the urinary albumin : creatinine ratio was higher in both the African groups than in the Caucasian groups. Only the African males however presented with levels constituting risk.

According to the new JSC of MetS, the African women was the only group with mean glucose levels below the risk threshold (<5.6 mmol/l) whilst all other groups were above this threshold. African men showed the highest risk for MetS prevalence with BP and glucose exceeding the cut-points. Only glucose predicted the albumin : creatinine ratio which could increase endothelial dysfunction and stroke risk.<sup>51</sup> In terms of triglycerides, Africans displayed low levels<sup>30,32,33</sup> and our study confirms these findings, especially in women. Although their triglycerides are favourable, African women presented with low HDL levels. These findings are in contrast with other studies which found that African women presented with higher HDL levels than their Caucasian counterparts.<sup>32,33</sup> The data of the afore-mentioned studies were obtained 5 years previous to the SABPA study and the difference in HDL levels could possibly be ascribed to time lapsed between these studies or an increase in MetS prevalence. Normal HDL levels are more easily obtained when BMI is below 28 kg/m<sup>2</sup>.<sup>52</sup> As we have mentioned, our African women group was obese, which may be related to their low HDL levels.

A limitation of our study is the cross-sectional design which cannot infer casualty. A follow-up study is in progress and future data dissemination should address biochemical measures e.g. serum creatinine and uric acid as indicators of renal function. Another limitation is that the sample was not selected from the whole African population and it is therefore recommended that our findings be verified in other African communities.

To conclude, Africans have a high prevalence of MetS, with the use of the new JS definition, accepting our hypothesis. African women, although obese, seem to be healthy when considering mean values of risk factors, individually, some African women have been identified as having MetS, but when considering mean values of risk factors, as mentioned, very few risk factors for MetS are presented. The number of African women with MetS may decrease once ethnic-specific cut-off points have been developed. The higher glucose values predicting microalbuminuria in both gender African groups contribute to endothelial dysfunction and stroke risk.

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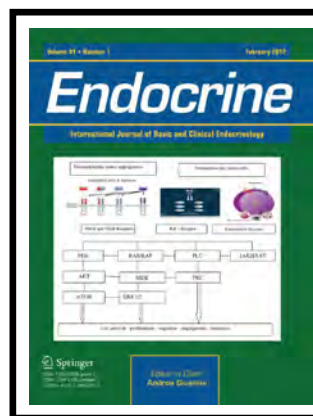
Chapter 4

*Determining cut-off values for neck circumference as a measure of the metabolic syndrome amongst a South African cohort: the GABRA Study.*

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**ABSTRACT**

**Purpose:** The aim was to determine receiver operating characteristic (ROC) neck circumference (NC) cut-offs best associated with the metabolic syndrome (MetS) in a South African cohort. **Method:** We included 409 urban Africans and Caucasians and stratified them into gender and age groups (25-45 years; 45-65 years). Measurements included anthropometric, fasting overnight urine and biological markers for the metabolic syndrome (MetS) (systolic and diastolic blood pressure, glucose, triglycerides and high-density lipoprotein/HDL). **Results:** ROC analysis determined pathological neck circumference (NC) cut-points of 39 cm and 35 cm for young and older African men; 32 cm and 35 cm for young and old African women; 40 cm and 41 cm for Caucasian men; 34 cm and 33 cm for Caucasian women. Pathological NC cut-points significantly predicted MetS in all ethnic-gender-age groups except in African women (ORs 2.3 - 5.4; 95% CI 1.36 - 16.5). Multiple regression analyses revealed that MetS prevalence and ROC cut-points were not associated with renal impairment in any groups. **Conclusion:** ROC NC cut-points demonstrated that NC may be used as an additional anthropometric marker to predict the metabolic syndrome (MetS) in a South African cohort but not in African women.

**Key Words:** Metabolic Syndrome (MetS), neck circumference (NC), African, Caucasian

## **Determining cut-off values for neck circumference as a measure of the metabolic syndrome amongst a South African cohort: the SABPA Study.**

### **4.1 INTRODUCTION**

Metabolic syndrome (MetS) prevalence is a rising epidemic, and this is no different in Africa as it has increased along with the rapid urbanization of Africans [1]. Recent research demonstrated that Africans have the highest prevalence of MetS compared to Caucasians [2]. This higher prevalence could, however, change with the use of ethnic specific waist circumference (WC) cut-points [3]. The recently renewed definition of the metabolic syndrome [4] suggested that ethnic specific cut-points for waist circumference (WC) should be made in order to more correctly identify Africans with underlying metabolic syndrome.

Microalbuminuria was previously a component of the MetS and research revealed the importance of specifically neck circumference (NC) as a parameter with which to identify the presence of microalbuminuria in Africans [5,6]. NC is known to be associated with sleep apnea in adults and children [7]. Sleep apnea has also been related with the MetS [8] and MetS can be highly prevalent among children [9].

However, literature is sparse on the topic of NC and metabolic health in adult Africans. Some findings demonstrated that NC is worthy of further investigation as an identifying measure of health risk [5, 10]. Furthermore, NC shows association with BMI (body mass index) and WC, which indicates central obesity [11-12]. Onat *et al.* 2009 [12] further demonstrated that associations between NC and physiological risk factors were more profound in men. Nielsen *et al.* 2004 [13], however, concluded that women are more prone to show associations between NC and adverse health risk factors.

Together with WC, NC might therefore be a good supportive or independent screening tool for MetS [11-12]. Furthermore, NC has been found to be a more ideal measure than WC because it does not change during the day [11].

Due to a distinct lack of information for NC and especially among Sub-Saharan

Africans, we will aim to identify possible cut-points for NC among an African and Caucasian cohort to predict MetS. We hypothesized that NC cut-off points will be higher in African than Caucasians and that NC can successfully be used as a MetS screening tool. These findings could lead to the development of cost effective screening measures, which would be of great importance to impoverished African communities.

## 4.2 MATERIALS AND METHODS

This sub-study (2008-2009) formed part of the prospective cohort study, Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) which was conducted during 2008 -2012.

### 4.2.1 Study Population

The study sample (N=409) comprised urban African and Caucasian teachers from the Dr. Kenneth Kaunda Education district in the North-West Province, South Africa. This sample was thus homogenous concerning socio-economic class and included 200 Africans (men, N=101; women, N=99) and 209 Caucasians (men, N=101; women, N=108). Participants were aged 25-65 years. Exclusion criteria for participation included pregnancy, lactation, temperature  $>37^{\circ}\text{C}$ , use of alpha and beta blockers and psychotropic substance abuse as well as blood donors and persons vaccinated in the 3 months prior to participation. Data from HIV positive participants (13 African men; 6 African women) and clinically diagnosed diabetics (7 African men; 3 African women; 1 Caucasian man; 1 Caucasian woman) were excluded from analysis. Participants were classified with the MetS using the guidelines of Alberti *et al.* (2009) (WC, men  $\geq 94$  cm and women  $\geq 80$  cm; triglycerides  $\geq 1.7$  mmol/L; HDL, men  $1.0$  mmol/L and women  $< 1.3$  mmol/L; glucose  $\geq 5.6$  mmol/L; SBP  $\geq 130$  mmHg; DBP  $\geq 85$  mmHg) [4]. The suggested cut-points for WC for Africans as suggested by Prinsloo *et al.* (2011) were used for Africans [3] when determining the presence of MetS. All participants signed an informed consent form and the study was approved by The Ethics Review Board of the North-West University (project nr: NWU-00036-07S6). The study conformed

to the ethical guidelines for human participants of the World Medical Association Declaration of Helsinki.

#### **4.2.2 Experimental Procedure**

Avoiding seasonal changes, collection of data for each participant continued over a 48 hour period in the working week from February–May 2008/2009. Each morning Actical® accelerometer (Montréal, Québec) devices were fitted and software programs activated for four participants after which they resumed their daily activities. Participants had to overnight at the Metabolic Unit Research Facility on the NWU campus. The Metabolic Unit consists of bedrooms for each participant, bathrooms, a kitchen and a dining room as well as a living room with a television. Participants were welcomed at 16:30 at the Metabolic Unit and introduced to the experimental setup. A standardized dinner was given and participants fasted from 22h00. The following day at 06h00 anthropometric measurements were taken in triplicate, followed by blood pressure (BP) and blood sampling.

#### **4.2.3 Assessment of Anthropometric Variables and Physical Activity**

Anthropometric measurements were performed by level 2 accredited anthropometrists with subjects wearing minimal clothing and without shoes.

Maximum stature was measured with a stadiometer to the nearest 0.1 cm while weight was measured to the nearest 0.1 kg on a KRUPS scale with the weight evenly distributed. The above-mentioned measurements were used to calculate body mass index (BMI) by dividing weight (kg) by length (m)<sup>2</sup> [14].

Circumferences were measured with the participant in a standing position using a non-extensible and flexible anthropometric tape. NC was taken immediately superior to the thyroid cartilage perpendicular to the long axis of the neck. WC was taken at the midpoint between the lower costal rib and the iliac crest, perpendicular to the long axis of the trunk and not at the narrowest point for

standardisation purposes [15].

Physical activity was measured by means of the Actical® physical activity monitor, which was water resistant, lightweight and small. The monitors were initialized and the results downloaded using a serial port computer interface. Acticals were fitted to participants' waists and were worn for 24 hours and removed after their overnight stay at NWU.

#### **4.2.4 Assessment of Biological Variables**

Blood pressure measures followed after participants had rested for 5 minutes in a semi-recumbent position. BP was measured with a sphygmomanometer using the Riva-Rocci/Korotkoff method on the non-dominant arm [16]. Two duplicate measures were taken with a 3-5 minute resting period between each measurement and the last measurement was used for screening for the MetS prevalence.

An overnight (8hr) fasting urine sample of 100 ml was obtained after waking. And used to determine albumin:creatinine ratio as a marker of microalbuminuria. Urine was stored at 4°C after collection and frozen at -80°C.

A fasting resting blood sample was obtained with a winged infusion set from the brachial vein branches from the dominant arm by a registered nurse. Sodium fluoride glucose and serum samples for MetS markers, cotinine and GGT were handled according to standardized procedures and stored at -80°. Biochemical analysis for urine which involved a measurement of immunoprecipitation enhanced by polyethylene glycol at 450 nm and blood sampling analyses were done using Sequential Multiple Analyzer Computer, Konelab™ 20i Sequential Multiple Analyzer Computer (ThermoScientific, Vantaa, Finland) and the timed-end-point method, (Unicel DXC 800 - Beckman and Coulter, Germany) at independent accredited laboratories.

#### 4.2.5 Statistical Analyses

Participants were stratified into African and Caucasian gender age groups of 24-45 years (hereafter referred to as the younger group) and 46-65 years (hereafter referred to as the older group).

Statistical analyses were performed with Statistica 9 computer program (StatSoft Inc. 2009). Normality was tested and Gamma Glutamyl Transferase (GGT) was log transformed. Results were expressed as mean  $\pm$  standard deviation (SD). Independent t-tests compared different age groups within African and Caucasian men and women. Comparisons were made with Chi-square analysis. Partial correlations determined associations between NC and WC in each ethnic-, gender- and age group, adjusting for the lifestyle risk factors, cotinine and log GGT. Thereafter, non-parametric receiver operating characteristic (ROC) curves were computed to examine the ability of neck circumference to suggest population specific cut-off points (SPSS, v17 for Windows). The optimal cut-off was obtained from the Youden index [maximum (sensitivity + specificity – 1)]. For all logistic and linear stepwise regression analyses, cotinine and log GGT were included as covariates.

### 4. 3 RESULTS

#### 4.3.1 African Men and Women

**Table 4.1** depicts the basic characteristics of the African groups. Concerning lifestyle factors, there were no differences between age groups for BMI, physical activity and GGT levels. Both older groups have higher cotinine levels, 58.1 ng/ml and 30.6 ng/ml for men and women respectively, compared to the 23.2 ng/ml and 7.5 ng/ml of their younger counterparts. GGT levels among the African groups indicated alcohol abuse [17].

In both male groups the MetS components (glucose, triglycerides, BP, WC) were above the recommended cut-points. It was however only SBP that was significantly higher in the older men, 149 mmHg, compared to the younger men,

136 mmHg. MetS was prevalent in 33 of the young men and 19 of the older men. ACR mean levels above cut-point were evident only in the young African men.

**Table 4.1:** Baseline characteristics of African Men and Women.

	<b>African Men (25-45 years) (n=56)</b>	<b>African Men (45-65years) (n=26)</b>	<b>P value</b>	<b>African Women (25-45 years) (n=46)</b>	<b>African Women (45-65years) (n=42)</b>	<b>P value</b>
<b>Lifestyle factors</b>						
Age	38.6±5.1	52.2±4.3	0.0	39.1±4.3	52.1±4.4	0.0
BMI, kg/m <sup>2</sup>	27.6±5.7	27.6±6.0	1.0	32.0±7.6	33.6±6.8	0.3
PA kcal/h	2818 ±851.4	2509.7 ±668.5	0.1	2608.5 ±758.5	2686.2 ±827.6	0.6
GGT, U/L	75.7±72.5	102.9±120.2	0.2	43.5±36	50.8±88.6	0.6
Cotinine, ng/ml	23.2±47.5	58.1±86.5	0.0	7.5±27.0	30.6±73.2	0.0
<b>Metabolic Syndrome Components</b>						
Glucose, mmol/l	5.8±1.9	6.4±2.2	0.1	5.0±1.4	5.6±2.6	0.2
HDL, mmol/l	1.0±0.4	1.1±0.3	0.1	1.2±0.3	1.2±0.3	0.2
TRIG, mmol/l	1.8±1.8	1.8±1.2	0.9	0.9±0.5	1.2±0.7	0.0
SBP mmHg	136±18	149±22	0.0	125±15	135 ±18	0.0
DBP mmHg	92±14	97±14	0.1	82.5±9.6	86±10	0.1
WC, cm	92.6±15.2	95.5±16.2	0.4	91.0	96.3±14.7	0.1
<b>Neck Circumference as possible MetS Predictor</b>						
NC, cm	37.8±3.2	37.4±3.4	0.5	33.6±2.8	33.6±2.6	1.0
<b>Metabolic syndrome prevalence</b>						
MetS n (%)	19 (73)	33 (59)	0.0	17 (37)	29 (69)	0.0
<b>Target organ damage</b>						
ACR	3.5±19.1	2.7±5.1	0.8	2.1±4.9	1.4±1.2	0.3

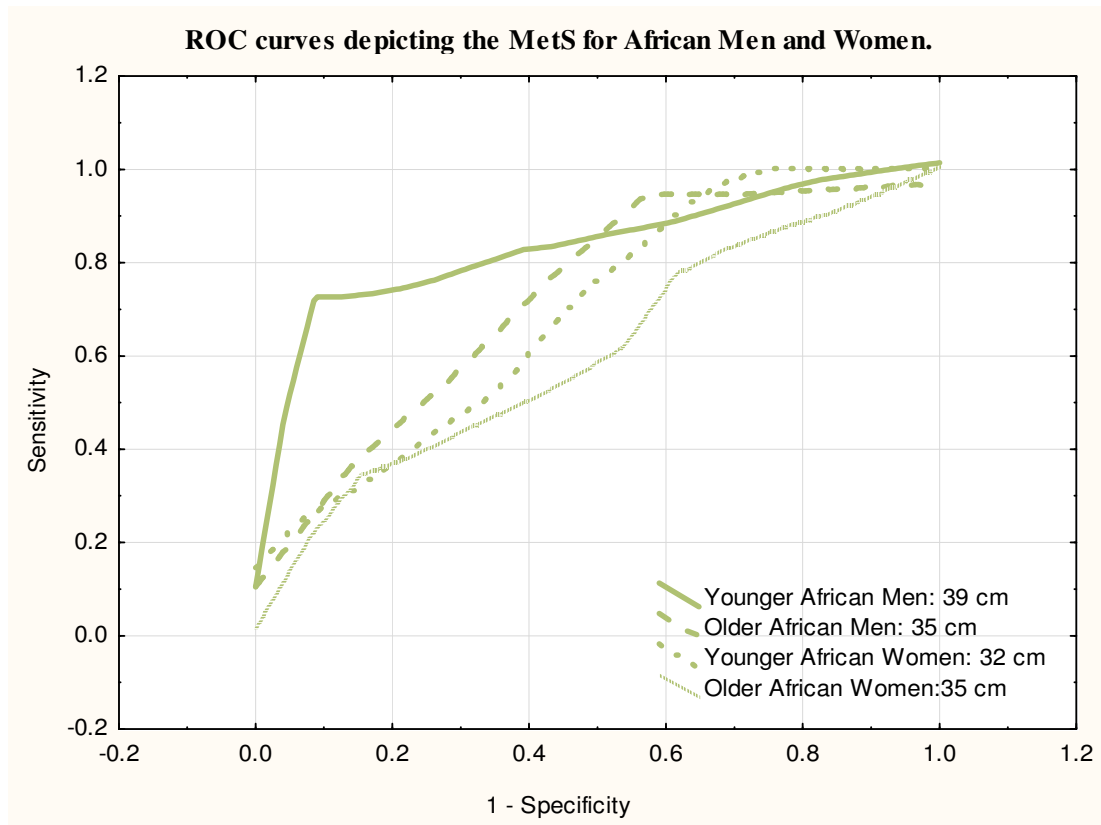
Values are arithmetic mean ± SD. Where; BMI, body mass index; PA, physical activity; GGT, Gamma Glutamyl Transferase; HDL, high density lipoprotein; TRIG, Triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; NC, neck circumference; WC, waist circumference; ACR, albumin: creatinine ratio.

In the older African women, the MetS components indicated more risk as their glucose (5.6 mmol/l), SBP (134 mmHg), and DBP (86 mmHg) were above, while HDL levels (1.2 mmol/l) were below recommended cut-points. Younger African women only revealed risk with lower than recommended HDL (1.2 mmol/l) levels. A similar trend pertaining to SBP in older men was evident in the older women.

Among the women it was however the older group that presented with a greater prevalence of MetS, 29, compared to the much lower 17 participants in the younger group.

Significantly strong partial associations existed between NC and WC within all African age groups (young African men:  $r=0.8$ ; older African men:  $r=0.8$ ; young African women:  $r=0.7$ ; older African women:  $r=0.7$ ) (not shown).

ROC analysis was used to determine the suggested cut-off values for NC for the MetS. **Figure 4.1** visually illustrates where the AUC was most optimal for the MetS and what the cut-points were according to the Youden index.



**Figure 4.1:** ROC curves depicting the MetS for African men and women.

ROC curves depicting the MetS for the African men and women predicting pathological NC. The area under the curve (AUC) (95%CI) was **0.8** (0.7; 0.9) for young African men, **0.7** (0.5; 1.0) for older African men, **0.7** (0.5; 0.8) for young African women, **0.6** (0.4; 0.8) for older African women

The respective ROC cut-off values, yielding maximum sensitivity and specificity were found at a cut-point of 39 cm (AUC: 0.8) for younger and at 35 cm (AUC: 0.7) for older African men while the younger African women revealed a cut-point at 32 cm (AUC: 0.7) and the older women at 35 cm (AUC: 0.6) for older women.

Odds ratios (**Table 4.3**) revealed that increased risk for MetS was evident in young (OR 5.4,  $p=0.0$ ) and old (OR 4.0,  $p=0$ ) African men above the suggested NC cut-points. This risk was most prominent for young African males. On the contrary, NC was not associated with risk for MetS in older and younger African women (OR 1.7,  $p=0.1$ ; OR 1.8,  $p=0.2$ ).

Forward stepwise linear regression analysis demonstrated that no associations existed between ACR and NC in any of the ethnic-gender-age groups.

**Table 4.2:** Logistic regression and Odds ratios are demonstrated to indicate if NC cut-points predict MetS in Africans.

	Young		Older		Younger		Older	
	African men		African men		African women		African women	
Metabolic syndrome (MetS)								
	OR	(± 95 CI)	OR	(± 95 CI)	OR	(± 95 CI)	OR	(± 95 CI)
Neck	5.4	(1.8, 16.1)	4.0	(1.2, 12.6)	1.7	(0.8, 3.6)	1.8	(0.7, 4.3)
Circumference		P=0.0		P=0.0		P=0.1		P=0.2

Data presented as Odds Ratio (OR) with 95% Confidence Interval and p-values for significance of OR. Co-variates included cotinine and log GGT.

## 4.3.2 Caucasian Men and Women

**Table 4.3:** Baseline characteristics of Caucasian men and women.

	Caucasian Men (25-45 years) (n=46)	Caucasian Men (45-65 years) (n=54)	P- value	Caucasian Women (25-45 years) (n=49)	Caucasian Women (45-65 years) (n=58)	P- value
<b>Lifestyle factors</b>						
Age	35.2±8.4	53.1±4.3	0.0	35.7±7.7	52.8±5.0	0.0
BMI, kg/m <sup>2</sup>	28.9±6.2	29.1±4.2	0.8	25.9±7.0	26.6±	0.6
PA kcal	3482.3±636.2	3481±814.1	1.0	2602±690.2	2574±609.0	0.8
GGT, U/L	32.2±33.1	36.8±26.2	0.4	15.4	23.3±47.7	0.3
Cotinine, ng/ml	33.6±94.4	28.6±99.4	0.8	27.7±71.9	4.1±23.6	0.0
<b>Metabolic Syndrome Components</b>						
Glucose, mmol/	5.8±1.0	6.1±0.8	0.2	5.2±0.4	5.5±0.7	0.0
HDL, mmol/l	0.9±0.2	1.0±0.3	0.1	1.3±0.4	1.5±0.4	0.1
TRIG, mmol/l	1.5±1.0	1.5±0.8	0.9	0.8±0.3	1.0±0.5	0.0
SBP mmHg	126±12	133±14	0.0	116±11	128±16	0.0
DBP mmHg	84±10	86±9	0.3	76±8	83±9	0.0
WC, cm	99.0±16.0	103.7±12.7	0.1	82.4±13.6	87.2±12.8	0.1
<b>Neck Circumference as possible Mets Predictor</b>						
NC, cm	40.8±3.3	41.0±2.7	0.7	33.5±2.3	34.2±2.7	0.1
<b>Metabolic syndrome prevalence</b>						
MetS n (%)	33 (72)	42 (77)	0.0	11 (22)	30 (52)	0.0
<b>Target organ damage</b>						
ACR	0.3±0.4	0.5±1.3	0.3	1.2±2.1	0.4±0.4	0.0

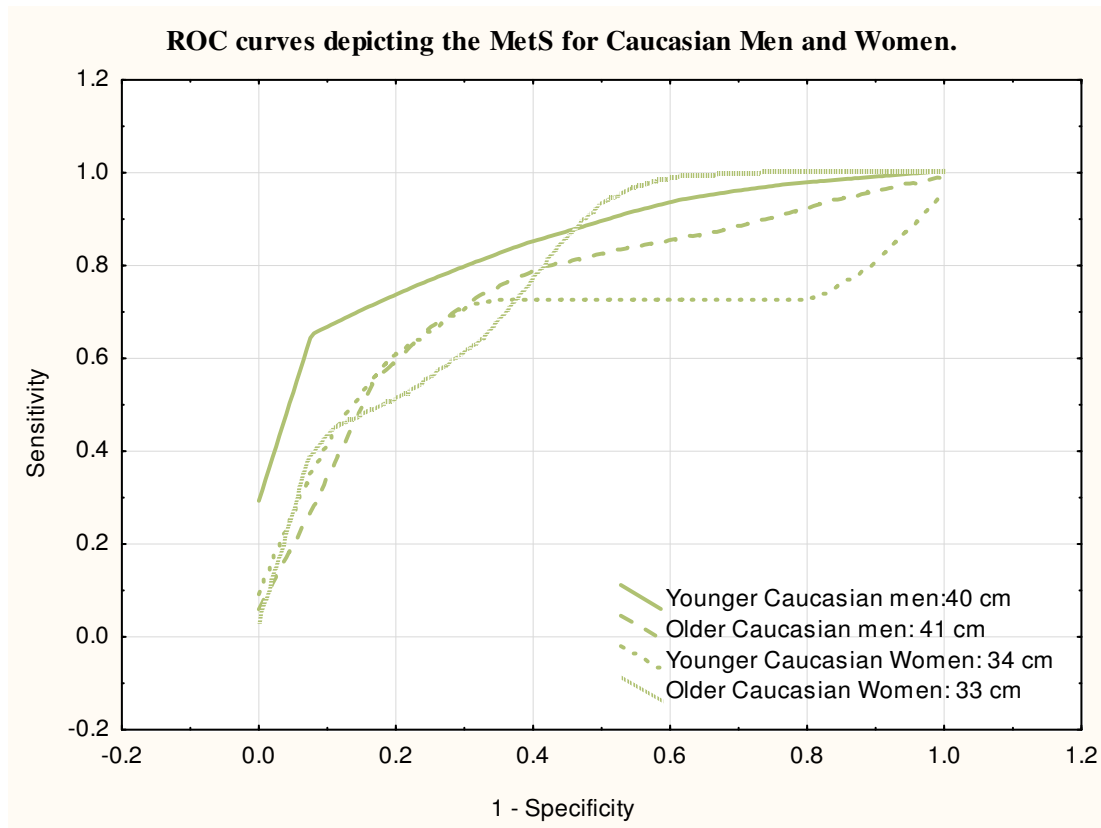
Values are arithmetic mean ± SD. Where; BMI, body mass index; PA, physical activity; GGT, Gamma Glutamyl Transferase; HDL, high density lipoprotein; TRIG, Triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; NC, neck circumference; WC, waist circumference; ACR, albumin: creatinine ratio.

**Table 4.3** depicts basic characteristics for Caucasians. Lifestyle factors did not differ within age groups. In both Caucasian male groups, glucose and WC exceeded cut-points. In older men, BP exceeded cut-points probably contributing to being identified with MetS (n=42) compared to the young men (n=33).

The younger Caucasian women had significantly higher cotinine levels (27.7 ng/mg) when compared to their older counterparts (4.1 ng/ml). No other lifestyle factor differences existed. Older Caucasian women revealed risk with glucose (5.5 mmol/l) and WC (87.2 cm), while the younger group only revealed risk according to their WC (82.4 cm). Despite triglycerides, SBP, DBP being significantly higher among the older women when compared to the young group, these levels did not constitute health risk. On the contrary ACR was significantly higher in the young women but also did not constitute health risk. More of the older Caucasian women (n=30) presented with MetS compared to the 11 younger women.

Significantly strong associations existed between NC and WC within all Caucasian age and gender groups (young Caucasian men:  $r = 0.8$ ; older Caucasian men:  $r = 0.8$ ; young Caucasian women:  $r = 0.8$ ; older Caucasian women:  $r = 0.8$ ).

ROC analysis was used to determine the suggested cut-off values for NC for the MetS. **Figure 4.2** visually illustrates where the AUC is most optimal for the MetS and what the cut-points were according to the Youden index. The respective ROC cut-off values, yielding maximum sensitivity and specificity were found at a cut-point of 40 cm (AUC: 0.9) and 41 cm (AUC: 0.7) for the young and older men respectively. NC cut-points for young women were found at 34 cm (AUC: 0.7) and 33 cm (AUC: 0.8) for the older group.



**Figure 4.2:** ROC curves depicting the MetS for Caucasian men and women.

ROC curves depicting the MetS for the Caucasian men and women predicting pathological NC. The area under the curve (AUC) (95%CI) **0.9** (0.8; 1.0) for young Caucasian men, **0.7** (0.6; 0.9) for older Caucasian men, **0.7** (0.4; 0.9) for younger Caucasian women and **0.8** (0.7; 0.9) for older Caucasian women.

We commenced with logistic regression and odds ratios in **Table 4.4**. The pathological NC, as determined with ROC analysis, determined risk for MetS in all Caucasian groups. Odds ratios revealed that increased risk for MetS was evident in young and old Caucasian men (OR 3.2,  $p=0.0$ ; OR 2.3,  $p=0.0$ ). High risk was also prevalent for young (OR 2.8,  $p=0.0$ ) and older women (OR 4.6,  $p=0.0$ ).

Multiple regression analysis revealed no associations between NC cut-point and ACR in any of the ethnic-gender-age groups.

**Table 4.4:** Logistic regression and Odds ratios are demonstrated to indicate if NC cut-points predict MetS in Caucasians.

	Young Caucasian men		Older Caucasian men		Younger Caucasian women		Older Caucasian women	
Metabolic syndrome (MetS)								
	OR	(± 95 CI)	OR	(± 95 CI)	OR	(± 95 CI)	OR	(± 95 CI)
Neck	3.2	(1.2, 8.7)	2.3	(1.0, 5.4)	2.8	(1.2, 6.3)	4.6	(1.8, 11.5)
Circumference		P=0.0		P=0.0		P=0.0		P=0.0

Data presented as Odds Ratio (OR) with 95% Confidence Interval and p-values for significance of OR. Co-variables included cotinine and log GGT.

## 4.4 DISCUSSION

The aim of this study was to determine the best ethnic-, gender- and age-specific NC cut-off points for the MetS. Our main finding demonstrated that ROC developed NC cut-points can be used to determine risk for MetS.

### 4.4.1 Africans: Lifestyle Factors

Urbanization or acculturation [18] and accompanying poor lifestyle factors, such as alcohol abuse, smoking and low physical activity could affect cardiometabolic health in African populations [19]. These risk behaviours have been found to be utilized as coping strategies in stressful environments with subsequent increase in hypertension prevalence [20] and waist circumferences [21], both of which are MetS indicators. Further research is needed to indicate whether these factors are also linked to NC.

High blood pressure has been found to be a concern among urban Africans [18, 22-23] and also apparent in our groups. A contributing factor namely high GGT concentration (>65 U/L) in both age groups may act as a surrogate marker of oxidative stress accompanying MetS but which can also be indicative of alcohol

abuse [17]. Other possible underlying mechanisms for increased GGT values may exist such as hepatic steatose, insulin resistance and increased oxidative stress [24]. Their increased BP as well as carotid intima media thickness (CIMT) [19] could add to cardiometabolic and atherogenic risk as Hamer et al. [19] showed that the odds of early structural vascular changes ( $\geq 0.9$  mm CIMT) based on high GGT levels were 3.1 (95% CI; 0.6-15.5) in the African men, independent of confounders.

Our African women groups revealed a mean value of obesity. African women believe that fatness reflects health and the absence of HIV [25-27]. Although obesity is considered a major health risk factor, our African women seemed to be healthier than their male counterparts with their lower BMI. This could imply that psychological wellbeing possibly has a positive effect on physical wellbeing. This phenomenon has been termed 'healthy obesity' and it states that although African women are overweight, they present with good health [25-27]. Although both women age groups revealed obese levels, older African women presented with more risk factors which may be attributed to age. Ageing women have less oestrogen protecting them against cardiovascular diseases [28]. Fat distribution changes with ageing and women develop an android build which has been associated with glucose intolerance, lipid and BP irregularities because of the metabolically active nature of visceral fat [29]. The aforementioned were more obvious for glucose, BP and HDL in our older African women. The younger women also revealed low levels of the protective factor HDL. Healthy HDL levels are more easily obtained when BMI is below  $28 \text{ kg/m}^2$  [30] which was not the case among our obese African women. Triglycerides were favourable in both women age groups suggesting high levels of lipoprotein lipase (LPL) which were demonstrated in Africans, especially in women [31]. This factor can lead to the under diagnosis of MetS in Africans and adjustments for this specific measure for Africans have been suggested [32-33].

#### **4.4.2 Africans: Neck Circumference as a predictor of MetS**

Concerning the NC the cut-points indicated that pathology for MetS may occur at a higher cut-point than the mean for the younger men and at a cut-point lower than the mean value for older men. Considering ageing, pathology can occur at a lower NC value than in younger persons. Cut-points for African women did however, not predict MetS as opposed to the men where NC predicted risk to develop MetS. This finding could support the notion of healthy obesity.

Lastly, regarding the target organ damage resulting from MetS, it can be seen among the young African men which could be a result of their high BP or the findings that Africans have a greater prevalence of end stage renal disease and tend to have higher albumin levels than Caucasians [34-35]. Our results support these findings in the young African men who revealed increased albumin:creatinine ratios. NC however did not predict ACR in any ethnic-gender-age groups.

#### **4.4.3 Caucasians: Lifestyle Factors**

Our Caucasian groups seem to be healthier than their African counterparts, as they present with less risk. Caucasians may be acculturated [18] longer than the Africans and as such, urbanization may have less of an effect on overall health of Caucasians. Lifestyle risk factors revealed more alcohol abuse among the men whilst younger groups smoked more. All groups revealed overweight BMIs, increased glucose levels and elevated WC. Even though BP was higher in older gender groups it did not constitute health risk.

#### **4.4.4 Caucasians: Neck Circumference as predictor of MetS**

NC in the Caucasian groups revealed a mean value of 41cm for all Caucasian men which were the cut-point for older Caucasian men. Young Caucasian men

revealed a cut-point of 40 cm. Women revealed a mean value of 34 cm which is in accordance to the cut-point for younger women while older women presented with a cut-point of 33 cm.

#### 4.4.5 Ethnic NC Recommendations

When comparing our cut-points with those of Onat *et al.* [12], it is apparent that a Turkish population presented with a 39 cm cut-point which only coincide with the cut-point for young African men. A higher cut-point (35cm) has been suggested for Turkish women compared to our cut-points for women except in older Africans. Dixon and O'Brien (2002)[10] found that an NC of more than 42 cm in women revealed insulin resistance. As we have not measured insulin resistance, we cannot comment on this cut-point but it should be mentioned that these findings were demonstrated in severely obese subjects. In our study, MetS is present in NC cut-points much lower than Dixon and O'Brien [10] has suggested for women. These different findings demonstrate the importance of developing ethnic, gender and age specific cut-points. It is important though that persons of a more muscular build would have a higher mean NC [36] when compared with more sedentary participants.

A limitation of our sub-study is the cross-sectional design which cannot infer causality and no surrogate markers of insulin resistance has been documented. A follow-up study is in progress and future data dissemination should address other laboratory markers such as increased mean red cell volume in order to better indicate alcohol abuse. The strengths of this study include the inclusion of a representative group of urban black Africans as well as Caucasians within a highly standardized experimental protocol.

To conclude, we carefully propose NC cut-points for young and older African men at 39 and 35 cm respectively while African women did not pose risk for MetS with NC cut-points. For Caucasian men we want to propose cut-points of 40 and

41 cm, and 34 and 33 cm for the Caucasian women. This could be useful in future to more easily identify persons at risk of having MetS especially in impoverished African communities. However, prospective cohort studies are needed in larger sample groups to strengthen our findings and to develop race and ethnic specific cut-points.

Our hypotheses are partially accepted as NC proved to be a good indicator of the presence of MetS but cannot be used as a MetS screening tool for African women. Furthermore, the African groups did not have greater NC cut-points than their Caucasian counterparts.

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#### **4.6 Disclosure**

No conflict of interest

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*Determining ethnic, gender, and age-specific waist circumference cut-points to predict the metabolic syndrome: the SAFLA-study*

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**ABSTRACT**

The aim was to determine receiver operating characteristic (ROC) waist circumference (WC) cut-offs best associated with the metabolic syndrome (MetS) in a South African cohort. We included 409 urban Africans and Caucasians and stratified them into gender and age groups (25-45 years; 45-65 years). Measurements included anthropometric, fasting overnight urine and biological markers for the metabolic syndrome (MetS) (systolic and diastolic blood pressure, glucose, triglycerides and high-density lipoprotein/HDL). ROC analysis determined pathological WC cut-points of 91 cm for all African male groups, 84, 81 and 84 cm for young, older and total group of African women. WC cut-point for Caucasian men were suggested at 93 cm for the young group and 97 cm for older as well as total Caucasian male groups. Mets risk increased in Caucasian women at WC cut-points of 87 cm, 79 cm and 84 cm for young, older and total Caucasian women groups. Pathological WC cut-points significantly predicted MetS in all ethnic-gender-age groups, especially among total male groups with odds ratios of 7.6 (95 % CI 3.4-17.1) for African men and 6.0 (95% CI 3.0-12.1) for Caucasian men. Multiple regression analyses revealed that ROC developed WC cut-points were not associated with renal impairment in any groups. We conclude that ROC WC cut-points demonstrated that ethnic-gender-age groups are good predictors of the metabolic syndrome (MetS) in a South African cohort especially among men.

**Key Words:** Metabolic Syndrome (MetS), waist circumference (WC), African, Caucasian

## **Determining ethnic-, gender- and age-specific waist circumference cut-points to predict the metabolic syndrome: the SABPA-study**

### **5.1 INTRODUCTION**

Anthropometric measures could be the final frontier to accurately identify the metabolic syndrome (MetS) in Africans since waist circumference (WC) is the last parameter that still has to be accurately developed among persons of different ethnic descents [1]. Prinsloo *et al.* (2011)[2] has taken up this challenge and demonstrated that increased systolic blood pressure best predicted WC cut-points of 90 cm in African men (OR 9.6, 95%CI 3.1-29.3) and 98 cm in African women (OR 3.1, 95% CI 1.3-7.4). These cut-points do, however, not reflect MetS status – only presence of specific risk factors. Consequently these cut-points differ from the suggested European cut-offs which are suggested for MetS as a whole [3]. Moreover, it is not clear whether the European cut-points are also accurate for Caucasian Africans. In addition, Cameron *et al.*, 2010 [4] has indicated the importance of developing country-specific rather than one universal ethnic-specific cut-point. WC and body mass index (BMI) can be seen as the golden standard anthropometric measurements of health risk and it is suggested that evaluations should at least include one of these measurements [5]. Various studies have shown that the WC is influenced by ethnicity, gender and age [4, 6-7] and as such should be further investigated in African age-specific populations. Further investigation is also warranted for target organ damage (TOD). The burden of MetS among urban black Africans [8] can contribute to the strain of microalbuminuria as a marker of TOD [9-14].

The aim was firstly to develop a WC cut-point for Africans and Caucasians in gender and age groups (25-45 years and 46-65 years) for the MetS in our co-hort. Thereafter we aimed at determining whether the newly developed WC cut-points increase the odds to predict MetS, and whether this screening tool will be associated with TOD, if any, in our African and Caucasian populations. Hypotheses for this

study included that Africans will have higher WC cut-points than Caucasians and that these newly developed cut-points will be effective in screening for MetS.

## 5.2 METHODS AND PROSEDURE

This sub-study (2008-2009) formed part of the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study which was conducted during 2008- 2012.

### 5.2.1 Study population

The study sample composed urban African and Caucasian teachers from the Dr. Kenneth Kaunda Education district in the North-West Province, South Africa. This sample was thus homogenous concerning socio-economic class and comprised 409 participants aged 25-65 years, 200 of which were African (men, N=101; women, N=99) and 209 Caucasians (men, N=101; women, N=108). Data from HIV positive participants (19 Africans) and clinically diagnosed diabetics (10 Africans and 2 Caucasians) were excluded from analysis. The total sample after exclusion comprised 378 participants. Exclusion criteria for participation included pregnancy, lactation, temperature  $>37^{\circ}\text{C}$ , use of alpha and beta blockers and psychotropic substance abuse. Blood donors and persons vaccinated in the 3 months prior to participation were also excluded. All participants signed an informed consent form and the study was approved by The Ethics Review Board of the North-West University (project nr: NWU-00036-07S6). The study conformed to the ethical guidelines for human participants of the World Medical Association Declaration of Helsinki.

### 5.2.2 Metabolic Syndrome

Participants were classified with the MetS when 3 or more of the risk factors were present when using the Joint Statement Criteria [1]. Waist circumference has been classified as a risk at  $\geq 94$  cm and  $\geq 80$  cm for Caucasian men and women respectively [1], while WC of Africans were classified using the suggested cut-points of Prinsloo. *et al.* (2011) (90 cm African men and 98 cm for African women) [2]. The

other components of MetS are classified as risk factors as follows: triglycerides  $\geq 1.7$  mmol/L; HDL for men at 1.0 mmol/L and for women at  $< 1.3$  mmol/L; glucose  $\geq 5.6$  mmol/L; SBP  $\geq 130$  mmHg; DBP  $\geq 85$  mmHg [1].

### 5.2.3 Experimental procedure

Avoiding seasonal changes, collection of data for each participant continued over a 48-hour period in the working week from February–May 2008 and again during the same period of time 2009. Each morning Actical® accelerometer (Montréal, Québec) devices were fitted and software programs activated for four participants after which they resumed their daily activities. Participants had to overnight at the Metabolic Unit Research Facility on the NWU campus. Participants were welcomed at 16:30 at the Metabolic Unit and introduced to the experimental setup to lessen anticipation stress [15]. After receiving a standardized dinner, participants were encouraged to go to bed at 22h00 and to fast until all measures were completed the next morning. The following day at 06h00, urine samples were obtained after which anthropometric measurements were taken, followed by blood pressure and blood sampling.

### 5.2.4 Assessment of Anthropometric and Biological Variables

All anthropometric measurements were done in triplicate by level-2 accredited anthropometrists.

Maximum stature was measured with a stadiometer to the nearest 0.1 cm while weight was measured to the nearest 0.1 kg on a KRUPS scale with the weight evenly distributed. The above-mentioned measurements were used to calculate body mass index (BMI).

Circumferences were measured with the participant in a standing position using a non-extensible and flexible anthropometric tape. NC was taken immediately superior to the thyroid cartilage perpendicular to the long axis of the neck. WC was taken at the midpoint between the lower costal rib and the iliac crest, perpendicular to the long axis of the trunk and not at the narrowest point for standardisation purposes [16].

Physical activity was measured by means of the Actical® physical activity monitor, which was water resistant, lightweight and small, using 1-min recording epochs. Acticals were fitted to participants' waists and were worn for 24 hours and removed after their overnight stay at NWU.

Blood pressure measures followed after participants had rested for 10 minutes in a semi-recumbent position. Blood pressure was measured with a sphygmomanometer using the Riva-Rocci/Korotkoff method on the non-dominant arm [17]. Two duplicate measures were taken with a 3-5 minute resting period between each measurement and the last measurement was used for screening for MetS prevalence.

A fasting resting blood sample was obtained with a winged infusion set from the brachial vein branches from the dominant arm by a registered nurse. Sodium fluoride glucose and serum samples for MetS markers, cotinine and GGT were handled according to standardized procedures and stored at -80°. Analysis was done using Sequential Multiple Analyzer Computer, Konelab™ 20i Sequential Multiple Analyzer Computer (ThermoScientific, Vantaa, Finland) and the timed-end-point method, (Unicel DXC 800 - Beckman and Coulter, Germany) at independent accredited laboratories.

An overnight (8hr) collected fasting urine sample as measure of albumine: creatinine ratio (ACR) was obtained after waking at 06h00. Urine was stored at 4° after collection and frozen at -80°. Analysis involved a measurement of immunoprecipitation enhanced by polyethylene glycol at 450 nm with Konelab™ 20i Sequential Multiple Analyzer Computer (ThermoScientific, Vantaa, Finland) and the timed-end-point method (Unicel DXC 800 - Beckman and Coulter, Germany) at independent accredited laboratories.

### 5.2.5 Statistical Analyses

Statistical analyses were performed with Statistica 10 computer program (StatSoft Inc. 2012). Participants were stratified into African and Caucasian gender age groups of 24-45 years (hereafter referred to as the younger group) and 46-65 years (hereafter referred to as the older group).

Normality was tested and Gamma Glutamyl Transferase (GGT) was log transformed. Independent t-tests compared different age groups within African and Caucasian men and women. Basic characteristics were expressed as mean with 95% Confidence Intervals (95% CI) with co-variables BMI, physical activity, cotinine, log GGT. Proportions were compared with Chi-square analysis. Thereafter, non-parametric receiver operating characteristic (ROC) curves were computed to examine the ability of waist circumference to suggest population- and age-specific cut-off points for MetS (SPSS, v17 for Windows). The optimal cut-off was obtained from the Youden index (maximum (sensitivity + specificity – 1). MetS was the dependent variable for logistic regression while albumin: creatinine ratio was the dependent variable for linear forward stepwise regression analyses. For regression analysis cotinine and log GGT were included as covariates. Data were regarded as statistically significant when  $p \leq 0.05$ .

## 5.3 RESULTS

### 5.3.1 Men: African versus Caucasian

**Table 5.1** depicts the basic characteristics of the male groups. Concerning lifestyle factors, there were no differences between ethnic-age groups for BMI and cotinine. Caucasian men seem to be significantly more active than African men while African men revealed significantly increased GGT levels. GGT levels among the African groups indicate alcohol abuse [18], especially in the younger African men.

Concerning MetS, 59% and 72% of the young African and Caucasian men respectively presented with this syndrome. In the older groups MetS was evident in 73% of the African and 77% of the Caucasian men.

Concerning MetS components, glucose and WC were above the recommended cut-points for all groups, although Caucasian men revealed significantly increased WC and NC above that of their African counterparts. High triglycerides were a risk only in Caucasian men, while blood pressure was the highest among the African men. ACR mean levels above cut-point were evident only in older African men, which was significantly higher than in their Caucasian counterparts.

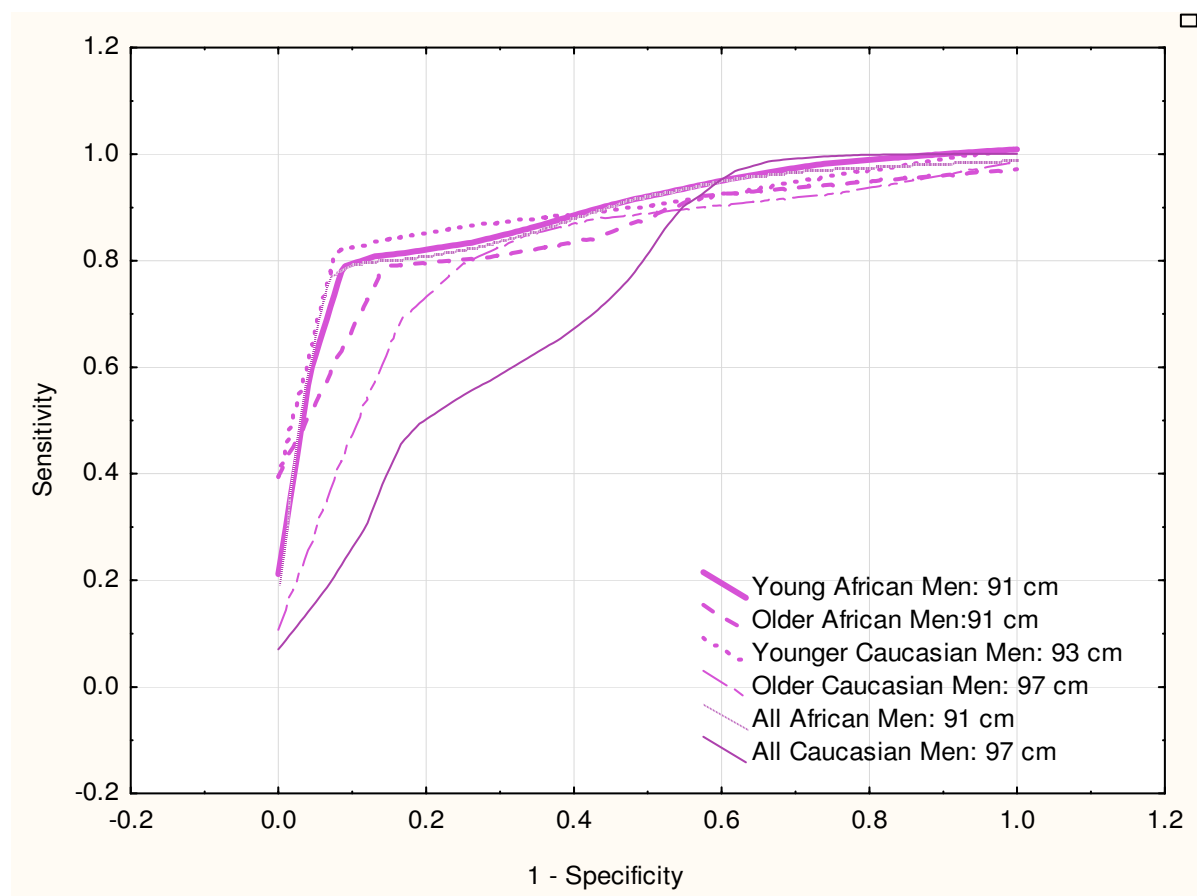
Table 5.I: Baseline characteristics of Africans and Caucasian Men

	African Men (25-45 years) (n=56)	Caucasian Men (25-45 years) (n=46)	P value	African Men (46-65years) (n=26)	Caucasian men (46-65 years) (n=54)	P value
<b>Lifestyle factors</b>						
<sup>†</sup> BMI, kg/m <sup>2</sup>	27.6±5.7	28.9±6.2	0.24	27.6±5.98	29.1±4.2	0.15
<sup>†</sup> PA kcal	2818.1±851.4	3482.0±814.1	0.00	2509.7±668.5	3482.3±636.2	0.00
<sup>†</sup> GGT, U/L	75.7±73.1	32.2±33.1	0.00	102.9±120.2	36.8±26.2	0.00
<sup>†</sup> Cotinine, ng/ml	58.2±86.5	33.6±94.4	0.47	23.2±47.5	28.6±99.4	0.16
<b>Metabolic Syndrome Components [ANCOVAS (95% CI)].</b>						
Glucose, mmol/l	5.7 (5.3, 6.1)	5.9 (5.4, 6.1)	0.55	6.3 (5.6, 7.0)	6.2 (5.7, 6.7)	0.29
HDL, mmol/l	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.62	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	0.71
TRIG, mmol/l	1.5 (1.1, 1.9)	2.0 (1.5, 2.5)	0.14	1.5 (1.1, 1.9)	1.7 (1.4, 1.9)	0.56
SBP mmHg	135 (131, 139)	127 (122, 132)	0.02	149 (141, 157)	133 (127, 138)	0.00
DBP mmHg	92 (89, 96)	83 (80, 88)	0.00	97 (92, 101.4)	86 (83, 90)	0.01
WC, cm	93.1 (91.7, 94.5)	98.5 (96.7, 100.4)	0.00	98.1 (95.7, 100.5)	102.1 (100.3, 103.8)	0.02
NC, cm	38.0 (37.5, 38.5)	40.6 (40.0, 41.3)	0.00	38.1 (37.2, 39.0)	40.5 (39.9, 41.2)	0.00
<b>Metabolic syndrome</b>						
MetS n (%)	33 (59)	33 (72)	0.0	19 (73)	42 (77)	0.0
<b>Target organ damage</b>						
ACR	2.6 (-1.6, 6.7)	1.7 (-3.6, 7.0)	0.82	3.0 (1.5, 4.4)	0.3 (-1.0, 1.4)	0.01

<sup>†</sup>Not adjusted, Mean ± SD; 95% CI, confidence interval; BMI, body mass index; PA, physical activity; GGT, Gamma Glutamyl Transferase; HDL, high density lipoprotein; TRIG, Triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; NC, neck circumference; WC, waist circumference; ACR, albumine: creatinine ratio. Adjusting for confounders (BMI, PA, Cotinine, GGT)

ROC analysis was used to determine the suggested cut-off values for WC for the MetS. **Figure 5.1** visually illustrates where the AUC was most optimal for the MetS and what the cut-points were according to the Youden index for men.

The respective ROC cut-off values, yielding maximum sensitivity and specificity were found at a cut-point of 91 cm both young and older African men as well as for the total group of African men. The best cut-points for WC were found at 93 cm for young and 97 cm for older and total group of Caucasian men.



**Figure 5.1: ROC curves depicting the MetS for African and Caucasian men.**

ROC curves depicting the MetS for the African and Caucasian men predicting pathological WC. The area under the curve (AUC) (95%CI) was **0.9** (0.8; 1.0) for young African men, **0.9** (0.7; 1.0) for older African men and **0.9** (0.8-1.0) for all African men, **0.9** (0.8; 1.0). The AUC for young Caucasian men was **0.9** (0.8-1.0), **0.8** (0.7; 1.0) for older Caucasian men and **0.9** (0.8-0.9) for all Caucasian men.

Odds ratios (**Table 5.2**) revealed that increased risk for MetS was evident in all groups above the suggested WC cut-points with the highest risk in groups that were not stratified according to age (All African: OR 7.6,  $p=0.00$ ; All Caucasian, OR 6.0,  $p=0.00$ ).

Table 5.2: Logistic regression to indicate if ethnic- and age-specific WC cut-points predict MetS in Men.

Young African Men			Younger Caucasian Men		Older African Men		Older Caucasian Men		All African Men		All Caucasian Men	
Metabolic syndrome (MetS)												
	OR	(± 95 CI)	OR	(± 95 CI)	OR	(± 95 CI)	OR	(± 95 CI)	OR	(±95 CI)	OR	(± 95 CI)
WC	4.1	(2.7, 6.0) P=0.00	4.5	(2.9; 6.9) p=0.00	4.1	(2.7; 6.0) P=0.00	4.5	(2.9; 6.9) p=0.00	7.6	(3.4; 17.1) p= 0.00	6.0	(3.0; 12.1) P=0.00

Data presented as Odds Ratio (OR) with 95% Confidence Interval and p-values for significance of OR, Co-variables included age, cotinine and log GGT.

### 5.3.2 Women: African versus Caucasian

**Table 5.3** depicts the basic characteristics of the women. Concerning lifestyle factors, African women had significantly increased BMI's as well as GGT above those of their Caucasian counterparts. However, GGT levels were only significantly higher in the younger group. Older African women would seem to smoke significantly more than their Caucasian counterparts.

Regarding MetS among the young groups, 37% of the African and 22% of the Caucasian woman could be regarded as having metabolic syndrome. Of the older Africans and Caucasians, 69% and 52% respectively were identified as having MetS.

**Table 5.3:** Baseline characteristics of African and Caucasian women.

	African Women (25-45 years) (n=46)	Caucasian Women (25-45 years) (n=49)	P value	African Women (46-65 years) (n=42)	Caucasian Women (46-65 years) (n=58)	P value
<b>Lifestyle factors</b>						
<sup>†</sup> <b>BMI, kg/m<sup>2</sup></b>	32.0±7.6	25.9±7.0	0.00	33.6± 6.8	26.6±5.6	0.00
<sup>†</sup> <b>PA kcal</b>	2608.5±758.5	2602.0±690.3	0.96	2686.2± 827.6	2574.7±609.0	0.43
<sup>†</sup> <b>GGT, U/L</b>	43.5±36.0	15.3±13.4	0.00	50.8± 88.6	23.3±47.7	0.00
<sup>†</sup> <b>Cotinine, ng/ml</b>	7.5± 27.0	27.7±71.9	0.07	30.6± 73.2	4.1±23.6	0.01
<b>Metabolic Syndrome Components [ANCOVAS (95% CI)]</b>						
<b>Glucose, mmol/l</b>	5.0 (4.7, 5.4)	5.2 (4.8, 5.4)	0.70	5.5(4.6, 5.8)	5.8 (5.3, 6.4)	0.18
<b>HDL, mmol/l</b>	1.2 (1.0, 1.3)	1.3 (1.2, 1.4)	0.13	1.2 (1.1, 1.4)	1.5 (1.3, 1.6)	0.05
<b>TRIG, mmol/l</b>	0.9 (0.7, 1.0)	0.8 (0.6, 0.9)	0.55	1.0 (0.83, 1.27)	1.0 (0.9, 1.3)	0.72
<b>SBP mmHg</b>	125 (120, 129)	117 (112, 121)	0.04	131 (125, 137)	132 (127, 137)	0.92
<b>DBP mmHg</b>	83 (80, 86)	76 (72, 79)	0.01	84 (81, 87)	85 (82, 87))	0.72
<b>WC, cm</b>	87.6 (85.2, 90.0)	86.1 (83.7, 88.5)	0.47	88.3 (85.7, 90.9)	93.8 (91.5, 96.0)	0.01
<b>NC, cm</b>	33.2 (32.5, 33.9)	33.9 (33.2, 34.6)	0.21	32.4 (31.8, 33.1)	35.2 (34.6, 35.8)	0.00
<b>Metabolic syndrome</b>						
<b>MetS n (%)</b>	17 (37)	11 (22)	0.0	29 (69)	30 (52)	0.0
<b>Target organ damage</b>						
<b>ACR</b>	1.3 (1.0, 1.6)	0.5 (0.2, 0.9)	0.01	2.2 (0.9, 3.5)	1.1 (-0.0, 2.3)	0.31

<sup>†</sup>Not adjusted, Mean ± SD; 95% CI , confidence interval; BMI, body mass index; PA, physical activity; GGT, Gamma Glutamyl Transferase; HDL, high density lipoprotein; TRIG, Triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; NC, neck circumference; WC, waist circumference; ACR, albumine: creatinine ratio. Adjusting for confounders (BMI, PA, Cotinine, GGT).

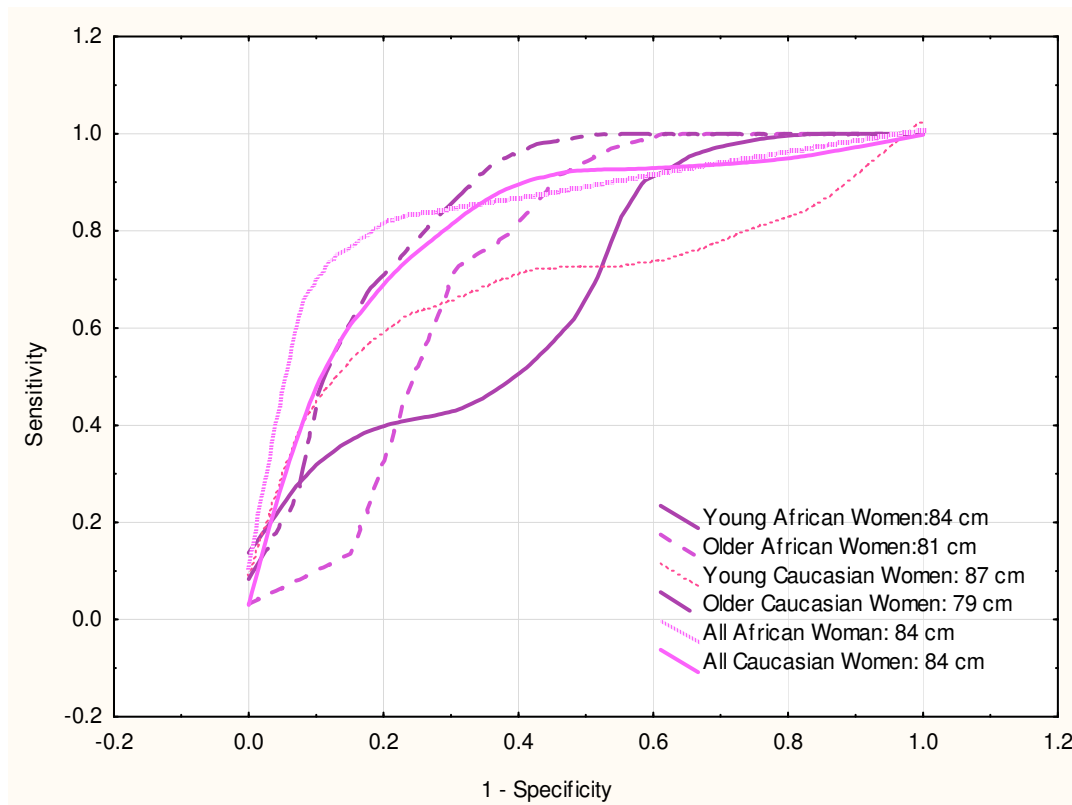
Concerning MetS components it would seem that the older groups presented with more risk factors. Glucose and SBP were above cut-points in both older groups. Significantly higher blood pressure was demonstrated in the African group. In the

older African group significantly lower HDL values were revealed compared to older Caucasians. This low HDL level constitutes MetS risk with cut-points below recommended levels. Young African woman also presented with HDL levels below recommended cut-points. Older Caucasian women had significantly increased WC and NC values above those of their African counterparts. ACR was significantly higher in the young African women than in their Caucasian counterparts; these levels were, however, below the risk threshold for this marker of target organ damage.

**Figure 5.2** visually illustrates where the AUC was most optimal for the MetS and what the cut-points were according to the Youden index for women. The respective ROC cut-off values were 84 cm for young as well as African women as a group. 81 cm has been found to be the most optimal cut-point for older African women. Cut-points suggested for Caucasian women were 87, 79 and 84 cm for young, older and total group of Caucasian women respectively.

We commenced with logistic regression and odds ratios in **Table 5.4**. The pathological WC, as determined by means of ROC analysis, determined risk for MetS in all women groups. Odds ratios revealed that increased risk for MetS was evident in African (OR 4.4,  $p=0.00$ ) and Caucasian (OR 4.5,  $p=0.00$ ) women. However, odds were lower when groups were not stratified according to age, as opposed to the findings concerning men.

Multiple regression analysis revealed no associations between WC and ACR in any of the ethnic-gender-age groups.



**Figure 5.2: ROC curves depicting the MetS for African and Caucasian women.**

ROC curves depicting the MetS for the African and Caucasian women predicting pathological WC. The area under the curve (AUC) (95%CI) was **0.7** (0.5; 0.8) for young African women, **0.7** (0.5; 0.9) for older African women and **0.7** (0.6-0.8) for all African women. The AUC was **0.7** (0.5; 0.9) for young Caucasian women, **0.9** (0.8; 1.0) for older Caucasian women and 0.8 (0.7, 0.9) for all Caucasian women.

**Table 5.4: Logistic regression to indicate if ethnic- and age-specific WC cut-points predict risk of MetS in Women.**

Young African Women			Younger Caucasian Women		Older African Women		Older Caucasian Women		All African Women		All Caucasian Women	
Metabolic syndrome (MetS)												
	OR	(± 95 CI)	OR	(± 95 CI)	OR	(± 95 CI)	OR	(± 95 CI)	OR	(±95 CI)	OR	(± 95 CI)
WC	4.1	(2.7; 6.0) p=0.00	4.5	(2.9; 6.9) P=0.00	4.1	(2.7; 6.0) p=0.00	4.5	(2.9; 6.9) p=0.00	3.3	(1.8; 6.2) P=0.00	3.8	(2.2; 6.5) P= 0.00

Data presented as Odds Ratio (OR) with 95% Confidence Interval and p-values for significance of OR. Co-variables included age cotinine and log GGT.

## 5.4 DISCUSSION

The main aim of this study was to determine ethnic-, gender- and age-specific cut-points for WC to predict MetS. Our main finding demonstrated that the newly developed WC cut-points increase the risk for MetS in all ethnic-, gender- and age-specific groups.

### 5.4.1 Men

African men were much less active and more inclined to alcohol abuse than the Caucasian men. These risk factors may be utilized coping strategies when living in an urban environment [10,19]. Björntorp (2001) suggested that it may be linked to increased waist circumference and the progression of the metabolic syndrome [20].

Although older Caucasian men have more MetS risk factors, their African counterparts had significantly higher mean levels of risk factors. Blood pressure is of great concern among Africans and this has been corroborated by other South African studies [21-22]. It would seem that African men have increased blood pressure above that of their Caucasian counterparts, regardless of age. This could possibly be ascribed to high alcohol abuse as seen in our urban African population [23-24]. Triglycerides were increased in both Caucasian age groups and not in either African counterpart group, which could possibly be ascribed to Africans having inherently higher lipoprotein lipase (LPL) levels which clear triglycerides from circulation [25].

Concerning anthropometry, WC and NC was elevated in both Caucasian age groups above that of the African age groups, which conforms to the findings of a South African health survey which established that African men are less likely to present as being obese than their Caucasian counterparts [26]. Contrary to these findings, it has been reported that African American men are more overweight than their Caucasian counterparts [27]. These contrasting findings strengthen the idea of ethnic- and

country of origin-specific research.

Lastly, concerning TOD, as reflected in albumin:creatinine ratios, African men of both age groups presented with higher albumine: creatinine ratios than their age-specific counterparts. Higher renal risk amongst Africans has been documented by other researchers [14, 28], however, ROC-developed WC cut-points were not associated with ACR in the current study.

#### **5.4.2 Women**

African women in both age groups revealed higher GGT levels and possible alcohol abuse than their Caucasian counterparts. In addition, older African women revealed the highest cotinine levels which could imply that smoking is used as an additional coping strategy. BMI levels were obese in both African age groups, which is consistent with the findings of other South African studies [26, 29-32]. In Africans, overweight is perceived as being healthy just as losing weight is perceived as having contracted a disease such as HIV [30-32]. Furthermore, Africans do not perceive themselves as being overweight or obese, while Caucasian women conversely perceive themselves as being overweight even while this may not be the case [29]. These beliefs could have contributed to the observed differences in BMI between African and Caucasian women.

Concerning the MetS factors, it would seem that the women groups are more healthy than the men. In both young women groups, only low HDL levels as a MetS risk factor was present among the young Africans. This low HDL could possibly be ascribed to the young Africans' obesity levels ( $\text{BMI} \geq 30.0 \text{ kg/m}^2$ ), as appropriate levels of HDL are more easily maintained in persons with a BMI below 28 [33]. The absence of MetS risk factors in the young Caucasians could possibly be accredited to their healthier lifestyle, compared to that of Africans. Ageing brings about physiological changes such as decreased oestrogen and a change in body fat distribution which could increase the likelihood of developing glucose intolerance, irregularities concerning lipids and blood pressure [34]. The aforementioned can be

seen for blood pressure in both older groups. Lipids were not adversely affected in older groups, except for low HDL in older Africans as was the case with the young African women.

As with the men, African women presented with the highest ACR values compared to their Caucasian counterparts. These levels were however below levels that constitute risk.

#### 5.4.2 Waist circumference cut-points

The WC cut-points for MetS differ from those set by Prinsloo *et al.* (2011), which were developed in the same population for individual markers of MetS and not in ethnic-, gender- and age-specific groups. In our sub-study, WC cut-points predicting MetS suggested for African men is 91 cm for both age groups and for all African men as a group. This is more or less similar to the 90 cm for African men set by Prinsloo *et al.* (2011) for the MetS component systolic blood pressure.

In African women, WC cut-points for MetS are suggested to be 84 and 80 cm for the young and old groups respectively, as well 84 cm for the overall African women group. This differs from the 98 cm cut-point [2] which was not developed for MetS as a whole but rather for systolic blood pressure as an individual component of MetS. This reflects that MetS is present at a lower WC and that increased SBP may develop at a greater WC. Our cut-point, however, is more aligned to the 80 cm cut-point of the IDF, which has not yet been ethnically or age adjusted.

Concerning the Caucasian groups we have a cut-point of 93 cm for young and 97 cm for both older and total group of Caucasian men. Caucasian women presented with three different cut-points, namely 87 cm for young, 79 cm for older and 84 cm for the overall Caucasian women groups. MetS presents at a much lower WC in older women than in their younger counterparts. These cut-points are mostly consistent with the suggested European cut-points of 94 and 80 cm for men and women respectively [3]. However it is noteworthy, especially in Caucasian women, how cut-points differ regarding age groups.

Our WC cut-points suggest that for African Caucasians, pathology occurs at a lower WC for older women and at a higher WC for older men. Overall it would seem that women develop pathology at a lower WC than do men. According to our cut-points, older Caucasian women develop pathology at the lowest WC while older Caucasian men develop pathology at the highest circumference. Differences in cut-points indicate the importance of ethnic-, age- and country of origin-specific cut-points in order to more accurately identify risk for MetS.

Looking at our WC cut-point's ability to predict MetS risk, it would seem that our WC cut-point increases the odds of developing MetS in all groups. It would seem that in the male groups, WC had the greatest potential of predicting MetS, especially when the groups were not classified according to age. Since the cut-points in either ethnic group are the same and odds are better in the total groups, age-specific cut-points need not be suggested for men.

Women have lower odds of developing MetS at the set cut-points than do the men, although the odds of having MetS are still good in all women groups. WC as a screening tool for MetS is of special importance, especially in African woman because NC, developed as a screening tool for MetS, cannot be used in African women groups, since this measure does not increase the MetS risk in African women [35].

WC may be a better measure of MetS risk because it is a more direct measure of subcutaneous adipose tissue central obesity [36] while NC is related to BMI and WC and [37-38] thus is an indirect measure of subcutaneous tissue.

A limitation of our sub-study is the cross-sectional design which cannot infer causality. However, a follow-up study is in progress. The strengths of this study include the inclusion of a representative group of urban black Africans as well as Caucasians within a highly standardized experimental protocol.

To conclude, we carefully propose WC cut-points for all African men at 91cm and at 97 cm for all Caucasian men. Designed for young and older African women we wish to suggest cut-points of 84 cm and 81 cm, respectively. Cut-points of 87 cm and 79

cm are suggested for Caucasian women. This could be useful to ultimately help develop ethnic-specific cut-points to more accurately identify persons with MetS, especially in impoverished African communities. However, prospective cohort studies are needed in larger sample groups to strengthen our findings and to develop race- and ethnic-specific cut-points.

## **5.5 ACKNOWLEDGEMENTS**

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## **5.6 DECLARATION**

No conflict of interest is declared

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## Chapter 6

### *Summary, Conclusions, Recommendations and Shortcomings*

#### **6.1 Summary**

The aim of the study firstly was to determine the presence of the prevalence of MetS markers in Africans and Caucasians and compare the prevalence thereof in them. Secondly, NC cut-points as a screening tool for MetS were developed after which ethnic-, gender- and age-specific cut-points were developed for WC. The last aim was to determine which of the newly suggested, ethnic-, gender- and age specific cut-points for NC or WC could best be used to determine the presence of MetS and ACR as a marker of target organ damage.

The thesis was presented in six main parts, namely an introduction (Chapter 1), a literature review (Chapter 2) and three research articles (Chapters 3-5). Subsequently a summary with conclusions and recommendations follows (Chapter 6).

The article format of the thesis was approved by the Senate of the North-West University (Potchefstroom Campus). The articles are presented in accordance with the guidelines of the appropriate and accredited journals.

Chapter 1 introduced the problem and stated the aims and hypotheses of this study.

Chapter 2 focused on the metabolic syndrome, anthropometry and target organ damage in different ethnic groups in Africa. Chapters 3, 4 and 5 took the form of articles.

Chapter 3, Article 1: Differences in MetS marker prevalence between Black and

Caucasian Africans: The SABPA Study (*Journal of Endocrinology, Metabolism and Diabetes of South Africa*, 2011. Vol 16, No1, 2011)

Chapter 4, Article 2: Determining cut-off values for neck circumference as a measure of the metabolic syndrome amongst a South African cohort: the SABPA Study (*Endocrine* [DOI] 10.1007/s12020-012-9642-y)

Chapter 5, Article 3: Determining ethnic-, gender- and age-specific waist circumference cut-points to predict the metabolic syndrome: the SABPA-study (*In review at Obesity*)

## 6.2 Conclusions

The conclusions drawn from this research project are presented in accordance with the set hypotheses (Chapter 1).

**Hypothesis 1:** The MetS prevalence is high amongst Africans when using the new joint statement criteria.

This hypothesis is accepted as Africans present with a higher prevalence of the metabolic syndrome when using the new Joint Statement criteria. Caucasian men, however, also have a high prevalence of this syndrome. Once ethnic-specific cut-points for waist circumference have been introduced into the metabolic syndrome criteria, this outlook may change, especially for African women.

**Hypothesis 2:** NC cut-off points will be higher in African than Caucasian South Africans and can successfully be used as a MetS screening tool.

This hypothesis is partially accepted, since NC proved to be a good indicator of the presence of MetS, except for African women. Furthermore, the African groups did not have greater NC cut-points than their Caucasian counterparts. Caucasian men seem to have a higher NC cut-off than do their African counterparts (African men: 39 and 35 cm; Caucasian men: 40 and 41 cm) as developed by ROC statistics. African and Caucasian women presented with the same NC cut-points. However, NC did not increase the risk of MetS prevalence in African women. Thus NC cannot be used as a MetS screening tool for African women.

**Hypothesis 3:** WC cut-points will be higher in African than in Caucasian South Africans and these newly developed cut-points will be effective as a screening tool for determining the presence of MetS.

This hypothesis is partially accepted. Firstly, Africans do not have higher WC cut-points than Caucasians. The second part of the hypothesis is accepted, as odds ratios revealed that WC is a good predictor of metabolic syndrome risk.

When comparing the findings of Chapters 4 and 5, we see that WC is the better anthropometric measure to use in order to determine MetS risk. In addition, NC could not be used as a predictive measure in African women (Chapter 4) while WC proved to be a more suitable anthropometric measure in this group (Chapter 5). Concerning TOD, neither anthropometric measure could predict risk of target organ damage in any ethnic, gender or age group.

### 5.3 Recommendations

The results from this study contributed to the data available on black African as well as African Caucasians. Results were refined to show ethnic-gender-age specific outcomes in order to more accurately define groups in terms of components of the MetS, metabolic syndrome prevalence, anthropometric measures as screening tools and target organ damage, as reflected by microalbuminuria.

It should be emphasized that further research in African populations is needed to solidify these findings. This would facilitate the identification of persons at an increased health risk and assist in developing accurate and specific cut-off values for anthropometric parameters for all African ethnic groups.

#### **5.4 Shortcomings and strengths**

Shortcomings regarding this study can be indicated. Longitudinal follow-up of participants is necessary in order to monitor physiological and anthropometrical changes over time. Cross-sectional design cannot infer causality. Longitudinal research will provide stronger evidence for determining associations between variables and for developing cut-off values in African populations. To address this problem, a follow-up study is in progress and future data dissemination should address other laboratory markers.

The population sample was selected on the basis of availability from local schools. Homogeneity was maintained by only including teachers with the same socio-economic status and working in the same education district. This selection limited sample size ( $n=409$ ). A greater sample size would yield more accurate results. It is recommended that more prospective cohort studies should be undertaken with larger sample groups to strengthen findings and to develop ethnic-specific cut-points. Furthermore, the results may not be generalized to the larger population, since certain discrepancies might occur. It is thus recommended that our findings be verified in other African communities.

The strengths of this study could be ascribed to the fact that a representative group of urban black Africans as well as Caucasians were included and that the experimental protocol was highly standardised.

*Appendices*

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**A.1\_DECLARATION OF LANGUAGE EDITING**



**19 April 2012**

Hiermee verklaar ek, **me Cecilia van der Walt**, dat ek die taalversorging van die proefskrif van **me Svelka Hoebel**, getitel *Metabolic syndrome marker cut-off points and target organ damage revisited in an urban South African cohort: The SABPA Study*, behartig het.

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## **A.2 REFERENCES ACCORDING TO THE GUIDELINES UNIVERSITY OF NORTH WEST.**

### **Books**

(Mahan & Escott-Stump, 2000:700)

MAHAN,\*L.K.\*&\*ESCOTT-STUMP,\*S.\*\*2000.\*\*Krause's Food, Nutrition & Diet Therapy.\*\*11<sup>th</sup> ed.\*\*Philadelphia\*:Saunders.\*\*1319\*p.

### **Chapter in a collected work**

(Beckman et al., 2008:1090)

BECKMAN,\*J.A.\*,LIBBY,\*P.\*&\*CREAGER,\*M.A.\*\*2008.\*\*Diabetes mellitus, the metabolic syndrome and atherosclerotic vascular disease\*(In Libby, P., ed. Brounwald's heart disease: a textbook of cardiovascular medicine 8<sup>th</sup> ed. Philadelphia.: Saunders, Elsevier).

### **Journals**

(Kruger\*et\*al.,\*2001:739)

KRUGER,\*H.S.\*,VENTER,\*C.S.\*&\*VORSTER,\*H.H.\*\*2001.\*\*Obesity in African women in the North West Province, South Africa is associated with an increased risk of non-communicable diseases: the THUSA study.\*\**British\*journal\*of\*nutrition*,\*86:733-740.

### **Internet**

WMA (2000)

(WMA)\*The\*World\*Medical\*Association\*Declaration\*of\*Helsinki.\*\*2000.\*\*Ethical\*Principles\*for\*Medical\*Research\*Involving\*Human\*Subjects.\*\*[Web:]\*\*<http://www.wma.net/e/policy/b3.htm> \*\*[Date\*of\*use:\*\*20 Feb \*2009].

**Source:** VAN DER WALT,E.J. 2006. Quoting Sources. Potchefstroom : Ferdinand Postma Library. 73 p.

### **A.3 GUIDELINES FOR AUTHORS**

Journal guidelines pertaining to abstracts, text sections and references as seen in chapter 3, 4 and 5

#### **A.3.1 JOURNAL OF ENDOCRINOLOGY, METABOLISM AND DIABETES OF SOUTH AFRICA**

##### **ABSTRACT**

250 words

Sections: Objective, Materials/Methods, Results, and Conclusions.

At the end of the abstract, 3-5 key words

##### **REFERENCES**

Within the manuscript text, references to the literature should be numbered consecutively using Arabic numerals in brackets (eg, [7]), in the order in which they first appear, and should be listed in the same numerical order at the end of the manuscript. Multiple references should be separated by a comma and a space (eg, [7, 8]) unless there are more than 3 consecutive references, in which case they should be grouped (eg, [7-9]).

In the reference list, all authors (last name, first and middle initials) should be listed when there are 3 or fewer; when there are 4 authors or more, the first 3 should be listed followed by "et al." The full title of the work should be cited. Journal names should be abbreviated according to Index Medicus and appear italicized, followed by the year, volume, issue and/or supplement in parenthesis (if applicable), and the full range of pages.

Journal articles:

Harris JA, Benedict FG. A biometric study of human basal metabolism. Proc Natl Acad Sci U S A 1918;4:370-3.

Keys A, Anderson JT, Aresu M, et al. Physical activity and the diet in populations differing in serum cholesterol. J Clin Invest 1956;35:1173-81.

Authored books:

Frayn KN. Metabolic regulation: a human perspective. 2nd edn. Oxford: Blackwell Science; 2003.

Edited books:

Bjorntorp P, ed. International textbook of obesity. Chichester: John Wiley & Sons; 2001.

Electronic Sources:

Beck M. Eating to live or living to eat? Assessed at <http://online.wsj.com> on 13 July 2010.

### **A.3.2 ENDOCRINE**

Original articles should not exceed 3000 words and 150 references.

#### **ABSTRACT**

150-250 words

Sections: Purpose, Methods, Results, and Conclusions.

4-6 key words

#### **REFERENCES**

Reference citations in text should be identified by numbers in square brackets.

##### Journal Article

Hamburger, C.: Quasimonotonicity, regularity and duality for nonlinear systems of Partial differential equations. *Ann. Mat Pura Appl.* 169, 321-354 (1995)

Use standard abbreviation of journals name according to the ISSN list of Title Word Abbreviations

##### Book

Geddes, K.O., Czapor, S.R., Labahn, G.: *Algorithms for Computer Algebra*, Kluwer, Boston (1992)

##### Online Document

Cartwrite, J.: Big stars have weather too. IOP Publishing PhysicasWeb.  
[Http://physicsweb.org/articles/news/11/6/16/1](http://physicsweb.org/articles/news/11/6/16/1) (2007). Accessed 26 June 2007

### A.3.3 OBESITY

#### ABSTRACTS

Should be written in freeform without headings.

Original articles should be organized under following main headings: Introduction, Methods and Procedures, Results, Discussion, and Disclosure.

#### REFERENCES

References are to be numbered in the order of citation within the article; with only one number per reference. Within the text, reference numbers should be placed within parentheses and appear on the same line as the text, not in superscript.

List all authors when six or fewer; when seven or more, list only the first three followed by “*et al.*”

Abbreviate journal titles according to MEDLINE style.:

##### **Journal articles:**

Tunceli K, Kemeng L, Williams LK. Long-term effects of obesity on employment and work limitations among U.S. adults, 1986-1999. *Obesity* 2006;9:1637-1646.

##### **Books:**

Baron EJ, Chang RS, Howard DH, Miller JN, Turner JA. *Medical Microbiology: A Short Course*. Wiley-Liss: New York, 1994, pp 39-41.

## A.4 INFORMED CONSENT

**NORTH-WEST UNIVERSITY  
POTCHEFSTROOM CAMPUS  
SCHOOL FOR PHYSIOLOGY, NUTRITION AND CONSUMER SCIENCES  
PARTICIPANT INFORMATION AND CONSENT FORM**

### PART 1

**PRINCIPAL RESEARCHER:** Prof Leoné Malan, Subject Group Physiology

**PROJECT LEADERS:** Prof Leoné Malan, Subject Group Physiology

Associate Researcher(s): The postdoctoral fellow involved in this trial is Dr. P Szabolcs. Other persons assisting in the study are Dr. Hugo W. Huisman, Prof. Johannes M. van Rooyen, Prof. Nico T. Malan, Mrs. Carla M.T. Fourie, Mrs. Tina Scholtz (Cardiovascular research group, Physiology), Prof. Salomé Kruger & Dr. Ramoteme Mamabolo, (Physical activity), Proff. Hans de Ridder (Anthropometry), Marié Wissing (Psychology), Linda Brand & Brian Harvey (Pharmacology), Kobus Mentz (Education), Francois van der Westhuizen (Biochemistry), Hester Klopper (Nursing), Nancy Frasure-Smith & Francois Lespérance (Psychology, Canada), Alaa Alkerwi (Epidemiology, Luxembourg), Yackoob Seedat (ECG, Kwazulu Natal), Paul Rheeder (Sonar, Pretoria Univeristy), Drs. Johan Potgieter & Michael Temane & Mr Thumi Khumalo (Psychology), Mrs Gedina de Wet (Nursing), Drs T Ziemssen & M Reimann (Autonomic function, Dresden).

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This Participant Information and Consent Form is **8** pages long. Please make sure you have all the pages.

### **Your Consent**

You are invited to take part voluntarily in this research project.

This participant information document contains detailed information about the research project which has been explained to you verbally. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part.

Please read this *Participant Information Form* carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Participant Information and Consent Form to keep as a record.

### **What is the study about?**

The aim of this project is to have an impact on the eventual prevention and treatment of lifestyle diseases in Africans from South Africa. New knowledge regarding the relationship between higher nervous system activity implicating cardiovascular, metabolic and psychological well-being will improve understanding and change strategies at the roots of treatment and prevention of lifestyle diseases.

Our research has shown that lifestyle diseases in urbanised Africans present higher obesity levels, high blood pressure or hypertension prevalence rates and the experiencing of more stress. This pattern is enhanced during psychosocial stress/urbanisation in participants with a specific coping style. Hence the planned SABPA project, which is the first study in South Africa where coping and direct markers of nervous system activity in Africans will be measured.

### **Purpose of study**

The purpose of this study is to investigate biological markers associated with higher sympathetic nervous system activity in urbanised teachers with a specific coping style.

To investigate the relationship between blood pressure, inflammation, obesity, stress and coping in more detail we are going to perform this study in 400 men and women from the North-West province, aged 25-60 years. A comprehensive assessment of the cardiovascular and nervous systems by means of non-invasive painless techniques will be performed and a blood sample will be taken by an experienced research doctor and nurse to determine your blood sugar, cardiovascular, inflammation and stress hormone levels amongst other health markers.

### **Procedures**

All measurements are performed in the Metabolic Unit (lipid clinic) of the University. A researcher has explained the entire procedure in detail and while you are reading this information document you have time to ask questions and to have clarified matters. If you are fine with the explained procedure you are requested to sign a \*consent form (at the end of this document). Remember all personal data will be handled with care and remain confidential.

*\*By consenting to participate in this study, you consent to the storage and later analysis and testing of your stored blood samples for the purposes noted above. Your blood will also be tested for preliminary results on HIV status, since your HIV status may directly influence the main purposes of this study. If you would like to know what your HIV-status is, we will provide it. If tested positive we will refer you to your doctor and he/she will perform the necessary tests which will allow you to apply for chronic medication benefit. Also, the blood cells from your donated blood sample will be used to investigate the molecular genetics of higher nervous system activity and type 2 diabetes in order to enable pre-symptomatic diagnosis of hypertension and diabetes in the long term.*

**Why was I chosen?** Teachers are exposed to changing curricula and disciplinary problems whilst living in an urbanised environment adding to higher stress experiencing and nervous system activity.

### **How was I chosen?**

### Inclusion criteria:

*Phase I: 200 black Africans aged 25-60 years (male=100, female = 100)*

*Phase II: 200 white Africans (n = male, 100 = female) aged 25-60 years.*

Exclusion criteria: *pregnancy, lactation, any acute/chronic medication (e.g. high blood pressure, TB/tuberculosis, high sugar/diabetes, arthritis, anti-clotting/stroke factors, epilepsy/mental diseases or being treated for it as well being addicted to the medicine). You can not be included if you have been vaccinated in the previous 3 months and if you are a regular blood donor.*

### **What will be expected of me?**

You, as participant will be screened once by a registered nurse to be eligible complying to the inclusion criteria. The following procedures will be followed:

- Recruitment, screening and informed sessions with all participants will be done two months prior to the study (October - November 2007, Phase I, and November, 2008, Phase II) and informed consent forms will be signed.
- After selection of all participants, the details of the project will be discussed with you in English or your home language, i.e. what the exact objectives of the study are, what procedures will be taken and what will be expected from each of you (e.g. overnight stay, resting blood pressure procedures and fasting urine and blood samples are required, importance of complying with the correct sampling methods, incentives). You will be given the opportunity to ask questions.
- Data collection for each participant will involve two days (15min in the morning and 2½ hours in the evening) on Day I; and 2 hours on Day II):

#### **DAY I**

- On day I at 07:00, the blood pressure apparatus, which will measure your blood pressure and heart function as well as a physical activity meter will be applied to your arm and waist at your school and you can then resume your normal daily activities. In the afternoon you must complete the Neethling Brain Instrument questionnaire which measures thought processes of the brain.
- At the end of Day I (± 16:30) you will be transported from your schools to overnight in the Metabolic Unit Research Facility of the North-West University. This unit is a research unit for human studies and equipped with 10 well furnished bedrooms, a kitchen, two bathrooms and a television room. Each of you will be subjected to the following procedures:
  - At the end of Day I between ± 17:15 and 18:00 you will be welcomed and each of you will receive your own private bedroom.
  - The procedures, which will be done, will be explained again and each of you will then complete a general socio-demographic health questionnaire. Afterwards you will receive dinner.

- After dinner, psychological questionnaires will be completed under supervision of registered education specialists and psychologists. Completion of questionnaires will take approximately 40 min, including a break of 20 minutes with coffee/tea and biscuits. This will be your last meal for Day I as you must be fasting on Day II for obtaining good results.
- Thereafter, you can relax and watch television or socialise with your c-participants. It will be wise to go to bed not later than 22:00 as the blood pressure apparatus will take measurements every hour during the night and it can be tiring.

### **DAY II**

- At 06:45 on Day II the AMBP will be removed and an urine sample collected. Once this has been done you will be directed to the anthropometric station where your weight, height and body circumferences will be measured.
- The next station involves the blood pressure measurement station. Whilst in a sitting position your blood pressure will be taken in duplicate with the sphygmomanometer (the same as used at clinics) with a resting period of 5 minutes in between. Our registered research doctor/nurse will take a fasting saliva sample as well as a blood sample of 45ml from a vein in your dominant arm. The infusion set will be left in your arm to lessen the effect of inserting a needle again for blood sampling after exposure to the two stressors. A small amount of diluted heparin will be left in the infusion set in your arm to prevent clotting.

Next the cardiovascular measurements will follow consisting of three separate procedures:

- The 1<sup>st</sup> measurement involves an ECG apparatus, which measures heart function, with 12 leads, which will be placed into position on your rib cage/front part of the body.
- The 2<sup>nd</sup> measurements are non-invasive and will be done by means of the Finometer device which also involves the assessment of heart functioning such as pulse (beats per minute), stroke volume (blood volume ejected by the heart per beat), cardiac output (blood volume ejected by the heart per minute), total peripheral resistance (resistance against the blood flow created by small arteries), central resistance (resistance against which the heart has to work while ejecting the blood into the aorta) as well as the elasticity of your large arteries (compliance). For this procedure a blood pressure cuff will be placed around your left arm and middle finger which will be inflated and stepwise deflated. You will not have more discomfort than during a common blood pressure measurement. This will take about 5 minutes.
- The stressor application procedure follows: You will now be exposed to a stressor for 1 minute whilst your blood pressure and ECG will still be taken. After exposure a saliva and blood sample (45ml) will be taken. After 10 minutes another saliva sample will be taken. Then the stressor application procedure will be repeated with the second stressor.
- At another station your 3<sup>rd</sup> measurement includes the assessment of pulse wave velocity, i.e. how fast your blood travels through your arteries. This measurement gives us an indication about how stiff your vessel walls are. The stiffer your vessel wall is the faster the blood travels from one point of your body to another. These painless measurements will require two technicians using blunt probes (tonometer) putting light pressure on the neck and on the foot to measure the velocity of the pulse waves. This takes only a few minutes. An ultrasound device will be taken of

your arteries in the neck with a blunt probe to indicate the intrinsic thickness of your arteries which contributes to high blood pressure.

The two stressors you will be exposed to for one minute include:

1. The *Colour-Word-Conflict Chart (applied for 1 minute)* is written in various colours. You must say or select the ink colour rather than the name of the colour spelled out by the word. A sliding scale with monetary incentives (maximum of R55.00) will be given if you can complete reading the chart.
  2. The *Cold Pressor Test (Foot) (applied for 1 minute)*: Immersion of your foot up to the wrist in ice water (4 degrees Celcius). As the cold can make you hold your breath you must quietly count to yourself during cold exposure to breath more rhythmic.
- You have reached the end of the sampling phase.
  - **Thank you for your participation! You now will have the opportunity to shower and a take away breakfast will be given.**
  - Immediate feedback on your HIV/AIDS status, obesity, blood pressure and blood glucose/sugar values will be given. *HIV/AIDS post-test counselling will be arranged if you are tested positive.*
  - You are now transported back to your school and after one week you will receive your Neethling Brain Instrument and 24-hour blood pressure reports.

### **Possible Risks**

The measurements performed in our study will include only non-invasive techniques that are not expected to reveal any risks but might cause little discomfort. The taking of blood samples is an invasive procedure with a minimal risk of bleeding. Thus the procedure may cause only a few seconds of light discomfort. All tests will be performed by experienced research nurses of our department. There may be additional unforeseen or unknown risks.

### **Precautions to protect the participant**

The Metabolic Unit facility of the NWU is fully equipped, and in case of an emergency which could not be handled by the registered nurse, the supervising medical doctor Emile Kotzé will be contacted. Dr. Kotzé was notified before the study commenced that this study will be taking place, and that there is a slight possibility that he may be contacted. Supporting medical treatment care facilities will be at hand anytime if needed.

### **Other Treatments Whilst on Study**

It is important to tell the research staff about any treatments or medications you may be taking, including non-prescription medications, vitamins or herbal remedies during your participation in the study.

### **Incentives**

1. All teachers will receive feedback on their health profile and if necessary references will be given to physicians/clinics/hospitals.

2. Blood pressure and ECG monitoring report (normally costing R637.60). Your benefit of participation is a comprehensive assessment of the cardiovascular and metabolic condition including investigation of blood pressure, inflammatory status and psychological well-being. These examinations will help us to assess the degree of vascular impairment of the arteries and to predict your risk of possible cardiovascular events such as heart attacks and stroke. The results may assist your doctor in decision making for further treatment or for instituting preventive measures. Our study will also contribute to the identification of possible factors leading to high blood pressure. As 24 hour ambulatory blood pressure monitoring is required for the diagnosis of hypertension, medical aids insist on this method of diagnosis to qualify for chronic medication. Additional testing could also reveal illnesses of a chronic nature and would serve as a motivation to qualify for chronic medication, such as metabolic syndrome, anti-inflammatory and cholesterol-lowering drugs.
3. Monetary incentive on completion of the colour word conflict chart.
4. Dinner and breakfast.
5. Neethling Brain Instrument profiles done by registered user of the Whole Brain (normally costing ± R350.00).
6. Coping skills workshop will be arranged on request.

**Privacy, Confidentiality and Disclosure of Information**

By consenting to participate in this study, you consent to the storage and later analysis and testing of your stored blood samples for purposes noted above. Your blood samples will be discarded immediately after analysis. All information provided by you and the results of tests will be treated in the strictest confidence, and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law. The results of your medical tests will be labelled only with a code number, and will be stored separately from any identifying information. When the results are analysed we will be looking for differences between groups of people, not at the results of individuals. No information that could identify any person taking part in the study will be revealed when the results are reported.

**Participation is Voluntary**

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the North-West University.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information

you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw.

### **Ethical Guidelines**

This project will be carried out according to Ethical Guidelines of the Helsinki declaration from 2000, with additional notes in 2002. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of **North-West University Potchefstroom**.

### **Further Information or Any Problems**

If you require further information or if you have any problems concerning this project, you can contact the principal researcher or *the other* researchers responsible for this project.

Prof Leoné Malan (018-299 2438)

Sr. Chrissie Lessing (018-299 2480)

**PART 2**

**To the subject signing the consent as in part 3 of this document**

You are invited to participate in a research project as described in paragraph 2 of Part 1 of this document. It is important that you read/listen to and understand the following general principles, which apply to all participants in our research project:

1. Participation in this project is voluntary.
2. It is possible that you personally will not derive any benefit from participation in this project, although the knowledge obtained from the results may be beneficial to other people.
3. You will be free to withdraw from the project at any stage without having to explain the reasons for your withdrawal. However, we would like to request that you would rather not withdraw without a thorough consideration of your decision, since it may have an effect on the statistical reliability of the results of the project.
4. The nature of the project, possible risk factors, factors which may cause discomfort, the expected benefits to the subjects and the known and the most probable permanent consequences which may follow from your participation in this project, are discussed in Part 1 of this document.
5. We encourage you to ask questions at any stage about the project and procedures to the project leader or the personnel, who will readily give more information. They will discuss all procedures with you.
6. We require that you indemnify the University from any liability due to detrimental effects of treatment by University staff or students or other subjects to yourself or anybody else. We also require indemnity from liability of the University regarding any treatment to yourself or another person due to participation in this project, as explained in Part 1. Lastly it is required to abandon any claim against the University regarding treatment of yourself or another person due to participation in this project as described in Part 1.
7. If you are married, it is required that your spouse abandon any claims that he/she could have against the University regarding treatment or death of yourself due to the project explained in Part 1.

**PART 3**

**Consent**

Title of the project:

“THE SABPA STUDY (SYMPATHETIC ACTIVITY AND AMBULATORY BBLOOD PRESSURE IN AFRICANS)”.

I, the undersigned ..... (full names)

read/listened to the information on the project in PART 1 and PART 2 of this document and I declare that I understand the information. I had the opportunity to discuss aspects of the project with the project leader and I declare that I participate in the project as a volunteer. I hereby give my consent to be a subject in this project.

(Signature of the subject)

Signed at ..... on .....2008

**Witnesses**

1. ....

2. ....

Signed at ..... on .....2008

## A.5. ANTHROPOMETRIC AND BLOOD PRESSURE PROFORMA

### PARTICIPANT SHEET: The SABPA Study

Subject no.			
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Date			2009
------	--	--	------

#### Checklist

#### INITIALS

1. **Consent form completed**

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2. **Anthropometry**

Date of birth (yyyy/mm/dd)		Gender		Age		
Height (cm)		}				
Weight (kg)						
Waist circumference (cm)	1.		2.		3.	
Hip circumference (cm)	1.		2.		3.	
Neck circumference (cm)	1.		2.		3.	

3. **Sphygmomanometer blood pressure (BP), Finometer, ECG**

**Sphygmomanometer BP (DUPLICATE) (mmHg)**

SBP		DBP		
SBP		DBP		

4. **Finometer BP (mmHg) & ECG**

**Resting:** 5 min BP + ECG .  
Filename:

**Ice:** 1 min BP & ECG

+ 1,3,5 min recovery. Filename:

**Col/Colour word conflict:** 1 min BP & ECG

+ 1,3,5 min recovery. Filename:

5. **COL chart, columns read**

6. **Perception of ICE stressor test** :Indicate with cross : 1 2 3 4 5 6 7

7. **Perception of COL stressor test:** Indicate with cross 1 2 3 4 5 6 7

8. Incentive received (Signed): .....

9.. Ambulatory BP (mmHg)

Down loaded

### 10. Questionnaires completed

Socio-demographic & lifestyle questionnaire

Norman Physical Activity questionnaire

Neethling Brain Instrument

Psychosocial battery questionnaires

### 11. Complior and sonar

D. body (cm)		Minus D.neck (cm)		= D.complior (cm)		
Pulse Wave Velocity (m/s)						
SONAR	OPTIMAL	PLAQUE SCORE				
Right						
Left						

### 12. Fasting urine, blood and saliva sampling

Value for fasting **Blood glucose** (mmol/L)

Urine

Urine

Guthry cards

Guthry cards

Ear temperature

**Blood:** Resting

ICE

Colour word conflict

**Saliva:** Resting

ICE

Colour word conflict

### 13. HIV/AIDS

Precounselling

Postcounselling

**14. Short Report Feedback given**

**15. Breakfast**

**16 Referred to doctor / clinic**

**Y/N (Y, Yes; N, No)**
