Coping, alcohol and cardiovascular risk: the SABPA study

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B.Sc. Hons. Physiology

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

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Firstly, I would like to thank God for giving me knowledge and strength, and for His undying love and grace.

I would also like to thank the following:

Prof L Malan, for always believing in me and my potential. I’ve learned so much from you and admire your work-ethic and tremendous knowledge. I wouldn’t have been able to complete this year without your unceasing encouragement.

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My family, for their constant love and encouragement, I would not have been able to do it without you. Specifically my dad, thank you so much for always supporting and helping me in every little way you can.

My boyfriend and best friend, for always being there for me and for understanding when work was my first priority. Thank you for sharing in my excitement for this project and for believing in my dreams.
**OPSOMMING**

**Titel:** Coping, alkohol en kardiovaskulêre risiko: die SABPA studie

**Motivering:** Die verskillende coping style wat gebruik word in reaksie op psigososiale stres is al geassosieer met die ontwikkeling van kardiovaskulêre siektes (KVS). Die manier waarop die kardiovaskulêre stelsel beïnvloed word verskil egter van een copingstil tot die volgende. Van die verskillende copingstyle blyk defensiewe aktiewe coping (AC) die nadeligste vir kardiovaskulêre gesondheid te wees. Dit word vererger deur versterkte α-adrenergiese vaskulêre reaksies by Afrikane. Verder het verskeie studies bevind dat die voorkoms van hipertensie en ander KVS baie hoër is in stedelike Afrikane vergeleke met hulle Kaukasiese eweknieë. Dit kan toegeskryf word aan sekere leefstilveranderinge wat deur Afrikane geïmplementeer moet word tydens die oorgang wat met verstedeliking gepaard gaan, omdat hulle genoodsaak is om die stedelike leefstil te hanteer. Een van hierdie leefstilfaktore, wat ook as 'n kardiovaskulêre risikofaktor figureer, is 'n toename in die gebruik, en in sommige gevalle misbruik, van alkohol. Daar is sekere teenstrydighede met betrekking tot die metabolisering van alkohol in die verskillende etniese groepe, wat die effek van alkohol op die individu beïnvloed. Alkoholgebruik as 'n moontlike coping-meganismie is in baie gevalle al ondersteun, maar die gesamentlike gevolge van alkoholgebruik en AC as kardiovaskulêre risikofaktore is nog slegs in Afrikaanmans gevind. Verdere ondersoek is nodig om vas te stel of coping of te wel streshantering en alkoholgebruik slegs in Afrikaanmans 'n gesamentlike of versterkende effek het, of ook in ander etiese groepe of geslagsgroepes. Wat ook bespreek moet word, is of die teenstrydighede tussen etniese groepe met betrekking tot alkoholmetabolisme 'n rol kan speel in die ontwikkeling van KVS in 'n bi-etniese geslagskohort.

**Doelstellings:** Die hoofdoelstellings van die studie was om die volgende te bereik: 1) om Relatiewe operasionele karakteristiek (ROC) etnies-spesifieke afsnypunte vir alkoholgebruik
in die voorspelling van ambulatoriese hipertensie te bepaal, en 2) om te meet of hierdie afsnypunte in defensiewe aktiewe groepé 'n toename in kardiometaboliese risiko toon in 'n bi-etniese geslagskohort, en indien wel, of die toename in risiko verbind kan word met 'n spesifieke ras of geslagsgroep.

**Metodologie:** Hierdie substudie vorm deel van die SABPA (Simpatiese aktiwiteit en Ambulatoriese Bloeddruk in Afrikané) studie wat tussen 2008 en 2009 uitgevoer is. Nadat uitsluitingskriteria toegepas is, het die bi-etniese geslagskohort bestaan uit 390 individue. Hierdie deelnemers was almal van die Kenneth Kaunda Onderwysdistrik van die Noordwesprovisie van Suid-Afrika, en hulle het almal ingeligte toestemming geteken voor deelname. Die SABPA-studie is goedgekeur deur die Etiëskomitee van die Noordwes-Universiteit met bykomende etiese goedkeuring vir hierdie substudie. Alle prosedures in die studie het voldoen aan die riglyne van die Helsinki Verklaring.

Elke deelnemer het 'n psigososiale toetsbattery voltooi onder die toesig van 'n geregistreerde kliniese sielkundige, en inligting rakende hulle medikasiegebruik en mediese geskiedenis is verkry. Hulle het verder die Coping Style Indicator-vraelys, soos ontwikkel deur Amirkhan, voltooi om te identifiseer watter copingstyl die deelnemers gewoonlik volg. Ambulatoriese bloeddruk en EKG-metings is afgeneem vir 'n 24-uur periode met die Cardiotens CE120®. Antropometriese metings is geneem deur ISAK (International Society for the Advancement of Kinanthropometry) vlak 2 geakkrediteerde antropometriste wat gekalibreerde instrumente gebruik het. Die liggaamsoppervlak is hieruit bereken. Rustende bloedmonsters is deur 'n geregistreerde verpleegster versamel. Die fisiese aktiwiteit van elke deelnemer is bepaal met behulp van die Actical® alomgerigte versnellingsmeter. Die volgende bloedserumvlakke is bepaal: gamma-glutamiel transferase (γ-GT) as merker vir alkoholgebruik, C-reaktiewe proteïen, cholesterol, hoë-digtheid lipoproteïen, trigliseriede, kotinien, reaktiewe suurstofspesies en bloedglukosevlakke. Alle statistiese analyses is gedoen deur gebruik te maak van Statistica weergawe 12.0. Beskrywende statistiek is gebruik om die basislyneienskappe van die hele groep te bepaal, terwyl Chi-kwadraattoetse
(X²) use is to determine the presence of medications and pathology. ROC analyses are used to determine a cutoff point for γ-GT that predicts ambulatory hypertension, to determine for each ethnic group and for the whole group. Independent t-tests have identified factors that influence the data, after which two-rigging covariance analyses (ANCOVA) are performed to test a 2 x 2 interaction effect (race x γ-GT cutoff points) for all cardiometabolic risk markers and to test the differences between the ethnic groups. ANCOVAs are then performed within the ethnic groups with high γ-GT levels, as well as in the average AC for the graphs that follow. Finally, relative risk ratios (OR's) with 95% confidence intervals are calculated in various models to determine the probability of high alcohol intake to predict ambulatory hypertension in the ethnic-gender groups and in the AC ethnic-gender groups. Significant values are noted as p ≤ 0.05.

Result: The Afrikaners had higher cardiometabolic risk markers, a greater defended active stress management, seeking social support with fewer psychological stress indicators. ROC analyses have shown that ambulatory hypertension in Afrikaners begins at a much higher level of γ-GT [55.7U/l (AUC=0.69; 95% CI: 0.61; 0.76)] with sensitivity/specifity of 47%/83%, compared to the Caucasians [19.5U/l (AUC=0.747; 95% CI: 0.68; 0.82)] with sensitivity/specifity of 70%/73%. The Caucasians show increased sensitivity for alcohol intake at a lower γ-GT cutoff point compared to Afrikaners.

When ethnic-specific ROC-cutoff point groups are compared, certain levels of cardiometabolic risk factors such as C-reactive proteins, systolic blood pressure, waist circumference, and ischemic events are significantly higher in the Afrikaner group, especially in ethnic-AC groups. Among the Afrikaners with high γ-GT levels, 73% use AC-style, indicating hyperactive AC-stress management and increased KVS-risk in Afrikaners.
Kliniese beduidendheid is bepaal by OR's, wat wys dat hoë γ-GT vlakke in AC-Afrikaanmans ambulatoriese hipertensie met 'n OR van 7.37 (95% CI: 6.71 – 8.05) voorspel. Hoër alkoholinnname voorspel ambulatoriese hipertensie in AC-Kaukasiërs met 'n OR van 2.77 (95% CI: 2.31 – 3.23) in mans en 6.42 (95% CI: 2.31 – 3.23) in vroue onderskeidelik.

**Gevolgtrekking:** γ-GT afsnypunte in defensiewe aktiewe coping groepe het verhoogde kardiometaboliese risikomerkers in 'n bi-etniese geslagskohort getoon. 'n Moontlike hipermetaboliese toestand in Afrikaanmans mag hulle aanvanklik beskerm teen KVS morbiditeit, maar as hulle kronies gebuk gaan onder 'n gebrek aan sosiale ondersteuning, is KVS-risiko dreigend.

**Sleutelwoorde:** Alkohol; Kardiovaskulêre gesondheid; Coping; Etnisiteit; Gamma-glutamiel transferase.
SUMMARY

**Title:** Coping, alcohol and cardiovascular risk: the SABPA study

**Motivation:** The different coping styles used to respond to psychosocial stress have been linked to the development of cardiovascular disease (CVD). However, the manner in which the cardiovascular system is influenced differs between the coping styles. Of the different coping styles, defensive active coping (AC) has been shown to be the most detrimental to cardiovascular health. This is worsened by augmented α-adrenergic cardiac responses found in Africans. Furthermore, many studies have found that the prevalence of hypertension and other CVDs is much higher in urban Africans when compared to their Caucasian counterparts. This can be attributed to certain lifestyle changes implemented by Africans in the transition that occurs with urbanization, where they are forced to cope with an urban-dwelling lifestyle. One of these lifestyle factors, which also poses as a cardiovascular risk factor, is increased usage and in some cases abuse of alcohol. Certain discrepancies exist between ethnicities with regard to the metabolism of alcohol, which influences the effect of alcohol on the individual. Alcohol usage as a possible manner of coping has been supported in many instances, but the interdependent effects of alcohol usage and AC as cardiovascular risk factors has only been found in African men. Further investigation is needed to determine if coping and alcohol abuse act in tandem only in African men, or also in other ethnic or sex groups. What also needs to be discussed is whether the inconsistencies between ethnicities regarding alcohol metabolism, plays a part in the development of CVD in a bi-ethnic gender cohort.

**Objectives:** The main aims of this study were to determine 1) receiver operated characteristic (ROC) ethnic specific cut points of alcohol usage in the prediction of ambulatory hypertension, and 2) to assess if these cut points in defensive active groups
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revealed increased cardiometabolic risk in a bi-ethnic sex cohort, and if so, whether the increased risk will be associated with a specific race or sex group?

**Methodology:** This sub-study forms part of the SABPA (Sympathetic activity and Ambulatory Blood Pressure in Africans) study, conducted from 2008 to 2009. After exclusion criteria were applied, our bi-ethnic sex cohort consisted of 390 individuals. These participants were all from the Kenneth Kaunda Education District of the North-West province in South Africa, and they all signed informed consent prior to participation. The SABPA study was approved by the Ethics Review Board of the North-West University, with additional ethical approval for this sub-study. All procedures in this study complied with the guidelines of the Declaration of Helsinki.

Each participant completed a psychosocial battery supervised by registered clinical psychologists, and information regarding their medication use and medical history was obtained. They also completed the Coping Style Indicator questionnaire which was developed by Amirkhan, to identify the coping style habitually used. Ambulatory blood pressure and ECG measurements were recorded for a 24h period with the Cardiotens CE120®. Anthropometric measurements were performed by ISAK (International Society for the Advancement of Kinanthropometry) level 2 accredited anthropometrists using calibrated instruments. Out of this, the body surface area were calculated. The physical activity of each participant was determined by use of the Actical® omnidirectional accelerometer. Resting blood samples were collected by a registered nurse. The following blood serum levels were determined: gamma-glutamyl transferase (γ-GT) as a marker for alcohol usage, C-reactive protein, cholesterol, high density lipoprotein, triglycerides, cotinine, reactive oxygen species and glycated haemoglobin levels. All statistical analyses were done using Statistica version 12.0. Descriptive statistics were conducted to state the baseline characteristics of the entire group, while Chi-square ($X^2$) tests were used to determine prevalence for medications and pathology. ROC analyses were computed to establish a cut point for γ-GT predicting ambulatory hypertension in each ethnicity as well as in the entire group. Independent t-tests
identified confounders, after which two-way analysis of covariance (ANCOVA) tests were computed to test a 2 x 2 main effects interaction (race x γ-GT cut points) for all cardiometabolic risk markers and to compare the different ethnic groups. ANCOVAs were then performed in the ethnic groups with high γ-GT as well as in above mean AC for the graphs that followed. Lastly, odds ratios (OR’s) with 95% confidence intervals (CI’s) were calculated in several models to highlight the odds of high alcohol intake to predict ambulatory hypertension in the ethnic-sex groups as well as in AC ethnic-sex groups. Significant values were noted as p ≤ 0.05.

Results: The Africans revealed higher cardiometabolic risk markers, above mean defensive active coping, seeking social support with less avoidance coping scores. ROC analyses revealed that ambulatory hypertension commences at a much higher level of γ-GT in the Africans [55.7U/l (AUC=0.69; 95% CI: 0.61; 0.76)] with sensitivity/specificity of 47%/83% compared to the Caucasians [19.5U/l (AUC=0.747; 95% CI: 0.68; 0.82)] with sensitivity/specificity of 70%/73%. The Caucasians thus reveal an increased sensitivity for alcohol ingestion at a much lower γ-GT cut point compared to the Africans.

When comparing ethnic specific ROC cut point groups, we found that certain levels of cardiometabolic risk factors such as C-reactive protein, systolic blood pressure, waist circumference and silent ischemic events, were significantly higher in the African group, especially in above mean AC groups. Out of the Africans with high γ-GT levels, 73% used the AC style, suggesting hypervigilant AC coping and increased CVD risk in Africans.

Clinical significance was determined by OR’s, which demonstrated that high γ-GT levels in AC African men predicted ambulatory hypertension with an OR of 7.37 (95% CI: 6.71 – 8.05). Higher alcohol intake predicted ambulatory hypertension in AC Caucasians with an OR of 2.77 (95% CI: 2.31 – 3.23) in men and 6.42 (95% CI: 5.85 – 7.0) in women respectively.
**Conclusion:** γ-GT cut-points in defensive active groups revealed increased cardiometabolic risk markers in a bi-ethnic sex cohort. A possible hypermetabolic state in African men may initially protect them against CVD morbidity but if chronically challenged with no forthcoming social support, CVD risk is imminent.

**Keywords:** Alcohol; Cardiovascular health; Coping; Ethnicity; Gamma-glutamyl transferase.
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<thead>
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<th>Description</th>
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<tr>
<td>24h</td>
<td>24 hour(s)</td>
</tr>
<tr>
<td>AC</td>
<td>defensive active coping</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>AST:ALT</td>
<td>aspartate amino transferase, alanine amino transferase ratio</td>
</tr>
<tr>
<td>AUC</td>
<td>area under curve</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CSI</td>
<td>Coping Strategy Indicator</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>γ-GT</td>
<td>Gamma-glutamyl transferase</td>
</tr>
<tr>
<td>HdL</td>
<td>high density lipoproteins</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>ISAK</td>
<td>International Society for the Advancement of Kinanthropometry</td>
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<tr>
<td>kcal</td>
<td>kilocalorie</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimetres of mercury</td>
</tr>
<tr>
<td>N</td>
<td>number of subjects</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver-operating characteristic</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<tr>
<td>SABPA</td>
<td>Sympathetic activity and Ambulatory Blood Pressure in Africans</td>
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<tr>
<td>SANHANES</td>
<td>South African National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>THUSA</td>
<td>Transition and Health during Urbanization in South Africa</td>
</tr>
<tr>
<td>α</td>
<td>Alpha</td>
</tr>
<tr>
<td>β</td>
<td>Beta</td>
</tr>
<tr>
<td>γ</td>
<td>Gamma</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>Chi square</td>
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CHAPTER ONE

Preface and Outline of the study
1.1 Preface and outline of the study

This dissertation has been completed in fulfilment of the requirements for the degree Master of Science in Physiology at the North-West University’s Potchefstroom Campus.

This study is divided into four chapters:

Chapter 1 contains the preface and outline of the study, and also includes an outline of the contributions made by each of the authors.

Chapter 2 comprises a general introduction to and the literature concerning the study, with questions arising from the literature and the hypotheses for this study compiled from the literature.

Chapter 3 contains the manuscript “Alcohol abuse as means of coping leads to increased cardiovascular risk: the SABPA study”, prepared according to the author’s instructions of the chosen journal.

Finally, Chapter 4 contains the summary of the findings of the study and a brief discussion, including the weaknesses of the study and recommendations for future research. Lastly, the conclusion of the study is provided.

The peer-reviewed Journal of Human Hypertension is considered for submission of the manuscript in Chapter 3. At the end of chapters 2, 3 and 4, the indicated references are consistent with the guidelines for publishing in the aforementioned journal, according to their bibliographic style.

1.2 Authors’ contributions

The researchers who formed part of this study contributed in the following ways:

- Miss W. Oosthuizen (BSc Hons) was responsible for planning, writing and presentation of dissertation, which included literature searches, statistical analyses, and interpretation of the results.
• Prof. L. Malan (RN, HED, PhD) as supervisor and Principle Investigator of the SABPA study, contributed to the process of study design, data collection and initial planning and guidance for the dissertation. She provided supervision for all statistical analyses and writing processes conducted as part of this dissertation.

• Prof. N.T. Malan (DSc), Mrs M. Cockeran (MSc) and Mr J.D. Scheepers (MSc), as co-supervisors, assisted in planning and supervising the writing processes and statistical analyses that formed part of this dissertation.

I, Woudri Oosthuizen, student number 22152873, at the Potchefstroom Campus of the North-West University, hereby declare that the aforementioned is an accurate reflection of my contribution and hereby give consent that this manuscript in Chapter Three may be published as part of the dissertation for the degree Master of Science in Physiology.

____________________
Miss W. Oosthuizen

As co-authors of the manuscript in Chapter Three, Prof. L. Malan, Prof. N.T. Malan, Mrs M. Cockeran and Mr J.D. Scheepers hereby give permission that the manuscript in Chapter Three may form part of the dissertation Coping, alcohol and cardiovascular risk: the SABPA study for the degree Master of Science in Physiology by Woudri Oosthuizen.

____________________  ________________  ________________
Prof. L. Malan        Prof. N.T. Malan        Mrs M. Cockeran

____________________
Mr J.D. Scheepers
CHAPTER TWO

Introduction and Literature overview
1.1 General introduction

The burden of cardiovascular disease (CVD), not only worldwide, but especially in developing countries like South-Africa, is still increasing and has recently been described as one of epidemic proportions.\textsuperscript{1-3} Urbanization, and the damaging lifestyle changes that comes with it, has been identified as a major contributing factor for this increase.\textsuperscript{4-6} Two of the main lifestyle factors that have been associated with development of CVD in South Africa are increased alcohol usage and coping with psychosocial stress.\textsuperscript{7-11}

Psychosocial stress itself has been identified as a cardiovascular risk factor, but even more so the manner in which a person attempts to cope with this stress.\textsuperscript{12, 13} Every person habitually uses a certain coping style in stressful situations, and each of these coping styles leads to a different cardiac response. Three coping styles have been identified. The first style, which was originally found to contribute to overall poorer cardiovascular health, is the emotional avoidance coping style.\textsuperscript{14} There has, however, been found that it is the second style, namely defensive active coping (AC), that actually contributes most to the development of CVD.\textsuperscript{5, 8, 15, 16} The last coping style, which entails social support as a manner of coping, has not been found to contribute to cardiovascular risk.\textsuperscript{17}

With the high levels of stress found in an urbanized environment, individuals have been found to turn to alcohol, possibly as part of a AC style.\textsuperscript{18-20} Alcohol has always been known to mediate cardiovascular health, and whether this contribution is negative or positive depends on the amount of alcohol consumed.\textsuperscript{21} Low to moderate consumption of alcohol is associated with good cardiovascular health, which has often been described as the cardio-protective effect of alcohol.\textsuperscript{22, 23} Conversely, high levels of alcohol intake have been identified as a cardiovascular risk factor, and associate with an increase in the prevalence of CVD.\textsuperscript{10, 24, 25}

The interaction between these two cardiovascular risk factors will be explained in the following sub-headings:
1.2 The prevalence of CVD in South-Africa

It is always difficult to determine the true prevalence of any non-communicable diseases, as can be seen in South-Africa where contradicting literature exists. The Demographic and Health Survey conducted in South-Africa in 1998 reported that 21% of South-Africans were hypertensive.\textsuperscript{26} This finding should not be accepted without caution, since much time has passed, and seeing that the burden of CVD is on the increase, it may not be a true representation of the hypertension prevalence anymore. However, in 2005, world wide data found the hypertension prevalence in South-Africa to be 23%, which correlates well with the afore-mentioned finding.\textsuperscript{27} This contradicts the most recent findings of 2013 on people over the age of 50, which found that 78% of South-Africans have hypertension, the highest prevalence of all the countries involved in the study. The prevalence in females and males was found to be 80.3% and 74.7% respectively.\textsuperscript{28} The same study also reported that only half of these individuals were aware of their condition, and only 7.8% of them were on blood pressure (BP) lowering medication. Out of these sources we can see that the true prevalence of hypertension in South-Africa is still unclear, but it can nonetheless be described as a very serious burden.

What most findings do however agree on, is that hypertension is more prevalent in urban compared to a rural environments.\textsuperscript{29-31} A possible explanation for this can be that the stress experienced when transitioning from a more rural to an urbanized living environment has been found to positively associate with an increase in BP. It is not only the transition that inflicts stress on an individual, but also the fact that such a person has to adapt to the more Westernized manner of living that is often found in urban environments.\textsuperscript{26, 31-33} This urbanization has been extensively researched in South Africa by the THUSA study (Transition and Health during Urbanization in South Africa), which found that it is a definite risk factor for the development of hypertension in the country.\textsuperscript{5, 31, 33}
1.3 Alcohol abuse as risk factor for CVD

As mentioned earlier, the effect of alcohol on the cardiovascular system depends on the amount of alcohol consumed. The more well-known, harmful effect of alcohol can be found in high alcohol intake, which is mediated by various mechanisms. The first, and possibly the most important mechanism entail the diuretic nature of alcohol, which causes an increased volume of urine excretion due to the suppression of the anti-diuretic hormone/vasopressin. This is further worsened by the alcohol-induced activation of the renin-angiotensin-aldosterone system. Both of these effects are well-known increasers of BP, and can partly explain the higher levels of BP found in individuals who consume high amounts of alcohol. Another manner in which alcohol contributes to an increase in BP is its ability to increase fibrinogen levels and a subsequent procoagulant state with higher blood viscosity. Pertaining to alcohol and hypertension, several epidemiological studies have proven the positive correlation between alcohol consumption and BP, independent of race, sex or age. Furthermore, it has been estimated that globally, about 16% of hypertension cases are alcohol induced.

Another damaging effect of alcohol is the increase in arterial stiffness found with high alcohol consumption. In long term alcohol abuse, increased levels of C-reactive protein (CRP), a marker for acute inflammation, is evident. An increase in the levels of CRP has been linked to acute ischemia, myocardial infarction, atherosclerosis and hypertension. It has also been found to associate with increased carotid intima media thickness through increased wall stress that leads to vascular remodelling.

The next risk factor for CVD that is influenced by high alcohol consumption is vascular tone. High intake of alcohol leads to greater levels of the powerful vasoconstrictor, endothelin-1, which is mediated by an increase in oxidative stress. The tone is further influenced by the alcohol-induced inhibition of endothelial-dependant vasodilation. Alcohol has also been linked to endothelial dysfunction, which increases sensitivity of the endothelium to certain
vasoconstrictive substances such as norepinephrine. High alcohol consumption has further been shown to increase the intracellular concentration of Ca$^{2+}$ in smooth muscle cells, which results in increased vascular contractility and reactivity. Since the perfusion to the heart is reduced in excessive vasoconstriction of the coronary arteries, the above-mentioned vasomotor tone effects of alcohol can explain why alcohol has also been found to associate with other CVDs, such as silent ischemia and coronary heart disease.

Additionally, a link has been proven between the central nervous system and alcohol use, and more specifically temporary or permanent withdrawal of alcohol. Withdrawal of alcohol is linked to certain autonomic cardiac responses, including hypertension and an elevated cardiac output.$^{45}$ The mechanisms responsible for these changes are still somewhat debatable, but an increase in central as well as peripheral adrenergic activity and elevated secretion of corticotrophin-releasing hormone has been found in most studies.$^{46-48}$

Good or even improved cardiovascular health has long since been related to low to moderate alcohol consumption. This can be due to elevated levels of high density lipoprotein (HdL) found in these conditions, where alcohol acts on the hepatic production and secretion of lipoprotein particles and lipolysis of triglyceride-rich particles, which all lead to an overall higher level of HdL.$^{49}$ Although this is the main mechanism by which alcohol lowers BP, other minor effects include increased synthesis of nitric oxide, which causes vasodilation, and lastly the inhibition of platelet reactivity.$^{23,50}$

These and other potential effects of alcohol are summarised in Figure 2.1.
Figure 2.1: Potential long-term effects of alcohol

1.4 Metabolism of alcohol and genetic variations

Alcohol is mainly metabolized (Figure 2.2) by the liver, by both oxidative and non-oxidative pathways, although the latter of the two is only minimally used. Concerning the oxidative pathways of liver metabolism, different enzymes and other systems are relevant, which includes alcohol dehydrogenases (ADH) and cytochrome P450 2E1 (CYP2E1).\textsuperscript{51}

The metabolism of ethanol with ADH produces acetaldehyde, which is known to be a highly reactive and toxic substance that has been linked to alcohol induced tissue damage, as well as the addictiveness to high alcohol usage.\textsuperscript{51} Acetaldehyde is oxidized by aldehyde dehydrogenase 2 (ALDH2) to form acetate, another tissue damaging substance.\textsuperscript{52} Acetate affects various metabolic processes and has been linked to a depressed central nervous system.\textsuperscript{53} Certain genetic and racial differences in the ADH enzyme can possibly explain
why some individuals are more susceptible to alcohol-related pathology. Two versions of the ADH enzyme, namely ADH1B*2 and ADH1B*3 (Figure 2.2) have been found only in very small quantities in people of African descent.\textsuperscript{54, 55} These two enzymes are known as protection against alcoholism,\textsuperscript{56} since they very efficiently metabolize alcohol. This leads to elevated levels of acetaldehyde soon after alcohol is ingested, making drinking unpleasant.\textsuperscript{57} Therefore, the small quantities of these enzymes found in Africans tend to make drinking, and especially the feeling of malaise after drinking, not so bad. Another study found that individuals of African descent rarely carry a certain variant of the ALDH2 gene, namely the ALDH2*2 allele (Figure 2.2).\textsuperscript{58} People with this allele display a reduced rate of alcohol metabolism, as well as an alcohol flush reaction even with consumption of only minute amounts of alcohol. Thus, in the case of Africans where this allele is mostly absent, alcohol is very efficiently and rapidly metabolized, with minor lingering effects on the liver.\textsuperscript{58} Subsequently, other studies support this finding and further states that the rate of alcohol metabolism is much higher in Africans when compared to their Caucasian counterparts.\textsuperscript{52}

The next enzyme which plays a part in the metabolism of alcohol is CYP2E1, which is mainly induced in individuals who consume alcohol chronically.\textsuperscript{51} This pathway produces reactive oxygen species (ROS) as a by-product, further increasing the risk of tissue damage by triggering the mitochondrial apoptosis pathway and subsequent hepatocyte death.\textsuperscript{59} CYP2E1 is the major alcohol metabolizer in the brain, where low levels and activity of ADH are found.\textsuperscript{51} Another function of the cytochrome P450 enzyme system is the metabolism of certain anti-hypertensive drugs.\textsuperscript{60} Since alcohol and these drugs then compete for metabolism by the cytochrome P450 enzyme system of the liver, one can understand that certain interactions may be present. What often happens is that active alcohol consumers will show increased elimination of these drugs, which will decrease their effectiveness, since the half-life of the drug will be shortened.\textsuperscript{52} Certain polymorphisms are also found with regard to the CYP2E1 enzyme, showing positive associations with alcoholic liver disease.
Once again, these polymorphisms are rarely found in African subjects, which shows that their livers are much more resistant to the damaging effects of alcohol metabolism.\footnote{61}

![The metabolism of alcohol showing possible polymorphism pathways](Figure used courtesy of Seitz & Becker, 2007)\footnote{62}

### 1.5 Determination of alcohol consumption in humans

True estimation of alcohol consumption poses a great challenge at best. Self-reporting on alcohol consumption has been found to mostly underestimate usage, as can be seen in a recent study where 84.5\% of South-Africans reported to being lifetime abstainers, and only 1\% stated that they could be classified as frequent, heavy alcohol consumers.\footnote{28, 63} This is clearly not a true indication of alcohol usage, since 46.8\% of households in South Africa has been found to have at least one member currently consuming alcohol.\footnote{64} Therefore, the usage of biochemical markers is much preferred by researchers globally. Alcohol usage is mainly measured by means of liver enzymes, such as gamma-glutamyl transferase (γ-GT), aspartate amino transferase and alanine amino transferase, and also carbohydrate-deficient-transferrin.\footnote{65-67} The use of these liver enzymes has however, also been highly debated, since they are not formed when alcohol is metabolized, but rather secreted when alcohol-induced liver damage commences, hence they are labelled as indirect markers of alcohol abuse.\footnote{65} Subsequently, the levels of these enzymes are also elevated in other
circumstances that are not alcohol related, such as non-alcoholic liver disease and oxidative stress. Consequently, higher than normal values of these markers cannot exclusively indicate alcohol abuse. Because of this, direct markers of alcohol abuse have been identified, including fatty acid ethyl esters and ethyl glucuronide, which are measured in human hair. These are referred to as direct, since they are not released in the case of alcohol related organ disease. Nevertheless, in 2013, Hastedt et al. declared the use of indirect markers such as γ-GT as suitable for the detection of alcohol abuse by comparing them to direct markers through receiver operating characteristics analysis with high sensitivity and specificity.

1.6 Alcohol usage in South Africa within different population groups

South Africa has often been referred to as one of the countries with the highest per capita alcohol consumption in the world, where alcohol related deaths contribute to 7.1% of all morbidities annually. The pattern of drinking in South-Africa has also been found to be one of the riskiest globally, where 45.4% of drinkers admitted to weekly heavy episodic drinking occasions where they drink at least 60 grams of pure alcohol in one sitting. This is very worrying, since the global average of these binges only amounts to 11.4%. Clearly, alcohol is currently a major problem in South-Africa, but who carries the burden most? Just as the case with CVD, alcohol usage has also been found to be a greater problem in urban compared to rural areas. The South-African National HIV, Incidence, Behaviour and Communication study conducted in 2008 found that all types of drinking, be it casual or hazardous, is more prevalent in urban areas. This corresponds with the 2012 South African National Health and Nutrition Examination Survey (SANHANES) which reported that alcohol abuse can be described as a “very serious” problem in nearly 23% of the cases in urban areas, compared to just 17% of the cases in rural areas.
Concerning racial and sex groups, the biggest consumption among all age groups is found in men, independent of ethnicity. Caucasian males specifically reported the highest prevalence of current drinking. However, what should correspondingly be mentioned is that Africans, independent of the sex, reported a much higher percentage of risky drinking, be it on the weekends or even in the week, as can be seen in the following figure (Figure 2.3), adapted from Parry.

Figure 2.3: The prevalence (%) of alcohol consumption in South Africa compared for race and sex. Current drinking: Consumption of alcohol during the past month; Risky drinking: Consumption of five or more or three or more standard drinks per day for males and females, respectively. Adapted from Parry (2001).

It is possible that the high prevalence of alcohol usage in South-Africa can be attributed to the fact that psychosocial stress is associated with certain lifestyle changes that individuals use to cope with the situation at hand. This is most likely the case, as alcohol use has been indicated as a possible coping strategy used by especially African males in stressful times.
1.7 Stress appraisal

Stress appraisal or coping is described as the behavioural and cognitive efforts of an individual to manage external or internal demands of the person-environment relationship that is sometimes experienced as taxing or far exceeding the person’s psychological resources. 72, 73 Thus, when a person feels stressed or if their resources are not sufficient for them to perform as expected, they will use a certain coping style in an attempt to change the situation.72, 74 Coping therefore has two functions, firstly to change the source of the stress, and secondly to regulate the emotional response caused by the problem. 72 Different coping styles exist, implied by the resources used by the individual when coping:

1) Coping directed at the management of the original stress-causing factor is referred to as problem-focused or defensive active coping. This usually includes people who seem in control in times of psychological strain.17, 72-74 AC has been found to link with overall promotion of health.75, 76

2) When a person focuses more on reducing the emotional stress experienced than the original stressor, they are said to be coping with the emotional avoidance coping style. They clearly would much rather avoid the problem than face it head on and this has been associated with poor well-being.17, 72-75

3) Another coping style entails the management of the stress-causing factor by means of relying on/or seeking social support by family and friends. These individuals would seek the help of loved ones for advice and comfort during difficult times.17, 77

The coping style of an individual can be determined by means of the Coping Strategy Indicator (CSI), developed and published by Amirkhan in 1990.17
1.8 Coping and sympathetic stimulation as risk factor for CVD

Stress and stress appraisal have been proven numerous times as a risk factor for CVD, being associated with increased BP, left ventricular hypertrophy, silent myocardial ischemia, endothelial dysfunction and many other pathologies of the cardiovascular system.\(^7, 8, 13, 16, 78-80\) The SABPA study (Sympathetic activity and Ambulatory Blood Pressure in Africans) was specifically designed to analyse the link between the brain and heart and associated cardiac responses.\(^81\) The link between emotional stress and hypertension is reportedly the activation of the sympathetic nervous system, which associates with increased cardiac responses.\(^8\) This mechanism can easily explain the link with acute stress, but the manner in which constant and prolonged stress increases BP and amounts to hypertension is poorly understood. It’s possible that when the system is activated with acute stress, cardiac responses may quickly return to resting values, but during chronic challenges or stress, cardiovascular recovery may be attenuated or delayed. In this case, the sympathetic nervous system is repeatedly activated and possibly overstimulated, which ultimately results in the development of hypertension.\(^82\)

Although stress is clearly a major risk factor for CVD, it is rather stress appraisal or coping with stress that has lately been linked to the development of hypertension and CVD.\(^13, 32\) One factor that plays a key part in the cardiovascular-coping relationship is the coping style that is used by the individual. There is currently sufficient evidence that cardiovascular pathology is mostly found in people who habitually utilize the AC style.\(^8, 15, 16, 80\)
Intricate cerebral pathways (Figure 2.4) are stimulated during stress appraisal, including the thalamic, amygdala, prefrontal cortex and the paraventricular nucleus in the hypothalamus.\(^83\)

![Diagram of cerebral pathways](image)

**Figure 2.4: Intrinsic pathways stimulated during stress appraisal (Used with courtesy of Malan, 2013)**\(^79\)

Each coping style elicits a different physiological response. AC implies an in-control defense response and increase in epinephrine, activating a β-adrenergic cardiac response\(^76-79,84\) with an increase in systolic BP, enhanced stroke volume, heart rate and cardiac output. Together with this, minor changes in the diastolic BP and total peripheral resistance are also observed.\(^85\) The emotional avoidance coping style implies a loss-of-control defeat response mediated by an α-adrenergic\(^76-79,84\) vascular response via the release of norepinephrine. This results in increased vasoconstrictive responses with increases in total peripheral resistance, after- and preload, diastolic BP and minor changes in the systolic BP, heart rate, stroke volume and cardiac output.\(^85,86\)

These changes associated with emotional avoidance coping could possibly lead to the development of cardiovascular pathology when utilized during chronic stress.\(^82\) But, contrariwise, it is rather the AC style that leads to overall poorer cardiovascular health.
Furthermore, it is the urban Africans utilizing the AC style that demonstrate the most vulnerability toward the development of CVD.\textsuperscript{4, 7, 13} This can possibly be explained by the newly-found dissociation between behaviour and physiology of a AC style. It was evident in urban Africans where they would show physiological loss-of-control α-adrenergic responses, as well as self-reported behavioural in-control β-responses. This is especially true for urban African males, where this dissociation is associated with sympathetic hyperactivity and autonomic exhaustion.\textsuperscript{8, 15, 16}

The Africans’ perception of stress may also be contributing to their vulnerability, since four times more African than Caucasian males reported feeling under immense amounts of stress.\textsuperscript{15} Disability to cope with an urban environment or taxing situations will show physiological loss-of-control responses and subsequent cardiovascular pathology, as seen in figure 2.5.\textsuperscript{80} All of these observations are possibly attributed to the fact that loss-of-control may result in a breakdown of control and neural fatigue.\textsuperscript{76-79, 84}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.5.png}
\caption{Defensive active coping responses in an urban environment facilitate chronic hyperglycaemia predicting early structural vascular changes. Physiological “loss of control” or neural fatigue may increase endothelial dysfunction and stroke risk.\textsuperscript{80}}
\end{figure}
1.9 The interaction of alcohol usage and coping as a risk factor for CVD

As previously mentioned, alcohol is known to be used as a coping mechanism.\textsuperscript{18-20} But what is the effect of these two apparent cardiac-damaging factors, namely AC and alcohol usage, when they act together? Malan et al. found that when alcohol abuse and coping act in tandem, their effects accumulate and seem to be even more harmful to cardiovascular health.\textsuperscript{87} This was, however, only found in African men, and no other studies exist to determine if this outcome is also witnessed in other ethnic or sex groups.
1.10 Questions arising from the literature

With the preceding literature in mind, certain questions arise that have to be investigated:

- What are the Receiver operating characteristic ethnic specific cut-off points of gamma-glutamyl transferase for the prediction of ambulatory hypertension?
- Will these Receiver operating characteristic ethnic specific cut-points of gamma-glutamyl transferase reveal increased cardiometabolic risk in a bi-ethnic sex cohort when defensive active coping is utilized?
- Will the detrimental effects found when alcohol and defensive active coping combine be associated with a specific race or sex in a bi-ethnic sex cohort?

1.11 The aim of the study

The literature makes it clear that cardiovascular disease is one of the major health issues, not only globally, but especially in South-Africa. What’s more, two of the leading risk factors for the development of cardiovascular disease seem to be alcohol use and the style of coping in urban-dwelling participants, more specifically AC. The high prevalence of alcohol abuse in South-Africa and the importance of coping with stress, underline the importance of further research into these risk factors, with specific reference to cardiovascular disease.

We, therefore, aim to determine:

1) Receiver operating characteristic ethnic specific cut-points of gamma-glutamyl transferase in the prediction of ambulatory hypertension.

2) If Receiver operating characteristic ethnic specific cut-points of gamma-glutamyl transferase will reveal increased cardiometabolic risk in a bi-ethnic sex cohort when defensive active coping is utilized.

3) If the detrimental effects found when alcohol and defensive active coping combine will be associated with a specific race or sex in a bi-ethnic sex cohort.
1.12 Hypotheses

- Receiver operating characteristic ethnic specific cut-off points of gamma-glutamyl transferase for the prediction of ambulatory hypertension are different in ethnic and sex groups.

- The Receiver operating characteristic ethnic specific cut-off points of gamma-glutamyl transferase will reveal increased cardiometabolic risk when combined with defensive active coping in ethnic and sex groups.

- The detrimental effects when alcohol and defensive active coping combine is associated mostly with the African group.
References


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Instructions For Authors: Journal Of Human Hypertension

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- Colour should be distinct when being used as an identifying tool
- Abbreviations should be preceded by the words they stand for in the first instance of use
- Use SI units throughout
- Text should be double spaced with a wide margin.

Abbreviations and Symbols

Must be standard and SI units used throughout. The following abbreviations are approved: BP-Blood pressure; SBP-Systolic blood pressure; DBP-Diastolic blood pressure. Acronyms should be used sparingly and must be fully explained when first used.
Alcohol abuse and coping - increasing cardiovascular risk? The SABPA study.

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Abstract

In an attempt to cope with psychosocial stress in an urban-dwelling environment, individuals commonly turn to alcohol, a cardiovascular risk factor, to alleviate stress. Thus, alcohol consumption (measured by gamma-glutamyl transferase [γ-GT]) and coping may act in tandem and increase the risk for cardiovascular morbidity. We therefore aimed to assess this interdependent association pertaining to the cardiometabolic risk profile in a bi-ethnic sex cohort in the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) study. Ambulatory blood pressure and -ECG, fasting blood and the Coping Strategy Indicator coping scores were obtained. Africans, particularly men, revealed above mean defensive active coping (AC) and high scores for seeking social support. They also showed increased γ-GT levels, -cardiometabolic risk markers, -prevalence of silent ischemia and a mean hypertensive state. Receiver-operating characteristic (ROC) γ-GT cut-point analyses predicted 24h ambulatory hypertension and revealed a higher γ-GT cut-point in Africans (55.4 U/l) compared to Caucasians (19.5 U/l). The γ-GT cut-point, when combined with AC, predicted 24h ambulatory hypertension in African males with an odds ratio of 7.37 (95% CI: 6.71-8.05), p = 0.003. In conclusion, a possible hypermetabolic state in African males may initially protect them from CVD morbidity. However, taxing situations can chronically challenge an individual and their defences, and if no social support is forthcoming, CVD risk is eminent.

Key words: Alcohol; Alcohol abuse; Cardiovascular health; Coping; Ethnicity; Gamma-glutamyl transferase; Gamma-glutamyl transferase cut-point.
Introduction

The increasing worldwide burden of cardiovascular disease (CVD) is currently a well-known and highly-researched topic, especially since the burden is following suit in developing countries like South-Africa. This can be attributed to harmful lifestyle changes that individuals may implement when they are confronted with the process of adapting to an urbanized way of living.\(^1\)\(^-\)\(^3\) These lifestyle changes include several factors that increase the risk for development of CVD, like tobacco and alcohol use, an unhealthy diet and psychosocial stress.\(^4\)\(^-\)\(^6\)

Psychosocial stress has for a long time been associated with the development of CVD. This is true especially in urban black Africans (hereafter referred to as Africans) in South-Africa, where the prevalence of hypertension is significantly higher compared to Caucasians.\(^7\)\(^-\)\(^9\) It is not only the stress itself that poses a cardiovascular risk factor, but also the manner in which a person copes with taxing emotional stress.\(^10\) There are different coping styles, each eliciting a unique physiological response and subsequent cardiovascular effects. Initially, it was the emotional avoidance coping style, provoking an \(\alpha\)-adrenergic cardiac response, which was associated with overall poorer cardiovascular health.\(^11\)\(^,\)\(^12\) Recent studies however, demonstrated that the prevalence of CVD is much higher in individuals who habitually use the defensive active coping style (AC), which elicits \(\beta\)-adrenergic cardiac responses.\(^11\)\(^,\)\(^13\) The third and final coping style, which entails seeking social support while coping with stress, has been mostly known to associate with good overall cardiovascular health.\(^14\)

Several studies support the notion that alcohol use is being utilised as a means of coping with psychosocial stress.\(^15\)\(^,\)\(^16\) It was also found that the amount of alcohol used in urban areas is much higher than that in rural areas.\(^17\) Research has shown that it is the amount of alcohol consumed that determines the effect this habit has on the cardiovascular system, where low to moderate consumption associates with a cardio-protective effect, while high
intake of alcohol has been shown to increase the risk for CVD, and specifically hypertension. Pertaining to the metabolism of alcohol, several variations occur between ethnicities, where genetic factors determine the efficiency and duration of the metabolism. Whether variations influence the effect of alcohol on the cardiovascular system between ethnicities remains to be known. The use of a certain biomarker for alcohol abuse, gamma-glutamyl transferase, (γ-GT), has been questioned and highly debated due to the fact that other non-alcohol related liver conditions, such as fatty liver disease, cannot be ruled out when increased levels of this enzyme is found. However, the use of γ-GT has recently been compared to direct and exclusive alcohol markers and it was declared suitable as an indicator of alcohol abuse. When the two above-mentioned lifestyle risk factors, namely alcohol abuse and usage of the AC style when coping with psychosocial stress in an urban-dwelling environment combine, it can be detrimental to cardiovascular health, as recently found in an African male cohort. We wanted to determine 1) the ethnic-specific γ-GT cut-points in the prediction of ambulatory hypertension in different ethnic groups; and 2) if these ethnic specific γ-GT cut-points, when combined with utilization of the AC style will reveal increased cardiometabolic and hypertensive risk in ethnic-sex groups, and if so, whether the risk exists mainly in a certain sex or ethnic group.

Methods of investigation

Study design and participants

This sub-study forms part of the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) study, a target population study that was conducted from 2008 to 2009. The study included 409 teachers who were selected to ensure a homogenous socio-economic study group. Of the 409 participants, 200 were Africans (101 males and 99 females) and 209 were Caucasians (101 males and 108 females). Participants were between 20 and 62 years of age, and the original exclusion criteria included users of alpha- or beta-blockers, psychotropic substance abusers, participants with tympanum temperature
above 37.5°C, those who have donated blood or received vaccinations during the 3 months
prior to the study, and lastly, participants who are HIV infected (N=19). The final sample
comprised 390 individuals. Ethical approval for the sub-study was obtained from the Ethics
Review Board of the North-West University (NWU-00036-07-A6), and all study procedures
complied with the guidelines set out by the Declaration of Helsinki.23

**Ambulatory blood pressure, electrocardiogram measures and procedures**

Clinical assessments were conducted over a 48-hour period. At approximately 07:30,
participants were fitted with ambulatory blood pressure and 2-lead electrocardiogram (ECG)
apparatuses and physical activity meters on working days (Mondays to Thursdays). The
applicable apparatuses were fitted onto the non-dominant arm and the hip of each
participant respectively (Cardiotens CE120®, Meditech, Budapest, Hungary; Actical®,
Montreal, Quebec), after which they proceeded with their normal daily activities. The
Cardiotens CE120® device was programmed to measure blood pressure at intervals of 30
minutes between 08:00-22:00 and at intervals of 60 minutes between 22:00 and 06:00 the
following morning,24 with a successful mean inflation rate of 72.8% and 84.6% for the African
and Caucasian groups respectively. The average 24h blood pressure (BP) of ≥ 130 mm Hg
systolic blood pressure (SBP) and/or ≥ 80 mm Hg diastolic blood pressure (DBP) was
classified as hypertensive.25 Ambulatory ECG analyses provided ischemic events, following
the 1-1-1 rule, namely, horizontal or descending ST-segment depression by 1 mm; duration
of the ST-segment episode lasts for 1 minute, and there was a 1-minute interval from the
preceding episodes.26

At 16:30 on day 1, participants were transported to the North-West University’s Metabolic
Unit Research Facility where they were familiarized with the study setup and completed a
psychosocial battery under the supervision of registered clinical psychologists. After this,
each participant received a standardized dinner and they were requested to go to bed at
22:00, fasting overnight to prepare for the clinical measures, which followed the next day.
Participants were woken at 05:45 the morning of day 2, after which anthropometric measurements were taken. A registered nurse obtained fasting blood samples and the General Socio-demographic and Health Questionnaire was completed to gain information regarding family medical history, medication usage and lifestyle habits.

Lifestyle factors and anthropometric measurements

The Actical® omnidirectional accelerometer fitted on the morning of day 1 measured the physical activity of each participant. The device was set to 15 second intervals to measure the movement of the participants while they engaged in normal daily activities. γ-GT levels were measured as a marker for alcohol abuse,21 and cotinine levels as indicator of smoking habits.27 All anthropometric measures were conducted in triplicate by ISAK (International Society for the Advancement of Kinanthropometry) level II accredited anthropometrists using calibrated instruments and standardised methodology. The body surface area (BSA) was calculated according to the Mosteller formula.28 Inter- and intraobserver variability was less than 10%.

Biochemical measures

A registered nurse collected fasting serum and plasma samples using a sterile winged infusion set, after which these samples were handled according to standardized procedures and frozen at -80°C until analysis. The γ-GT levels were analysed with the enzyme rate method, C-reactive protein (CRP) levels with the turbidimetric method and the timed-end-point method was used to determine cholesterol, high density lipoprotein (HdL) and triglyceride levels. All abovementioned variables were measured using the Unicel DXC 800 analyser (Beckman and Coulter, Germany). Serum cotinine levels were measured using the homogeneous immunoassay on the Modular ROCHE automized analyser (Konelab™ 20i; Thermo Scientific, Vantaa, Finland). Glycated haemoglobin was measured with the Cobas® Integra 400 (Roche, Switzerland), using the turbidimetric inhibition immunoassay method. The liver enzymes, alanine aminotransferase and aspartate aminotransferase were
determined with the sequential multiple analyser computer (Konelab™ 20i, Thermo Scientific, Vantaa, Finland).

Lastly, the serum reactive oxygen species (ROS) were determined by The Bio-Tek FL600 Microplate Fluorescence Reader (Bio-Tek, Instruments, Inc., Highland Park, Winooski, VT, USA), according to the method described by Hayashi et al.29

Coping assessment

The Coping Strategy Indicator (CSI)14 was used to successfully identify each participant’s coping style. The CSI is a self-report measure consisting of 33 items that determine whether a person utilizes the problem solving, avoidance or seeking social support coping style in difficult times. The CSI demonstrated Cronbach’s alpha (α) reliability coefficients of 0.69 - 0.84. The 33 items in the questionnaire are divided into 3 sub-sets of 11 items each. The participant answers each item using a three-point Lickert scale, 3 being “a lot”, 2 “a little”, and 1 “not at all”. They choose 1, 2 or 3 as an answer while keeping in mind a stressful event they recently encountered. The accumulated answers indicate the use of a certain coping style. A total score of ≥ 26 indicates above mean usage of the problem solving or active coping style, ≥ 23 showing above mean use of the social support style, and ≥ 19 showing above mean use of the avoidance style.14

Statistics

Analyses were done using Statistica version 12.0 (Statsoft Inc., Oklahoma, USA, 2013). The Shapiro-Wilk’s W-test for normality was used to determine if a variable is normally distributed. If this was not the case, these variables were logarithmically transformed. Independent T-tests were used to compare the baseline characteristics, such as body mass index, BSA, physical activity and the waist circumference of the racial groups, and Chi-square (X²) tests determined the proportions and prevalence of certain pathologies and medications. Independent t-tests identified the confounders for the two-way analysis of
covariance (ANCOVA) tests that proceeded, which were adjusted for BSA and physical activity.

Several nonparametric receiver operating characteristic (ROC) curves,\textsuperscript{30} together with the area under the curve (AUC) were computed and the optimal cut-off points obtained from the Youden index (J) maximum (sensitivity + specificity − 1). ROC curves were used to explore the association between γ-GT and ambulatory hypertension cut-points in three different groups. They were the total bi-ethnic sex group, the entire African group and lastly, the Caucasian group. The sensitivity and specificity values were determined to identify the cut-points that maximize the sum of the number of true positive and true negative predictions. The AUC had to be more than 0.5 and closer to 1, indicating accuracy and not random chance.

For the graphs that followed, we once again computed ANCOVA’s adjusted for BSA and physical activity. In these analyses, we included only participants with γ-GT levels higher than the determined ROC cut-points.

Lastly, odds ratios (OR’s) with 95% Confidence Intervals (CI’s) were calculated in several models to highlight the odds of high alcohol intake to predict ambulatory hypertension.

For all of the abovementioned analyses, significant values were noted as $p \leq 0.05$.

**Results**

Table 1 presents both the unadjusted and adjusted variables of the bi-ethnic sex cohort, stratified by race. These include descriptive, lifestyle, and other variables that could potentially have an effect on the vasculature and cardiovascular health. Furthermore, this table includes the prevalence of certain pathology and medication taken by the participants. Significant differences between ethnicities can be found in almost all these variables, where the African group revealed higher levels of cardiometabolic variables such as HdL, total cholesterol, glycated haemoglobin and triglycerides. They also showed higher alcohol
consumption, and significantly higher BP levels. The African group further demonstrated more silent ischemic events, low grade inflammation (>3 mg/l), higher prevalence of hypertension and they take more medication to treat it. Both ethnic groups revealed a defense coping score above mean (≥ 26) whereas the Africans showed significantly higher social support and lower avoidance scores.

ROC analysis was used to determine the cut-off value for γ-GT levels predicting ambulatory hypertension in the entire bi-ethnic gender cohort, as well as the ethnic groups. Figure 1 demonstrates the level of γ-GT where the AUC was most optimal for ambulatory hypertension in these groups. It also illustrates the cut-point according to the Youden index. At γ-GT levels of 23.4 U/l, maximum sensitivity (77%) and specificity (62%) were found with an AUC=0.752, for the entire group. For the African group, the cut-point of γ-GT was found to be 55.4 U/l (AUC=0.69) at maximum sensitivity (47%) and specificity (83%). The Caucasian group’s cut-point was 19.5 U/l at maximum sensitivity (70%) and specificity (73%) with the AUC=0.747.

In Figure 2, we included only Africans with a γ-GT level of ≥ 55.4 U/l and Caucasians with γ-GT levels ≥ 19.5 U/l, according to the ROC analyses. We then determined several of their cardiometabolic risk factors and compared the groups (Figure 2a). In Africans, all cardiometabolic risk factors, except HdL, were increased compared to their Caucasian counterparts (p ≤ 0.001). When ROC γ-GT cut-point levels are combined with AC, most of the findings are augmented in the Africans (Figure 2b) (p ≤ 0.001), with the exception of HdL.

Table 2 contains the OR’s for each ethnic sex group, which determines the probability of high γ-GT levels predicting ambulatory hypertension in each of these 4 groups. In the African male group, high γ-GT levels significantly predicted ambulatory hypertension with an OR of 7.28 (95% CI: 6.61 – 7.95). High alcohol intake predicted ambulatory hypertension in the Caucasian males with an OR of 2.51 (95% CI: 2.06 – 2.95) and in the Caucasian women,
the same prediction was found with an OR of 6.44 (95% CI: 5.86 – 7.01). The odds increased when high γ-GT cut-point levels are combined with an AC style in all the groups except the Caucasian women.

Discussion

The main aim of this study was to determine if the cardiovascular vulnerability described in an African male cohort that consumes high amounts with alcohol and utilizes the AC style, also exists in participants of different ethnicities or sexes in the same population study. Our primary finding shows that the bi-ethnic sex cohort revealed increased cardiometabolic risk markers when alcohol usage and AC combine, which can be seen in especially the African male group. Furthermore, according to the ROC γ-GT cut-point for the development of ambulatory hypertension, the African group showed vulnerability at a much higher level of alcohol consumption (γ-GT ≥55.4 U/l) than the Caucasians (γ-GT ≥19.5 U/l). However, at these ethnic specific cut-points, the cardiometabolic risk was found to be significantly higher in the African compared to the Caucasian group.

Africans had significantly higher waist circumferences, elevated blood pressure, reduced perfusion to the heart as seen by the prevalence of silent ischemia, and their mean CRP-levels are indicative of low-grade inflammation (>3 g/l). This profile can be indicative of a defensive coping physiological loss-of-control, which has previously been found in specifically African men. Dissociation between physiology and behaviour occurs when a person reports a feeling of being in control in a stressful situation, thus utilizing the AC style, but presents physiological α-adrenergic rather than β-adrenergic cardiac responses, which are associated with sympathetic hyperactivity and autonomic exhaustion. It is therefore important to mention that 73% of the Africans who had γ-GT levels that predicted ethnic-specific ambulatory hypertension, reported habitual use of the AC style. Out of their 91 Caucasian counterparts, 72 utilized the AC style (79%). The Caucasians also revealed increased cardiometabolic risk factors, but not to the same extent as their African
counterparts, which may imply a healthy in-control defensive coping style. Our findings therefore suggest that the same dissociation between behavioural and physiological responses isn’t evident in urban-dwelling Caucasians, and that the already vulnerable cardiovascular profile of Africans may mask the “loss-of-control” that they experience in stressful situations. Furthermore, a pattern of neural fatigue may emerge if control is not exerted in chronic situations.

Concerning alcohol abuse and its effects on the cardiovascular system, it is clear that certain risk factors such as chronic defensive AC may increase CVD risk when a person consumes high volumes of alcohol. For both ethnicities, elevated SBP was shown which can be attributed to the vasopressor effect of alcohol. In African men, however, this can further be aggravated by α-adrenergic vascular responses, impairing endothelial function when they use the AC style, thus explaining the even higher SBP levels found in the African group.4, 32

The next risk factor, namely increased WC, has been found to associate with increased alcohol intake.34 More recently WC or abdominal obesity was associated with cognitive psychological distress.35 Alcohol has been identified as a means of coping with stress,36 and the high levels of γ-GT might exemplify this link. When a person has to cope with chronic stress, it may change behavioural lifestyle factors, which include intake of increased amounts of alcohol. Chronic stress ultimately associates with an increased secretion of cortisol,37 which binds to glucocorticoid receptors that are present in high concentration in visceral fat depots. When cortisol binds to the receptors, it leads to accumulation of fat in specifically the abdominal area, since the concentration of these receptors are the highest in the fat depots of this area.38 The accumulation of fat then leads to an increase of the WC. These two factors, namely alcohol usage and chronic stress, possibly act in conjunction with one another to ultimately lead to a significant increase in the WC.

Low-grade inflammation was evident in the high-alcohol consumption group of our study population, which correlates with findings where high CRP levels associated with especially
long-term alcohol abuse. CRP is produced by the hepatocytes of the liver, which is also known to be the primary site of alcohol metabolism. When alcoholic liver disease commences with long-term use, a vicious circle of increased inflammation commences, which further triggers CRP release. The high levels of CRP are associated with increased arterial stiffness, which can contribute to the pathological SBP levels that we found. Silent ischemia was more prevalent in ethnicities if high amounts of alcohol are consumed, which is confirmed by previous findings that supports a notion of alcohol-induced vasoconstriction of the coronary arteries. The latter induces silent ischemia, which mediates the release of vasoconstrictive agents such as norepinephrine. Attenuated norepinephrine metabolite levels suggesting neural fatigue were related to a defensive coping style in the current African male cohort, which augmented α-adrenergic dissociative responses. As the majority of the African participants habitually utilize the AC style, the prevalence of silent ischemia may increase the risk for coronary artery disease. Silent ischemia underscores the higher central demand if homeostatic blood pressure cannot be maintained in the Africans. The enhanced vasoconstrictive responsiveness found during high alcohol consumption, together with the previously mentioned increase in inflammatory responses and subsequent arterial stiffness, may augment a higher central demand to control blood pressure at a lower level. This can further imply an aftermath of alcohol-induced myocardial damage, which is associated with increased coronary artery disease.

Concerning the levels of alcohol usage at which pathology in the form of hypertension commences, it is interesting to note that this happens at a much lower level in the Caucasian (γ-GT level of 19.5 U/l) compared to the African (γ-GT level of 55.7 U/l) group. This can possibly indicate that the livers of the Caucasian group aren’t as resistant to the effect of alcohol as might be the case in the African group. The African group can consequently tolerate higher intake of alcohol before it begins to damage their liver, mostly by means of alcohol metabolism.
Further addressing the differences in ethnicities pertaining alcohol, the γ-GT cut-point in Africans revealed an odds ratio of $7.28$ (95% CI: $6.62, 7.95$), $p = 0.004$, in predicting 24h ambulatory hypertension. A hypermetabolic state in Africans may also explain the lower γ-GT cut-point when compared to Caucasians. Indeed, metabolomic pathway analysis revealed perturbations in several systems involved in ethanol metabolism via shifted global reduced nicotinamide adenine dinucleotide (NAD) to oxidized NAD (NADH/NAD+) ratio. The alcohol metabolism in a cohort of 25 African males suggests a main metabolic shift towards hypertension (unpublished data). This may imply that hepatic metabolism of ethanol in the Africans results in the generation of large quantities of cytosolic and mitochondrial NADH, disrupting the normal metabolic processes in the liver and contributing to the progression of liver damage. An increased production of ROS within the mitochondria presents as a consequence of the increased levels of mitochondrial NADH. The ROS cause mitochondrial stress, leading to the triggering of the mitochondrial apoptosis pathway. Whether this holds true for African males is not clear. Indeed, higher ROS levels were evident in our African male cohort, which were positively associated with ambulatory BP. In our study population, we also found ROS to be significantly higher in the African group compared to the Caucasians. What may further explain the higher tolerance of the African group to alcohol, is the small quantities of two variations of the alcohol dehydrogenase (ADH) enzyme, ADH1B*2 and ADH1B*3, that has been found in people of African descent. These enzymes have been found to associate with the “hangover” feeling present after high consumption of alcohol, therefore Africans (and their livers) do not experience this to the same extent as other ethnicities. Another genetic discrepancy found in specifically Africans are that they rarely display the ALDH2*2 variation of the ALDH2 gene. This enzyme is associated with a reduced rate of alcohol metabolism. Subsequently, Africans will very efficiently and rapidly metabolize alcohol, thus resulting in minor effects on the hepatocytes of the liver. It is therefore possible that alcohol related problems are influenced by other genetic or environmental factors. This may support our findings of the dissociative
defensive coping response that was associated with CVD risk in an individualized urban environment. It counteracts the Africans' preference of a collectivistic cultural environment, as seeking social support does not associate with the worsening of distress. This may enforce neural fatigue in individuals where chronic defense coping associates with a behavioural feeling of being in control, but also reveals a "loss-of-physiological control".

From a clinical point of view, alcohol is not only metabolized by the abovementioned ADH pathway, but also by the cytochrome P-450 enzyme system, and specifically CYP2E1. Since it activates this system, alcohol is known as a cytochrome P-450 inducer. Several antihypertensive medications, such as calcium channel blockers, β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are metabolised, partially or fully, by the same system. Certain drug-alcohol interactions can therefore occur when this enzyme system attempts to cope with higher demand, and is induced by simultaneous alcohol intake. In our study group, significantly more Africans than Caucasians reported hypertensive medication usage, which is understandable since the prevalence of hypertension is also higher in the African group. It is possible that when the system is induced by alcohol intake, the effect of the medication may be blunted and efficiency decreased. We cannot, however, declare that the information given by the participants is true, since self-report of medication usage can often be under- or over-reported. Therefore, we carefully suggest that this drug-alcohol interaction may explain the increased prevalence of hypertension in the African group, even though they are currently on medication for treatment thereof. Polymorphisms are also present in the CYP2E1 enzyme, and they have been found to associate with alcoholic liver disease. In Africans, these polymorphisms are very scarce, once again maybe explaining why the African group in our study sample only showed signs of CVD at a much higher level of alcohol compared to the Caucasians.
The OR that we found in the Caucasian women, where pathological levels of alcohol consumption predicted 24h hypertension is another finding where self-report plays a role. It is possible that the OR of 6.42 that we found can be due to the type of alcohol consumed by the participants, which can never truly be determined due to the nature of self-report collection of data. The alcohol content of the alcoholic beverage consumed plays a significant role in the metabolism of the alcohol, since it is the metabolism of the alcohol that leads to the destruction of hepatocytes, and ultimately alcoholic liver disease. It is possible that the Caucasian females consume drinks with higher alcohol content, thus damaging their livers at a lower level of γ-GT. This can explain why a lower, but still clinically relevant OR of 2.77 was found in the Caucasian men, who possibly consume beverages of lower alcohol content. The recently published South African National Health and Nutrition Examination Survey (SANHANES) found that males consume more alcoholic beverages than women, but they did not report information about the type of beverage consumed by either sex.

Limitations of this study include the much debated use of γ-GT as a true marker for alcohol abuse. Furthermore, the small study sample size poses a limitation, as well as the cross-sectional rather than longitudinal study design. Our results contribute to an already vast amount of literature, and nonetheless, the study has a well-designed protocol and methodology where a socio-economic homogenous group was assessed, which excluded certain disparities.

In conclusion, the African cohort, and specifically the African males, revealed a vulnerable cardiometabolic profile when compared to their Caucasian counterparts, but at a significantly higher level of γ-GT. A hypermetabolic state with possible polymorphisms of the alcohol metabolizing enzymes found in Africans may explain this higher γ-GT cut-point for the prediction of ambulatory hypertension when compared to Caucasians. Higher alcohol abuse may be toxic to blood vessel walls, which is evident in the augmented silent ischemia that may induce vasoconstriction of the coronary arteries. A physiological dissociative defensive
coping response is apparent when comparing two ethnicities with ROC γ-GT ethnic specific cut-points. The Africans are still at higher risk for future coronary artery disease when combining defensive coping and consumption of more alcohol.

Acknowledgements

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Conflict of interest statement

The authors declare no conflicts of interest with the content of this article.
### Tables

**Table 1:** Characteristics of a South African bi-ethnic sex cohort.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Africans</th>
<th>Caucasians</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>44.4 ± 8.25</td>
<td>50 ± 10.91</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Unadjusted lifestyle factors</strong> (arithmetic mean ± SD):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>200 (49)</td>
<td>209 (51)</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>101 (50.5)</td>
<td>101 (48)</td>
<td></td>
</tr>
<tr>
<td>Body surface area, (m²)</td>
<td>1.92 ± 0.23</td>
<td>2.0 ± 0.28</td>
<td>0.001</td>
</tr>
<tr>
<td>Physical activity, (kcal/24h)</td>
<td>2691.73 ± 794.75</td>
<td>3131.76 ± 1613.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, (cm)</td>
<td>93.79 ± 15.5</td>
<td>93.47 ± 16.08</td>
<td>0.844</td>
</tr>
<tr>
<td><strong>Variables adjusted for lifestyle factors (Body surface area; Physical activity):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotinine, (ng/ml)</td>
<td>27.78 (17.87, 37.70)</td>
<td>22.33 (12.71, 31.95)</td>
<td>0.442</td>
</tr>
<tr>
<td>γ-Glutamyl transferase, (u/l)</td>
<td>49.25 (44.64, 54.35)</td>
<td>18.67 (16.97; 20.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aspartate aminotransferase:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>0.48 (0.46, 0.51)</td>
<td>0.43 (0.41, 0.46)</td>
<td>0.004</td>
</tr>
<tr>
<td>(ALT:AST)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychological variables:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defensive coping score</td>
<td>27.80 (27.20, 28.41)</td>
<td>28.53 (27.93, 29.14)</td>
<td>0.098</td>
</tr>
<tr>
<td>Seeking social support score</td>
<td>24.97 (24.14, 25.83)</td>
<td>18.23 (17.64, 18.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Avoidance score</td>
<td>20.73 (20.13, 21.36)</td>
<td>23.42 (22.76, 24.11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Variables potentially affecting the vascular structure:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive oxygen species, (mg/l)</td>
<td>91.87 (88.31, 95.57)</td>
<td>86.96 (83.69, 90.35)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total cholesterol, (mmol/l)</td>
<td>4.47 (4.32, 4.63)</td>
<td>5.38 (5.21, 5.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glycated haemoglobin, (%)</td>
<td>6.02 (5.92, 6.12)</td>
<td>5.47 (5.38, 5.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>C-reactive protein, (mg/l)</strong></td>
<td>4.52 (3.91, 5.21)</td>
<td>1.96 (1.70, 2.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Triglycerides, (µmol/l)</strong></td>
<td>1.20 (1.11, 1.30)</td>
<td>0.98 (0.91, 1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>High density lipoprotein, (mmol/l)</strong></td>
<td>1.05 (1.01, 1.09)</td>
<td>1.16 (1.12, 1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cholesterol:High density lipoprotein (Chol:HdL)</strong></td>
<td>4.26 (4.08, 4.46)</td>
<td>4.63 (4.44, 4.84)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Cardiovascular variables:**

| **24hr SBP, (mmHg)** | 133 (132, 135) | 122 (121, 124) | <0.0001 |
| **24hr DBP, (mmHg)** | 83 (82, 85) | 76 (75, 77) | <0.0001 |
| **24hr Heart rate, (beats/min)** | 79 (78, 81) | 73 (71, 74) | <0.0001 |
| **Ischemic events, (n)** | 6.10 (4.46, 7.74) | 2.51 (0.91, 4.11) | 0.002 |

**Pathology and medications:**

| **Hypertensive, n (%)** | 132 (66) | 82 (39.23) | <0.0001 |
| **Anti-hypertensive drugs, n (%)** | 69 (34.5) | 27 (12.9) | <0.0001 |
| **Anti-diabetic drugs, n (%)** | 10 (5) | 2 (1) | 0.015 |
| **Experiencing ischemic events, n (%)** | 101 (50.5) | 86 (41.2) | 0.05 |

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. Values presented as mean (-95% confidence interval: +95% confidence interval), adjusted for body surface area and physical activity.
Table 2: Probability of ambulatory hypertension in high alcohol consumption, and high alcohol consumption as well as AC utilization.

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of 24h Ambulatory Hypertension</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Nagelkerke R²</td>
<td>Odds Ratio</td>
<td>5th Percentile</td>
<td>95th Percentile</td>
<td>P</td>
</tr>
<tr>
<td><strong>African Males –</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High γ-GT levels (≥55.4 U/l)</td>
<td>0.31</td>
<td>7.28</td>
<td>6.62</td>
<td>7.95</td>
<td>0.004</td>
</tr>
<tr>
<td>High γ-GT levels (≥55.4 U/l) + AC</td>
<td>0.31</td>
<td>7.37</td>
<td>6.71</td>
<td>8.05</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>African Females –</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High γ-GT levels (≥55.4 U/l)</td>
<td>0.11</td>
<td>1.33</td>
<td>0.81</td>
<td>1.85</td>
<td>0.59</td>
</tr>
<tr>
<td>High γ-GT levels (≥55.4 U/l) + AC</td>
<td>0.13</td>
<td>1.28</td>
<td>0.76</td>
<td>1.81</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Caucasian Males –</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High γ-GT levels (≥19.5 U/l)</td>
<td>0.17</td>
<td>2.51</td>
<td>2.06</td>
<td>2.95</td>
<td>0.04</td>
</tr>
<tr>
<td>High γ-GT levels (≥19.5 U/l) + AC</td>
<td>0.20</td>
<td>2.77</td>
<td>2.31</td>
<td>3.23</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Caucasian Females –</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High γ-GT levels (≥19.5 U/l)</td>
<td>0.39</td>
<td>6.44</td>
<td>5.86</td>
<td>7.01</td>
<td>0.001</td>
</tr>
<tr>
<td>High γ-GT levels (≥19.5 U/l) + AC</td>
<td>0.39</td>
<td>6.42</td>
<td>5.85</td>
<td>7.0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Significant odds ratios shown with P values ≤0.05.
Figures

Figure 1: ROC curves depicting the γ-GT cut-points for Ambulatory hypertension in the total, and the African and Caucasian groups respectively. The area under the curve (AUC) (±95%CI) was 0.752 (0.71 0.80) for the bi-ethnic sex group, 0.69 (0.61; 0.76) for the African group, and 0.747 (0.68; 0.82) for the Caucasian group.
Figure 2: Cardiometabolic risk factors in a bi-ethnic sex cohort stratified by race, adjusted for body surface area and physical activity (Figure 2a). Figure 2b depicts ROC γ-GT cut-point levels combined with AC for cardiometabolic risk factors. Only Africans (N=54) with γ-GT levels ≥ 55.4 U/l and Caucasian (N=72) with γ-GT levels ≥ 19.5 U/l were included.

Values presented as mean, standard error. ***P ≤ 0.001.
References


CHAPTER FOUR

Summary, Recommendations and Conclusions
4.1 Introduction

In this chapter a summary is presented of the findings of our study with a concise discussion of the aim, results and conclusion. The recognised weaknesses of the study and recommendations for future research regarding coping and alcohol abuse are also discussed in this chapter.

4.2 Summary and conclusion based on main findings

The purpose of this study was to determine, by means of receiver operating characteristic (ROC) analyses, the levels of gamma-glutamyl transferase (γ-GT) that predicted ambulatory hypertension in ethnic and sex sub-groups. Following this, we aimed to determine whether γ-GT ROC ethnic specific cut-points will reveal increased cardiometabolic and hypertensive risk when combined with defensive active coping (AC) in the bi-ethnic sex cohort.

Therefore, for each ethnic group, we calculated a specific cut-point for γ-GT at which hypertension commences. Ethnic specific cut-points were determined and differed in the ethnic-sex sub groups with Africans having a γ-GT cut-point of 55.7 U/l compared to Caucasians, who already exhibited risk for development of hypertension at γ-GT levels of 19.5 U/l. Therefore, our first hypothesis can be accepted.

Observing the groups with high alcohol usage, i.e. those with γ-GT levels above the ethnic specific cut-points, the majority reported habitually utilizing the AC style. This was found independent of race. Furthermore, we found that even when comparing cardiometabolic risk factors between ethnic groups with high alcohol consumption based on their ethnic specific cut-points, the African group displayed the highest vulnerability for cardiovascular disease, with significantly higher levels of C-reactive protein, waist circumference, blood pressure and a higher number of ischemic events when compared to the Caucasians. These findings were accentuated in participants when utilizing an AC style and can be indicative of a physiological loss-of-control despite self-reported behavioural in-control responses.\textsuperscript{1,2} This is
further proven by the odds ratio's that increased when high γ-GT levels and utilization of the AC style act in tandem. Therefore, the combined effect of γ-GT ROC ethnic specific cut-points and a AC revealed higher odds of increased hypertensive risk, which proves that our second hypothesis is also true.

When we refer to the γ-GT levels that predict the development of hypertension in the respective ethnicities, we found that alcohol-related cardiovascular pathology begins to manifest at a much lower γ-GT level in Caucasians (19.5U/l) than their African counterparts (55.4U/l). This can be explained by a hypermetabolic state in Africans that makes them less susceptible to alcohol-related damage and subsequent development of cardiovascular disease. Moreover, certain polymorphisms are absent in Africans, which lessens the extent of the effects of alcohol in these individuals. The first polymorphism entails the “hangover” feeling that exists after the intake of large amounts of alcohol; therefore Africans tend not to experience this phenomenon as intensely as other ethnicities.³⁴ Secondly, Africans rarely display an enzyme which is associated with reduced alcohol metabolism.⁵ They subsequently metabolize alcohol very efficiently and quickly after ingestion, so that the effects of alcohol do not linger in their system for long periods of time and do not cause as much harm to the hepatocytes of the liver.

Subsequently, our third hypothesis can be partly accepted, as Africans do show the highest levels of cardiometabolic risk factors when ingesting ROC determined high amounts of alcohol. However, this increased risk is only displayed at a much higher level of γ-GT when compared to their Caucasian counterparts, which implies that Caucasians will develop a prevalence of these risk factors at a lower level of alcohol consumption.
4.3 Confounders and chance

Confounders in this study were determined as body surface area and physical activity. These confounders were addressed in the statistical analyses of the data, where adjustments were made to ensure credible results.

The element of bias or chance was a definite possibility in this study, due to the small sample size included. Nonetheless, the study showed controlled data collection, overall data integrity and all analyses were conducted with strict protocols. With this in mind, we can declare that if chance was present in this study, it was unknown to the authors.

4.4 Limitations of the study

- The cross-sectional nature of this study posed an important limitation. The effects of the coping styles may show altered outcomes when observed over a period of time. Also, the long-term effects of alcohol on cardiometabolic health can be more successfully determined with follow-up data.

- The uncertainty of using biochemical markers, mainly liver enzymes such as \( \gamma \)-GT, for determination of alcohol usage can also be seen as a limitation. These enzymes can also be elevated in non-alcohol related pathology, like oxidative stress and non-alcoholic fatty liver, and are therefore described as indirect markers of alcohol abuse.\(^6\)

4.5 Recommendations for future research

- It is recommended to assess prospective findings of the participants of this study to determine the long term effects of alcohol on the cardiovascular system and especially cardiometabolic risk.

- It is recommended to use hair samples to determine chronic alcohol abuse of participants more accurately, since alcohol abuse will directly reflect alcohol usage \textit{per se}, unlike the indirect effect of alcohol on liver enzymes.\(^6\)
4.6 Conclusion

In the study cohort, the African group displayed a vulnerable cardiometabolic profile when ingesting alcohol, especially when combined with utilization of a AC style. They may have a hypermetabolic tendency where the effects of alcohol abuse at a much higher level of γ-GT, is evidenced in higher cardiometabolic risk markers. This can be due to the fact that certain genetic discrepancies are present with regard to the metabolism of alcohol, which greatly influences its effects on the cardiovascular system. We also found dissociation between a physiological and behavioural AC response in Africans, which was not evident in the Caucasian group. The AC responses in Caucasians are in line with current literature, whereas the Africans’ dissociative responses may mask behavioural ‘loss-of-control’ responses before neural fatigue sets in.
References


APPENDICES
Appendix A: Involvement of student in M.Sc year (2014)

To whom it may concern:

I am the Head of the Hypertension Research & Training Clinic where Miss Woudri Oosthuizen is working as a M.Sc student in Cardiovascular Physiology. She exhibits important life skills such as good communication, reliability, honesty and leadership. Miss W Oosthuizen is actively involved in The Hypertension Research & Training Clinic where she works hands-on as part of a multi-disciplinary team in the African-PREDICT study. As a member of the Hypertension in Africa Research Team (HART) she receives valuable practical experience in the field of Cardiovascular Physiology and is therefore well familiar with the research method. She has experience with various cardiovascular apparatus which include the following:

- Blood pressure measurements with various apparatus such as ambulatory blood pressure and Finometer
- Electrocardiography measurement as well as interpretation
- Sphygmocor measurements – to determine arterial stiffness and central blood pressure
- Basic laboratory skills (pipetting, centrifugation etc.)

Kind regards

Sr. A Burger
Head: Hypertension Research & Training Clinic
Appendix B: Turnitin Originality Report

22152873:Turn-it-in_W_Oosthuizen_22152873.docx by WOUDRI OOSTHUIZEN

From Post-graduate reports (19c4d674-2dba-48a9-bac6-fac00abf8790)

- Processed on 13-Nov-2014 09:11 SAST
- ID: 477195465
- Word Count: 9122 (Bibliography excluded)

Similarity Index:
5%

Similarity by Source

Internet Sources:
2%
Publications:
4%
Student Papers:
1%
Appendix C: Declaration of language editing

DECLARATION OF LANGUAGE EDITING

I, Christina Maria Etrecia Terblanche, hereby declare that I edited the article entitled:

Coping, alcohol and cardiovascular risk: The SABPA study

for Woudri Oosthuizen for the purposes of submission as a postgraduate study. No changes were permanently affected and were left to the discretion of the student.

Regards,

CME Terblanche

Cum Laude Language Practitioners (CC)

SATI reg nr: 1001066

PEG registered
Appendix D: Ethical approval for umbrella and sub-study

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Fax: (018) 299-4910
Web: http://www.nwu.ac.za

Dr L Malan

Ethics Committee
Tel +27 18 299 2542
Fax +27 18 297 5308
Email Ethics@nwu.ac.za

Dear Dr Malan

6 February 2008

ETHICS APPROVAL OF PROJECT

The North-West University Ethics Committee (NWU-EC) hereby approves your project as indicated below. This implies that the NWU-EC grants its permission that, provided the special conditions specified below are met and pending any other authorisation that may be necessary, the project may be initiated, using the ethics number below.

| Project title: SABPA (Sympathetic activity and Ambulatory Blood Pressure in Africans) | Ethics number: NWU-00036-07-386 |
| Approval date: 12 November 2007 | Expiry date: 11 November 2012 |

Special conditions of the approval (if any): None

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:

- The project leader (principle investigator) must report in the prescribed format to the NWU-EC:
  - annually (or on otherwise requested) on the progress of the project;
  - without any delay in case of any adverse event (or any matter that interrupts sound ethical principles) during the course of the project.
- The approval applies strictly to the protocol as stipulated in the application form. Any changes to the protocol must be deemed necessary during the course of the project, the project leader must apply for approval of these changes at the NWU-EC. Would there be deviations from the project protocol without the necessary approval of such changes, the ethics approval is immediately and automatically forfeited.
- The date of approval indicates the first date that the project may be started. Would the project have to continue after the expiry date, a new application must be made to the NWU-EC and new approval received before or on the expiry date.
- In the interest of ethical responsibility the NWU-EC retains the right to:
  - request access to any information or data at any time during the course of or after completion of the project.
  - withdraw or postpone approval if:
    - any unethical principles or practices of the project are revealed or suspected;
    - it becomes apparent that any relevant information was withheld from the NWU-EC or that information has been false or misrepresented;
    - the required annual report and reporting of adverse events was not done timely and accurately;
    - new institutional rules, national legislation or international conventions deem it necessary.

The Ethics Committee would like to remain at your service as scientist and researcher, and wishes you well with your project. Please do not hesitate to contact the Ethics Committee for any further enquiries or requests for assistance.

Yours sincerely

Prof M M J Lowes (chair NWU Ethics Committee)
12 November 2014

Dear Prof Malan

Ethics Application: NWU-00036-07-A6 "The SABPA Study"

All ethical concerns have been addressed and your application to include the sub-study “Coping, alcohol and cardiovascular risk” under the umbrella project has been approved by the HREC until 31/12/2015.

Yours sincerely

[Signature]

Prof Minnie Greeff
Health Research Ethics Committee Chairperson
Appendix E: Coping Strategy Indicator by Amirkhan (1990)

INSTRUCTIONS:
Listed below are several possible ways of coping. Indicate to what extent you, yourself, used each of these coping methods. Try to think of one problem you have encountered in the last six months or so. This should be a problem that was important to you, and caused you to worry (anything from the loss of a loved one to a traffic fine, but one that was, important to you). Describe this problem in a few words.

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

With this problem in mind, indicate how you coped by ticking the appropriate box for each coping behaviour listed on the following pages. Answer each and every question even though some may sound similar.

Keeping your chosen stressful event in mind, indicate to what extent you...

<table>
<thead>
<tr>
<th></th>
<th>A lot</th>
<th>A little</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Let your feelings out to a friend?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Rearranged things around you so that your problem had the best chance of being resolved?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Brainstormed all possible solutions before deciding what to do?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Tried to distract yourself from the problem?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Accepted sympathy and understanding from someone?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Did all you could to keep others from seeing how bad things really were?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Talked to people about the situation because talking about it helped you to feel better?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Set some goals for yourself to deal with the situation?</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Weighed your options very carefully?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Daydreamed about better times?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Tried different ways to solve the problem until you found one that worked?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Confided your fears and worries to a friend or relative?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Spent more time than usual alone?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Told people about the situation because just talking about it helped you to come up with solutions?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Thought about what needed to be done to straighten things out?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Turned your full attention to solving the problem?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Formed a plan of action in your mind?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Watched television more than usual?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Went to someone (friend or professional) in order to help you feel better?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Stood firm and fought for what you wanted in the situation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Avoided being with people in general?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Buried yourself in a hobby or sports activity to avoid the problem?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Went to a friend to help you feel better about the problem?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Went to a friend for advice on how to change the situation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Accepted sympathy and understanding from friends who had the same problem?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Slept more than usual?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Fantasized about how things could have been different?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Identified with characters in novels or movies?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Tried to solve the problem?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Wished that people would just leave you alone?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Accepted help from a friend or relative?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Sought reassurance from those who know you best?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Tried to carefully plan a course of action rather than acting on impulse?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>