Low body mass index and the associations with cardiovascular function in Africans: the PURE study

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Dissertation submitted in fulfilment of the requirements for the degree Master of Science in Physiology at the North-West University.

November 2011

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ACKNOWLEDGEMENTS

I would like to thank the following people:

- Prof HW Huisman for his patience and guidance through the whole process of completing this dissertation.
- Prof JM van Rooyen for his advice and input.
- Eleanor Louw for proof-reading this manuscript.
- Teagan-Leigh, my parents, family and friends for their support.

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OPSOMMING

Titel: Lae liggaamsmassa-indeks en verbande met kardiovaskulêre funksie in Afrikane: die PURE studie.

Agtergrond: Kardiovaskulêre siekte is wêreldwyd bekend as een van die grootste oorsake van dood, waarvan die lae-inkomste lande of ontwikkelende lande die hoogste voorkoms van kardiovaskulêre siekte toon. Een van die vernaamste redes vir hierdie statistiek is akkulturasie wat lei tot veranderinge in gedragleefstyl en wanvoeding in hierdie lande. Verskeie studies toon dat lae liggaamsmassa-indeks 'n onafhanklike risikofaktor vir kardiovaskulêre siekte is. Vanuit die literatuur is dit gevind dat liggaamsmassa-indeks wat laer is as die ideale liggaamsmassa-indeks gekoppel is aan kardiovaskulêre siekte. Volgens Higashi (2003) word 'n liggaamsmassa-indeks van 22,2 kg/m^2 geassosieer met die laagste morbiditeit. As die liggaamsmassa-indeks tot waardes laer as die ideale liggaamsmassa-indeks daal, sal ‘n J-kurwe sigbaar wees, wat ‘n hoër oorwig van kardiovaskulêre siekte verbonde aan lae liggaamsmassa-indeks voorstel. Hierdie bevindings dui daarop dat nie slegs ‘n hoë liggaamsmassa-indeks maar ook ‘n lae liggaamsmassa-indeks moontlik ‘n risikofaktor vir kardiovaskulêre siekte, sieklikheid en sterfte kan wees. Dit is steeds onduidelik of lae liggaamsmassa-indeks verbind is met kardiovaskulêre risiko in ‘n Afrika-bevolking.

Doelstelling: Die doel van hierdie studie was om die moontlike verbande tussen lae liggaamsmassa-indeks en veranderlikes van kardiovaskulêre funksie in Afrikane met ‘n lae sosio-ekonomiese stand te ondersoek.

Metodologie: Hierdie voornemende groepstudie (N= 2 010) is deel van die “Prospective Urban and Rural Epidemiology study” (PURE) uitgevoer in die Noordwes Provinsie van Suid-Afrika in 2005, waartydens die verandering in gesondheid van stedelike en landelike proefpersone ondersoek is in ‘n oënskynlik lae sosio-ekonomiese stand groep. Ons dwarsdeursnee PURE substudie het bestaan uit 496 Afrikane van ‘n landelike en ‘n stedelike agtergrond (mans, N= 252 en vrouens, N= 244) tussen die ouderdomme 35 tot 65 jaar met ‘n liggaamsmassa-

indeks kleiner as 25 kg/m^2. Die proefpersone is in twee groepe onderverdeel. Die eerste groep het bestaan uit Afrikane met ‘n lae liggaamsmassa-indeks kleiner of gelykstaande aan 20kg/m^2 (mans; N= 152, vrouens; N= 94), terwyl die tweede groepe bestaan het uit Afrikane met ‘n normale liggaamsmassa-indeks groter as 20kg/m^2 en kleiner of gelykstaande aan 25kg/m^2 (mans; N= 100, vrouens; N= 150). Metings van sistoliese bloeddruk en diastoliese bloeddruk is uitgevoer deur gebruik te maak van die geldige OMROM HEM-757 apparaat. Die polsgolfsnelheid is gemeet met gebruik van die Complior SP apparaat. ‘n Geregistreerde verpleegkundige het bloed uit die antebragiale vene met ‘n steriele gevleuelde onttrekkingstel en inspuitnaalde getrek. Analises vir cholesterol, hoë digtheids lipoproteïen, trigliseriede, gamma glutamyl transferase en hoë sensitiwiteit C-reaktiewe proteïen is met behulp van die Konelab 20i uitgevoer. Statistiese analises is uitgevoer om vas te stel of daar beduidende verskille tussen ouderdom, liggaamsmassa-indeks en lewenstylfaktore sowel as kardiovaskulêr-verwante veranderlikes bestaan in die verskillende groepe. T-toetse was gebruik om beduidende verskille tussen onafhanklike groepe te toon. ANCOVA toetse was gebruik om liggaamsmassa indeks-groep verskille, onafhanklik van ouderdom, rook en alkohol gebruik, te toon. Parsiële korrelasies, aangepas vir ouderdom, rook en alkohol gebruik, toon assosiasies tussen die liggaamsmassa indeks-groepe en kardiovaskulêre funksie.

Resultate: Ons resultate het getoon dat daar betekenisvol hoër gemiddelde waardes vir die Afrikaan mans, met lae liggaamsmassa-indeks, vir kardiovaskulêre-veranderlikes (Diastoliese bloeddruk, 88.0 ± standaardafwyking (SA) 13.4 mmHg; gemiddelde arteriële druk, 103.8 ± SA 14.4 mmHg en karotis-radiale polsgolfsnelheid, 12.6 ± SA 2.47 m/s) in vergelyking met die normale liggaamsmassa-indeks groep (Diastoliese bloeddruk, 84.2 ± SA 12.2 mmHg; gemiddelde arteriële druk, 100.0 ± SA 13.2 en karotis-radiale polsgolfsnelheid, 11.6 ± SA 2.00 m/s) bestaan. Die Afrikaan vroue met 'n lae liggaamsmassa-indeks het slegs ‘n beduidende verskil vir karotis-radiale polsgolfsnelheid (11.3 ± SA 2.43 m/s) in vergelyking met die normale liggaamsmassa-indeks groep (10.6 ± SA 2.10 m/s) getoon. Ons het getoon dat die Afrikaan mans, nadat die veranderlikes aangepas is vir ouderdom, rook en alkohol gebruik, se diastoliese bloeddruk (88.0 met vertroue interval (VI) [86.0-90.0] mmHg) en die karotis-radiale polsgolfsnelheid (12.5 (VI)

[12.1-12.9] m/s) aansienlik hoër was as die van in die lae liggaamsmassa-indeks groep. Daarbenewens het die karotis-radiale polsgolfsnelheid ‘n omgekeerde assosiasie teenoor die liggaamsmassa-indeks in Afrikaan mans getoon. In die lae liggaamsmassa-indeks groep is Pearson en parsiële korrelasies van r = -0,204, p = 0,012 en r = -0,200, p = 0,020 onderskeidelik in die karotis-radiale polsgolfsnelheid gevind. Verder in ons onaangepaste spreidiagram met liggaamsmassa-indeks teenoor polsgolfsnelheid was hierdie negatiewe tendens van toenemende karotis-radiale polsgolfsnelheid met dalende liggaamsmassa-indeks waarneembaar in beide Afrikaan mans en vroue. Selfs wanneer aanpassings vir karotis-radiale polsgolfsnelheid gemaak was vir ouderdom, rook, alkohol gebruik, gemiddelde arteriële bloeddruk en hartklop, was 'n J-kurwe tussen karotis–radiale polsgolfsnelheid en liggaamsmassa-indeks nog steeds sigbaar.

Gevolgtrekking: Daar bestaan ‘n nadelige effek in kardiovaskulêre funksie by Afrikane as gevolg van lae liggaamsmassa-indeks. As die liggaamsmasa-indeks van die optimum waarde van 22.2 kg/m^2 na laer waardes daal, word ‘n J-kurwe sigbaar tussen liggaamsmassa-indeks en kardiovaskulêre veranderlikes, wat op ‘n hoër waarskynlikheid van kardiovaskulêre siekte verbonde aan lae liggaamsmassa-indeks dui. In ons substudie is daar ‘n beduidende styging in die karotis-radiale polsgolfsnelheid by manlike Afrikane met ‘n lae liggaamsmassa-indeks, wat dus die teorie ondersteun dat verharding van arteries by Afrikane met ‘n lae liggaamsmassa-indeks voorkom. Lae liggaamsmassa-indeks dra moontlik by tot die hoë waarskynlikheid van kardiovaskulêre siektesterftes binne ontwikkelende lande, en dus die risiko van kardiovaskulêre siekte verhoog.

Sleutelwoorde: Afrikane, kardiovaskulêre funksie, lae liggaamsmassa-indeks.

SUMMARY

Title: Low body mass index and the associations with cardiovascular function in Africans: the PURE study.

Background: Cardiovascular disease is known as one of the leading causes of mortality worldwide, where low income countries or developing countries have the highest prevalence of cardiovascular disease. One of the main reasons for this statistics is acculturation that leads to changes in behavioral lifestyle and malnutrition within these countries. Low body mass index was found to be an independent risk factor for cardiovascular disease in several studies. From literature it is found that body mass index is lower than the ideal body mass index and is associated with cardiovascular disease. According to Higashi (2003) a body mass index of 22.2 kg/m^2 is associated with the lowest morbidity. If body mass index decreases to lower values than the ideal body mass index, a J-curve will be evident suggesting higher prevalence of cardiovascular disease associated with low body mass index. These findings imply that not only high body mass index but also a low body mass index may be a risk factor for cardiovascular disease, morbidity and mortality. Whether low body mass index is associated with cardiovascular risk in an African population remains unclear.

Objective: The aim of this study was to investigate the possible associations of low body mass index with variables of cardiovascular function in Africans, with a low socio-economic status.

Methodology: This prospective cohort study (N= 2 010) is part of the Prospective Urban and Rural Epidemiology study (PURE) conducted in the North-West Province of South Africa in 2005, where the health transition in urban and rural subjects was investigated within an apparently low socio-economic status group. Our cross-sectional PURE sub-study included 496 African people from rural and urban settings, (men, N= 252 and women, N= 244) aged between 35-65 years and body mass index lower than 25 kg/m^2. Subjects were sub-divided into two groups. The first group consisted of Africans with a low body mass index smaller or equal to 20 kg/m^2 (men;

N= 152, women; N= 94) whilst the second group consisted of Africans with a normal body mass index larger than 20 kg/m^2 and smaller or equal to 25 kg/m^2 (men; N= 100, women; N= 150). Systolic blood pressure and diastolic blood pressure measurements were obtained with the validated OMRON HEM-757 device. The pulse wave velocity was measured using the Complior SP device. Blood was drawn by a registered nurse from the antebrachial vein using a sterile winged infusion set and syringes. Analyses for cholesterol, high density lipoprotein, triglycerides, gamma-glutamyl transferase and high sensitive C-reactive protein were completed utilizing the Konelab 20i. Data analyses were performed using the Statistica 10 program. Statistical analyses were executed to determine significant differences between age, body mass index and lifestyle factors as well as cardiovascular related variables in the different groups. T-tests were used to determine significant differences between independent groups. ANCOVA tests were used to determine BMI group differences independent of age, smoking and alcohol consumption. Partial correlations, which were adjusted for age, smoking and alcohol consumption, determined associations between the BMI groups and cardiovascular variables.

Results: Our results indicated significantly higher mean values for the African men, with low body mass index, for cardiovascular variables (Diastolic blood pressure, 88.0 ± standard deviation (SD) 13.4 mmHg; mean arterial pressure, 103.8 ± SD 14.4 mmHg and carotid-radial pulse wave velocity, 12.6 ± SD 2.47 m/s) compared to the normal body mass index group (Diastolic blood pressure, 84.2 ± SD 12.2 mmHg; mean arterial pressure, 100.0 ± SD 13.2 mmHg and carotid-radial pulse wave velocity, 11.6 ± SD 2.00 m/s). The African women with low body mass index had a significant difference for carotid-radial pulse wave velocity (11.3 ± SD 2.43 m/s) compared to the normal body mass index group (10.6 ± SD 2.10 m/s). In African men, after the variables were adjusted for age, smoking and alcohol consumption, we revealed that diastolic blood pressure (88.0 with confidence interval (CI) [86.0-90.0] mmHg) and carotid-radial pulse wave velocity (12.5 with CI [12.1-12.9] m/s) remained significant higher in the low body mass index group. Additionally, carotid-radial pulse wave velocity was negatively associated with body mass index in African men. In the low body mass index group, Pearson and partial correlations of r= -0.204; p= 0.012 and r= -0.200; p= 0.020 were found respectively in carotid-radial pulse wave velocity. Furthermore, in our unadjusted scatter plot with body mass

index versus pulse wave velocity this negative trend of increasing carotid-radial pulse wave velocity with decreasing body mass index was noticeable in both African men and women. Even when carotid-radial pulse wave velocity was adjusted for age, smoking, alcohol consumption, mean arterial pressure and heart rate, a J-curve between carotid-radial pulse wave velocity and body mass index was still evident.

Conclusion: A detrimental effect of low body mass index is evident on cardiovascular function in Africans. If body mass index decreases from the optimum value of 22.2 kg/m^2 to lower values, a J-curve is evident between body mass index and cardiovascular variables suggesting higher prevalence of cardiovascular disease associated with low body mass index. In our sub-study the carotid-radial pulse wave velocity increases significantly in African men with low body mass index, thus supporting the theory that stiffening of the arteries is evident in Africans with a low body mass index. Low body mass index may contribute to the high prevalence of cardiovascular disease mortality within developing countries and therefore, increase the risk for cardiovascular disease.

Keywords: Africans, cardiovascular function, low body mass index.

PREFACE

For the purpose of this study it was decided to use the article format. The manuscript in chapter 2 will be submitted in the peer-reviewed Journal of Human Hypertension.

In chapter 1 a literature overview is given of the socio-economic status and health co-morbidity that is applicable to this study. The influence of acculturation on behavioral lifestyle factors is also shown. Further cardiovascular and body mass index variables are discussed.

In the end, the conclusion and recommendations of this study are discussed in chapter 3.

OUTLINE OF THE STUDY

This study is divided into three chapters consisting of the following information:

Chapter 1: The first chapter comprises of the introduction, main literature overview, the motivation for the study, the aim as well as the hypothesis of the study.

Chapter 2: Chapter two is the actual manuscript of the study named:
Low body mass index and the associations with cardiovascular function in Africans: the PURE study

Chapter 3: The final chapter includes the discussion, conclusion and recommendations for future research.

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LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
ANCOVA	Analyses of covariance
BMI	Body mass index
c-r PWV	Carotid-radial pulse wave velocity
CAD	Coronary artery disease
CI	Confidence interval
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
GGT	Gamma-glutamyl transferase
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HR	Heart rate
Hs-CRP	High sensitive C-reactive protein
LDL	Low density lipoprotein
MAP	Mean arterial pressure
MI	Myocardial infarction
PP	Pulse pressure
PURE	Prospective Urban and Rural Epidemiology
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socio-economic status
TB	Tuberculosis
TC	Total cholesterol
TG	Triglyceride
WC	Waist circumference
WHO	World Health Organization

AUTHOR'S CONTRIBUTIONS

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

Mr HL Venter (Hons BSc) Physiologist	Responsible for literature research, statistical analysis, design and planning of manuscript, interpretation of results and writing of manuscript.
Prof HW Huisman (PhD) Physiologist	Supervisor. Supervised the writing of the manuscript, collection of data, initial planning and design of manuscript.
Prof JM van Rooyen (DSc) Physiologist	Co-supervisor. Supervised the writing of the manuscript and collection of data.

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

I declare that I have approved the above-mentioned dissertation, that my role in the study, as indicated above, is representative of my actual contribution and that I hereby give my consent that it may be published as part of the degree: Master of Science dissertation of Herman Louwrens Venter.

Mr HL Venter

Prof HW Huisman

Prof JM van Rooyen

CHAPTER ONE

Introduction, literature study, overview, motivation, aim, hypothesis and references

1.1. Introduction

Cardiovascular disease (CVD) is known as one of the leading causes of mortality worldwide, where low income countries or developing countries have the highest prevalence of CVD.[1] One of the main reasons for this statistic is the behavioral lifestyle factors and malnutrition of individuals within these low socio-economic status (SES) conditions.[2,3] Unhealthy dietary habits, alcohol and tobacco use are crucial lifestyle risk factors for CVD.[3-5] These risk factors can cause increased blood pressure, blood glucose and lipid levels.[1] Cost-analyses showed that these developing countries cannot afford the same treatment for CVD as developed countries.[4] Prevention of CVD and health care control in developing countries may therefore be more challenging than that in developed countries.[6]

High body mass index (BMI) is associated with CVD.[7] There has been much emphasis on obesity as a risk factor for CVD and mortality, [8-10] but there has been little focus on possible risk associations with low BMI.[11-14] A BMI of 22.2 kg/m^2 is associated with the lowest morbidity.[15] If the BMI decreases to lower values than 22.2 kg/m^2 a J-curve is evident suggesting higher prevalence of cardiovascular disease associated with low BMI.[8,15] These findings imply that not only obesity but also a low BMI may be a risk factor for cardiovascular disease.[14,16] A small number of studies have shown that not only high BMI but also low BMI increases risk of cardiovascular morbidity and mortality.[8,12,16,17] Low BMI and the association with mortality has often been explained as being due to confounders like smoking or pre-existing illness.[8] However, certain studies that control for these confounders still find a J-shaped relation.[8]

Furthermore, several studies have been conducted to explore these associations between low BMI and CVD within Western countries or developed countries. Low BMI was found to be an independent risk factor for mortality and stroke within a study conducted in the United States of America.[8] In contrast to the former, little or no focus have been given to this topic within Africans in South Africa.

1.2. Literature study

1.2.1. Socio-economic status (SES)

Developing countries (low SES) vs. developed countries (high SES)

According to the World Health Organization (WHO) over 80% of the world's deaths from CVD occur in low- and middle-income countries.[1]

Individuals in low- and middle-income countries (developing countries) are more exposed to risk factors leading to CVD and are less exposed to prevention efforts than individuals in high-income countries (developed countries).[1,6]

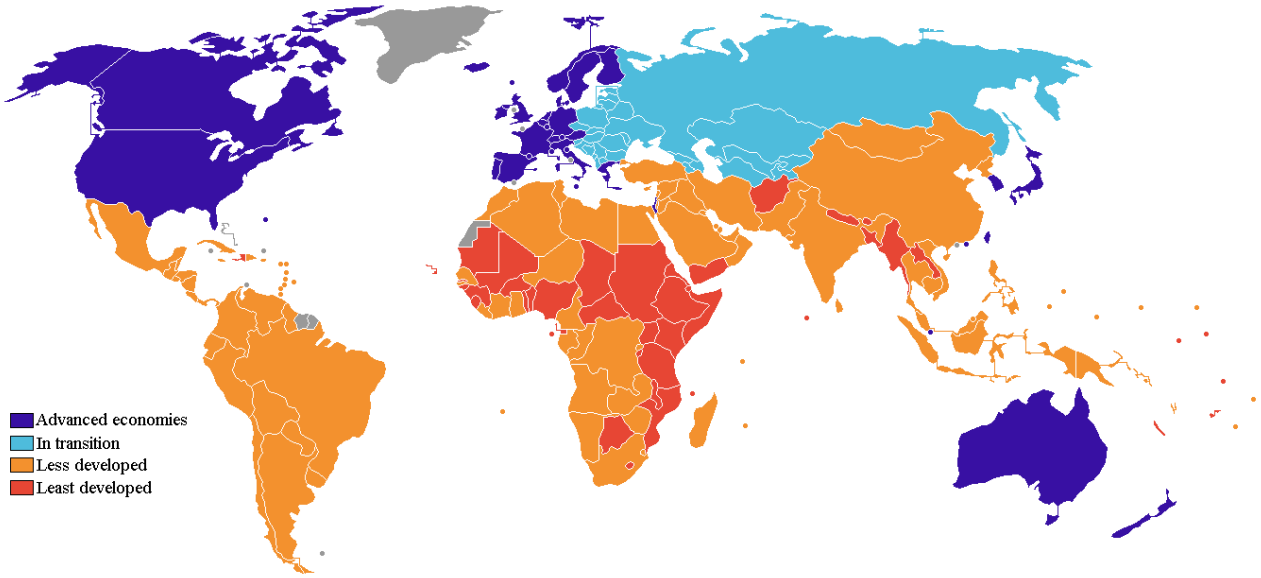

Figure 1 The map highlights a visual representation of the geographic distribution of developed (purple), developing countries (orange), as well as those in transition (blue). Areas shaded grey indicate countries for which no data was available.[18]

Less access to effective and reasonable health care services are present for individuals in developing countries who suffer from CVD.[1] As a result, many individuals in developing countries die younger from CVD, often in their most productive years.[1] The poorest individuals in developing countries are affected most in this situation.[1,6] WHO further mentions that at household level, adequate evidence is emerging to prove that CVD contribute to poverty. CVD also place a heavy burden

on the economies of developing countries at macro-economic level thus initializing a detrimental cause and effect cycle between CVD and poverty.[1]

There are also a number of other factors which may contribute to this higher risk prevalence. They reflect the major forces driving social, economic and cultural change namely acculturation. Other risk factors of CVD include genetic traits, stress and poverty.[1] Due to Sub-Saharan Africa's population of 650 million and increasing acculturation, hypertension has now become a major health problem.[4]

Moreover, there is an emerging burden of CVD among acculturated Africans in South Africa, which can be largely explained by the transition from traditional African lifestyles to a more Westernized behavior.[5,19]

1.2.2. Acculturation

Acculturation is when members of one cultural group adopt the beliefs and behaviors of another group.[20] Acculturation has been studied in relation to prevalence of chronic diseases and health services. Behavioral lifestyle factors like dietary habits and patterns of physical activity of particular cultural groups may affect the development of specific diseases like CVD.[3] Also beliefs about causes, treatment, and prevention of diseases may affect utilization of health services through acculturated individuals.[21]

The most important behavioral risk factors of heart disease and cerebrovascular stroke are unhealthy diet, harmful consumption of alcohol and tobacco use. The effects of these behavioral life style changes may show up in individuals as raised blood pressure, raised blood glucose, raised blood lipids, and a detrimental BMI.[5]

1.2.2.1. Unhealthy diet

Dietary intake is an important modifiable risk factor according to Hamer (2010).[19] Dietary patterns have been associated with various disease risk markers. The role of dietary intake may be particularly relevant in high risk groups with a low SES.[19] Persons from socio-economically disadvantaged backgrounds with a detrimental food intake tendency leads to higher rates of chronic disease.[3] As acculturation begin

to exert its influence, we see the adoption of different diets that no longer conform to the traditional local habits.[22] The evolving diets are distinctly higher in salt and fat content relative to traditional diets that accentuate carbohydrates.[22] It is evident that an unhealthy diet or malnutrition will contribute to morbidity corresponding with CVD especially in developing countries.[5,19,22] Conversely higher social status participants consume more food items from a healthy dietary pattern supporting longevity.[19]

1.2.2.2. Alcohol consumption

Moderate alcohol consumption by healthy individuals is known to be associated with lower cardiovascular morbidity and mortality than in avoiders.[23] Mechanisms supporting this include beneficial regulation of lipids and fibrinolysis, decreased platelet aggregation and coagulation factors, favorable effects on endothelial function, and inflammation resistance.[23] Some epidemiological studies have suggested that individuals consuming wine have a lower incidence of CVD than drinkers of other types of alcohol.[24] It has been shown in some populations that beer, wine, and spirits may also have a different effect on cardiovascular morbidity.[24]

According to literature these differences in effect on health may be explained by true differences; there are experimental studies to support several plausible biological explanations.[24] Wine contains numerous components that may contribute to a possible anti-thrombotic and anti-carcinogenic effect.[24]

However the abuse of alcohol is unquestionably harmful.[23-25] The relationship between alcohol consumption and ischemic cardiovascular events or all-cause mortality in healthy individuals has been depicted as a J-shaped curve attributed to combination of beneficial and harmful effects.[25]

The debate of the effects of moderate to light alcohol consumption reducing the risk of CVD has continued for numerous years.[23-25] However, some concern has been raised whether it is advisable to encourage people to drink small amounts regularly rather than abstain completely; especially in developing countries with such a high CVD mortality rate.[23]

1.2.2.3. Smoking

Epidemiologic studies strongly support the statement that cigarette smoking in both men and women increases the incidence of CVD like myocardial infarction (MI) and fatal coronary artery disease (CAD).[26] Even low-tar cigarettes and smokeless tobacco have been shown to increase the risk of CVD in comparison to non-smokers.[26] Furthermore, passive smoking with a smoke exposure about one-hundredth that of active cigarette smoking is associated with approximately a 30% increase in risk of CAD, compared with an 80% increase in active smokers.[26] Thus, the evidence linking cigarette smoke exposure with CVD is clearly present.[26]

According to literature cigarette smoke contains over 4 000 known components, of which only a few components have been examined in isolation. For instance the component polycyclic aromatic hydrocarbons found in the tar of cigarette smoke has been recognized to accelerate atherosclerosis.[26] Probably the most studied component in cigarette smoke is nicotine. Although nicotine plays a major role in smoking-related increases in heart rate (HR) and blood pressure, its role in cigarette smoking related athero-thrombotic disease remains controversial.[26]

Nevertheless smoking is harmful and will contribute to morbidity and promote development CVD.[3,5,26]

1.2.3. Body mass index (BMI)

1.2.3.1. Cut-off discrepancy for BMI

The principle behind the new guidelines is that increasing categories of BMI are related to increasing health risks associated with obesity.[27,13] According to the WHO, BMI values are age-independent and the same for gender.[27] However, BMI may not correspond to the same degree of overweight in different populations due to different body proportions.[13,27] The health risks associated with increasing BMI are constant and the interpretation of BMI grading in relation to risk may differ for different populations.[13]

Table1 The U.S. National Institutes of Health (NIH) and the WHO have standardized the classification of weight based on categories of BMI (kg/m^2):

Classification	**BMI (kg/m^2)**
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25-29.9
Obesity class I	30-34.9
Obesity class II	35-39.9
Obesity class III	≥40

There was a growing debate recently on whether there are possible needs for developing different BMI cut-off points for different ethnic groups due to the increasing evidence that the associations between BMI, percentage of body fat, and body fat distribution differ across populations.[12,13,15] For example in a South India study, the conventional cut-off limits for BMI might not define overweight and obesity optimally because of their higher percentage of body fat compared with Caucasians.[12] Some investigators have reported lower BMI cut-offs for Asian Indians according to average body fat.[12] Based on the former data, lower cut-off values of BMI to define overweight (23 kg/m^2) and obesity (25 kg/m^2) have been proposed for South Asians by the WHO.[12] Alternative results for a 35 year cohort study of more than 5000 Jewish Israeli adults recently showed that in males, an initial BMI of below 20 kg/m^2 or above 30 kg/m^2 were both significantly associated with increased mortality.[26]

Consequently studies are required to redefine the “normal” limits of BMI in different ethnic groups on the basis of morbidity and mortality data.[12]

1.2.3.2. Low BMI hidden in the shadow of obesity

There has been much emphasis on obesity as a risk factor for CVD and mortality, [8-10] but there has been little focus on possible risk associations with low BMI.[11,12,19] An epidemiology study demonstrated that subjects that have a BMI of 22.2 kg/m^2 have the lowest morbidity, suggesting that there is a J-curve phenomenon between prevalence of CVD and BMI.[15] Low BMI was found to be an independent risk factor in a Western country (high SES) for mortality and stroke in the Systolic Hypertension in the Elderly Program (SHEP), a placebo-controlled, randomized, clinical trial of antihypertensive therapy for isolated systolic hypertension.[8] In a South India study (low SES) a significant number of hypertensive patients with low BMI had myocardial infarction (MI), but not those with a higher BMI.[17] In addition to this, a cohort study of Jewish Israeli adults recently showed that an initial BMI of below 20 kg/m^2 or above 30 kg/m^2 were significantly associated with increased mortality within men.[28] Low and high BMI should be considered as a critical factor for CVD and should be more widely implemented for the initial diagnosis of malnutrition.[28] Thus not only obesity, but also the neglected low BMI may be a risk factor for CVD.[14]

1.2.3.3. J-curve

The majority of studies have reported a J-shaped association between BMI and all-cause mortality as illustrated in figure 2.[29] Nevertheless the relation between body weight and mortality remains controversial. In a prospective cohort study data indicated that men and women with high and low BMI had an increased risk of death at all ages.[30] The optimal body mass index for longevity fell between 20.5 kg/m^2 and 24.9 kg/m^2 for men and women.[30] Former data prove a similar J-shape theory and propose the uphold of a single recommended range of body weight throughout life.[30]

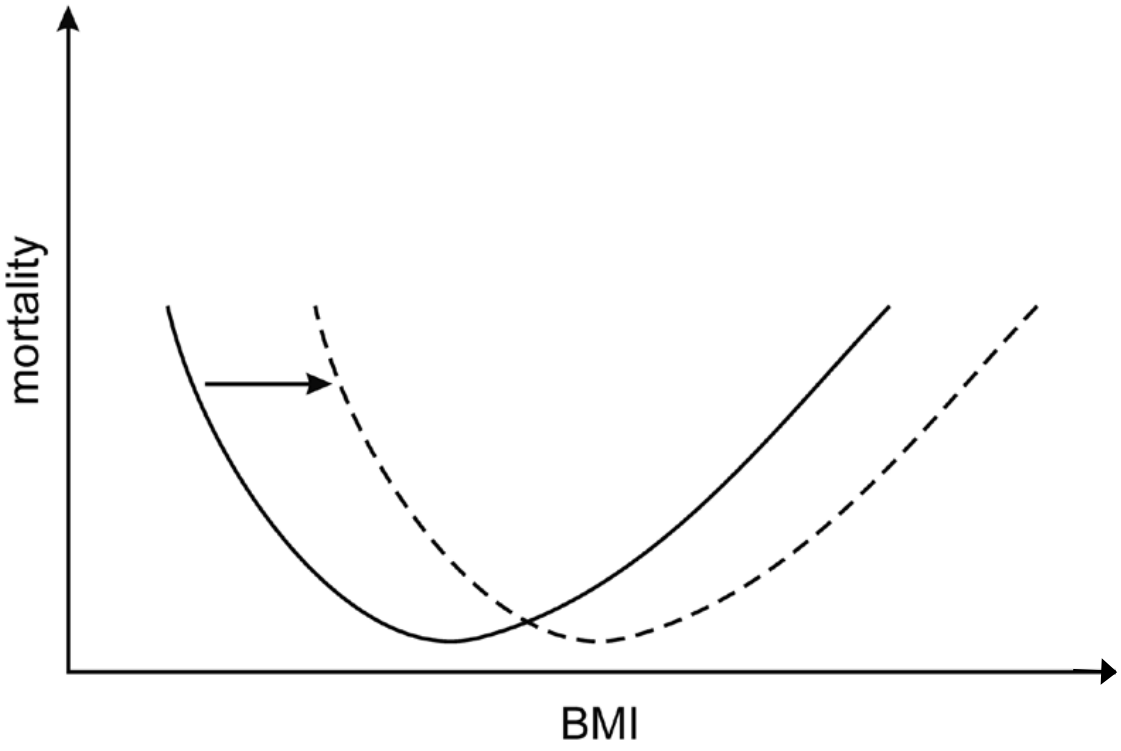

Figure 2 J-curve correlation between body mass index (BMI) and mortality. The magnitude of the mortality rate (Y axis) is greater at the extremes of BMI (X axis). Long-term mortality is higher in relatively healthy middle-aged adults (continuous line curve). The J-curve appears to be shifted to the right (dotted line curve) in participants older than 65 years and in patients with severe disease and chronic organ failure. Adapted from Singer et al. [28]

1.2.4. Main variables

1.2.4.1. Cardiovascular variables

1.2.4.1.1. Systolic blood pressure (SBP) and diastolic blood pressure (DBP)

Using population-attributable risk methods, the Global Burden of Disease study suggests that approximately 54% of all stroke and 47% of all ischemic heart disease are attributable to high blood pressure (hypertension) causing nearly 7.6 million premature deaths.[31] Epidemiologic studies, including the landmark Framingham Heart Study, have resulted in the precise definition of the association of blood pressure and major vascular events such as cerebrovascular stroke and ischemic heart disease.[31]

Table 2 Definitions and classification of blood pressure levels (mmHg) with category systolic blood pressure (SBP) and diastolic blood pressure (DBP) according to Mancia (2007):

Classification	**SBP (mmHg)**	**DBP (mmHg)**
Optimal	<120	<80
Normal	120–129	80-89
Pre-hypertension	130-139	85-89
Grade 1 hypertension	140-159	90-99
Grade 2 hypertension	160-179	100-109
Grade 3 hypertension	>180	>110

Blood pressure profiles change with advanced years. SBP rises with age whereas DBP increases until around 50 years of age and decreases thereafter.[32] The reason for this outcome is that high blood pressure in younger individuals, is mainly caused by an increase in peripheral vascular resistance generated by narrowing of the resistance arteries and arterioles.[32] However, in older individuals, damage of the endothelium in larger conduit arteries becomes a more vital cause of high blood pressure.[32] Adaptation in large arteries results in arterial stiffening and a decreased vascular compliance, thereby reducing the protecting capacity of the arterial system.[33] As a result, progressive rise in SBP with age, accompanied by a decrease in DBP and a widening in pulse pressure (PP).[33] Subsequently, Cecil's Textbook of Medicine in 1927 stated that DBP is more important than SBP. It is important to bear in mind that those individuals whose DBP remains relatively low, in spite of high SBP, are decidedly less suitable to suffer cardiac disorder. This indicated an association of DBP with coronary and cerebral damage.[31] Thus, in patients younger than 50 years of age, a continued emphasis on both SBP and DBP remains appropriate.[32]

1.2.4.1.2. Mean arterial pressure (MAP)

Blood pressure is respectively characterized by its pulsatile and steady components. Literature states that the pulsatile component, estimated by PP, represents blood pressure variation and is affected by left ventricular ejection fraction, large-artery stiffness, early pulse wave reduction and HR.[34] The steady component, estimated by MAP, is a function of left ventricular contractility, HR and vascular resistance averaged over time.[34] MAP is a function of SBP and DBP. An uncomplicated way to calculate MAP is to determine the PP (SBP – DBP), then multiply the result with 1/3. Increased PP is therefore indicative of large artery disease and is also associated with increased cardiovascular risk.[34]

1.2.4.1.3. Pulse wave velocity (PWV)

Aging of the vasculature is influenced by structural changes of the arterial system.[35] Structural changes include degeneration of elastin, increases in collagen, hardening of the arterial wall and progressive dilation of the arteries.[35] These changes result in a gradual stiffening of the arteries and an increase in the velocity of the pressure wave as it moves through the cardiovascular system. [35] Arterial stiffening has been particularly implicated in the development of isolated systolic hypertension with considerable excess morbidity and mortality.[36] As changes can be detected before the appearance of clinically apparent vascular disease, arterial stiffness may act as a marker for the development of future atherosclerotic disease.[36]

The method to determine PWV is to acquire two blood flow waveforms by means of an ultrasound probe at two locations of an artery (carotid-radial artery). The delay in the arrival time of the flow wave at the two points of measurement divided by the distance between the two points provides the PWV. The distance of travel is determined by the separation of the two gaps at the two ends of a linear transducer as illustrated subsequently in figure 3.[37]

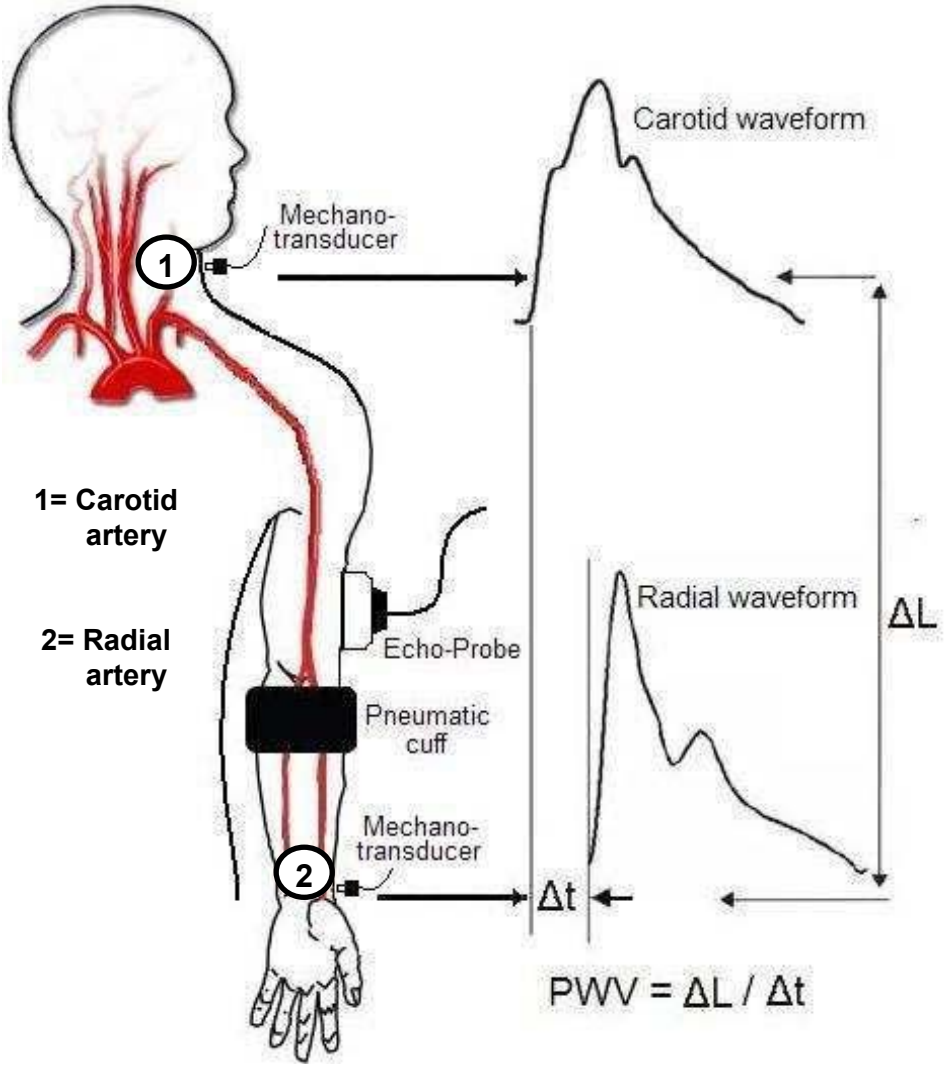

Figure 3 Schema of the instrumental approach employed to measure the carotid-radial pulse wave velocity (mechano-transducers) and brachial artery diameter (B-Mode echography).[37]

The rate of stiffening of arteries is different for each individual, and it can be used as a marker of the aging of the vascular system, the prognosis of systolic hypertension and the risk of vascular disease (atherosclerosis).[35,36] PWV is generally accepted as a simple, non-invasive, cost-effective and reproducible method to evaluate the arterial stiffness.[37]

For this reason, studying vascular stiffness has become an important part of studying CVD.

1.2.4.2. Biochemical analyses

1.2.4.2.1. Gamma-glutamyl transferase (GGT)

Although serum GGT is a non-specific marker of liver function and has traditionally been used as a marker of alcohol intake, it is increasingly regarded as a marker of CVD and the conditions associated with CVD such as the metabolic syndrome and oxidative stress.[38-40] Oxidative stress is an imbalance of the pro-oxidant anti-oxidant ratio in which insufficient anti-oxidants are produced or ingested or excessive oxidizing agents are produced leading to the reduced bioavailability of nitric oxide.[41] A reduced amount of nitric oxide, synthesized by the endothelium to maintain vascular homeostasis, will lead to an impaired vascular dilator tone causing a diminished vascular system.[42] The evidence is growing in favor of a detrimental role where GGT triggers a pro-oxidant action within the atherosclerotic plaque.[43] A prospective study with 163 944 Austrian adults studied for 17 years showed that GGT is independently associated with cardiovascular mortality.[43] Additionally Wannamethee et al. found that GGT significantly predicts CVD outcomes in a population with no history of CVD.[38] Consequently augmented serum GGT provides a bio-marker of oxidative stress in the vasculature, predicting CVD.[38,39]

1.2.4.2.2. C-reactive protein (CRP)

Several prospective clinical studies in different populations have established CRP as an important indicator for CVD risk.[44] CRP is an essential component of the immune system and is primarily produced by the liver as an acute phase reactive protein in response to inflammatory stimuli.[45] In addition; recent evidence supports a role for CRP in mediating atherothrombosis.[44]

Pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), interleukin 1 (IL-1), and interleukin-8 (IL-8) are known to contribute to the underlying cause of systemic inflammation that is indicated by excess CRP in the blood.[46] Therefore elevated serum CRP provides a sensitive biomarker of chronic systemic inflammation, an independent predictor of future cardiovascular events.[45]

1.2.4.2.3. Cholesterol

Elevated cholesterol (> 5.0 mmol/ℓ) is a major risk factor for CVD and forms part of the condition known as dyslipidaemia.[47] Consequently, dietary guidelines recommend limiting the amount of saturated and trans-fatty acids, and cholesterol in the diet.[48] Previous observational studies have shown an association between specific types of dietary fats and CVD risk.[48] Cardiovascular risk factors, such as blood lipids, appear to be less harmful at older ages and are therefore age-dependant.[48]

1.2.4.2.4. High density lipoprotein cholesterol (HDL-Cholesterol)

Increased levels of HDL-Cholesterol are considered to protect the cardiovascular system against atherosclerosis by promoting the efflux of excess cholesterol from cells, returning that cholesterol to the liver for secretion into the bile.[49] Low concentrations of HDL-Cholesterol (< 1.1 mmol/ℓ) have been known to be associated with an increased risk of developing CVD like coronary heart disease and the condition dyslipidaemia.[47,49] This increased risk remains in individuals treated with statins, even when very low concentrations of low density lipoprotein cholesterol (LDL-Cholesterol) are achieved.[50]

Thus, the low concentration of HDL-Cholesterol may be a conditioning factor for the persistence of the cardiovascular risk, regardless of treatment with statins.[50] In addition, HDL-Cholesterol seems to have a greater impact in women.[50] In the Framingham study, the risk of developing MI associated with a low HDL-Cholesterol concentration was greater in women than in men. In a few American studies, an increase in HDL-Cholesterol produced a greater cardiovascular benefit in women than in men.[50]

1.2.4.2.5. Triglycerides (TG)

The specific role of TG as a CVD risk factor has been controversial for some time.[51] Partially because TG have a high variability within individuals compared with biologically related and more stable factors such as serum cholesterol.[51]

The TG raise after consuming a high-fat serving of food is also associated with endothelial dysfunction, such as impairment in flow-mediated vasodilatation, which precedes the atherosclerotic lesion formation.[51] Observational studies have shown that TG levels reflect the presence lipoproteins that may promote atherosclerosis and are thus significant predictors of CVD. The rising TG levels (> 1.7 mmol/ℓ) in the population are thus a major concern and forms part of the condition dyslipidaemia.[47,51]

1.3. Overview

Over 80% of the world's deaths from cardiovascular disease occur in developing countries. In accordance to this essential statistic, there is an emerging burden of cardiovascular disease among acculturated Africans in South Africa. This vital evidence of increasing cardiovascular disease requires more exploration for additional clarification on the associations between cardiovascular variables and risk.

The combination of elevated gamma-glutamyl transferase, augmented cholesterol, increased blood pressure and total peripheral resistance will promote the risk for stiffened arteries detectable with the pulse wave velocity. Low body mass index may partly increase the potential for cardiovascular disease in Africans, though this issue has not yet been researched in South Africans.

1.4. Motivation

If body mass index decreases to lower values than the ideal body mass index, a J-curve may be evident suggesting higher prevalence of cardiovascular disease associated with low body mass index. These findings may imply that not only high body mass index but also a low body mass index may be a risk factor for cardiovascular disease, morbidity and mortality. Whether low body mass index associates with cardiovascular risk in an African population, remains unclear.

1.5. Aim

The aim of this part of the PURE study was to establish whether low body mass index is associated with cardiovascular function in an African population.

1.6. Hypothesis

There is a detrimental association of low BMI on variables of cardiovascular function in Africans.

1.7. References

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CHAPTER TWO

Manuscript

Journal of Human Hypertension

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Original Articles must include an extra table named ‘Summary Table’, with two parts: 'What is known about topic’ and 'What this study adds'.

Abstract: (200 words) A short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results and the main conclusion.

Keywords: Three to six keywords for indexing.

Introduction: The Introduction should assume that the reader is knowledgeable in the field and should therefore be as brief as possible but can include a short historical review where desirable.

Methods: This section should contain sufficient detail, so that all experimental procedures can be reproduced, and include references

Results: The Results section should briefly present the experimental data in text, tables or figures. Tables and figures should not be described extensively in the text, either.

Discussion: The discussion should focus on the interpretation and the significance of the findings with concise objective comments that describe their relation to other work in the area. It should not repeat information in the results. The final paragraph should highlight the main conclusion(s), and provide some indication of the direction future research should take.

Reference: We request a maximum of 35 references. References should follow the Vancouver format. In the text they should appear as numbers starting at one and at the end of the paper they should be listed (double-spaced) in numerical order corresponding to the order of citation in the text. All authors should be quoted for papers with up to six authors; for papers with more than six authors, the first six only should be quoted, followed by et al.

For example:
Gasowski J, Fagard RH, Staessen JA, Grodzicki T, Pocock S, Boutitie F et al. Pulsatile blood pressure component as predictor of mortality in hypertension: a meta-analysis of clinical trial control groups. *J Hypertens* 2002; **20**: 145–151.

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Low body mass index and the associations with cardiovascular function in Africans: the PURE study

Running Head: Low body mass index in Africans

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Summary Table

What is known about topic
• Most studies were done in developed countries and have reported a J-shaped association between body mass index and all-cause mortality, suggesting an increase in cardiovascular disease risk in both high and low body mass index groups. • Cross-sectional studies investigated the effect of low body mass index on cardiovascular function with cardiovascular risk factors like diabetes mellitus and unfavorable lipid profiles. • Low body mass index is considered an independent risk factor for cardiovascular disease in some developed countries as well in a few developing countries.
What this study adds
• A J-shaped association between low body mass index and cardiovascular disease markers, suggesting an increase in cardiovascular disease risk in both high and low body mass index Africans living in South Africa. • A cross-sectional cohort study investigated the effect of low body mass index for cardiovascular function with cardiovascular disease markers like pulse wave velocity, gamma-glutamyl transferase and blood pressure profiles. • The detrimental effect of low body mass index on cardiovascular function in an African black population.

ABSTRACT

We aimed to assess the association between low body mass index (BMI) and markers of cardiovascular function like carotid-radial pulse wave velocity (c-r PWV), blood pressure and biochemical variables in Africans aged 35-65 years with low socio-economic status; N= 496. Africans were stratified into a low BMI group with BMI ≤ 20 kg/m^2 and a normal BMI group with BMI > 20 kg/m^2 and ≤ 25 kg/m^2. Blood pressure (OMRON HEM-757) was recorded and the Complior SP device determined c-r PWV. African men with low BMI revealed an increased arterial stiffness with significantly higher c-r PWV (12.6 ± 2.47 m/s) compared to the normal BMI group (11.6 ± 2.00 m/s). The significant higher c-r PWV remained after adjusting for known confounders. The unadjusted BMI scatter plot illustrated a negative tendency towards c-r PWV in Africans. Stepwise regression analyses indicated a negative c-r PWV association with BMI in African men. When c-r PWV was adjusted for age, smoking, alcohol, mean arterial pressure and heart rate a J-curve was evident suggesting a detrimental effect of low BMI on cardiovascular function in Africans. Low BMI may contribute to the high prevalence of CVD, morbidity and mortality within a developing country like South Africa.

Word Count: 200

Keywords: Africans, cardiovascular function, low BMI.

INTRODUCTION

Cardiovascular disease (CVD) is known as one of the leading causes of death worldwide, where low income countries or developing countries have the highest prevalence for CVD.[1] According to the literature, low socio-economic status (SES) is inversely related to cardiovascular health and related to morbidity and mortality.[2,3] One of the main reasons for this prominent statistics is behavioral lifestyle factors.[2] With Sub-Saharan Africa's population of 650 million and increasing acculturation, hypertension has now proliferated into a major problem.[4] "The African Union has called hypertension one of the continent's greatest health challenges after AIDS."[4] Acculturation is associated with hypertension in black South Africans (Africans), living in informal settlements with low SES in the North-West province.[5] The medical consequences of the expected significant increase in the burden of CVD will be catastrophic for the developing countries.[6] Cost-analyses showed that these developing countries cannot afford the same treatment for CVD as developed countries.[4] As indicated by Panagiotakos (2008), the important lifestyle risk factors of CVD are: unhealthy dietary habits and alcohol and tobacco use.[3] These risk factors can cause increased blood pressure, blood glucose and lipid levels.[1]

High body mass index (BMI) is known to be associated with CVD.[7,8] There has been much emphasis on obesity as a risk factor for CVD and mortality, [9-11] and less focus on possible CVD risk associations with low BMI.[12-14] According to Higashi (2003) a BMI of 22.2 kg/m^2 is associated with the lowest morbidity, an epidemiologic study conducted in Japan.[15] In accordance with the World Health Organization, the median BMI should be in the range of 21 to 23 kg/m^2 to achieve optimum health.[7] This range has the lowest morbidity and mortality. If the BMI decreases to lower values a J-curve will be evident between BMI and cardiovascular disease suggesting higher prevalence of cardiovascular disease associated with low BMI.[9,14,16-18] These findings imply that not only high BMI but also a low BMI may be a risk factor for cardiovascular disease, morbidity and mortality.[15,17]

Low BMI was found to be an independent risk factor in a Western country for mortality and stroke in the Systolic Hypertension in the Elderly Program (SHEP), a placebo-controlled, randomized, clinical trial of antihypertensive therapy for isolated systolic hypertension.[9] In a South India study (low SES) a significant number of

hypertensive patients with low BMI had myocardial infarction (MI), but not those with a higher BMI (Risk of developing MI [Odds Ratio = 2.94; $P < 0.05$]).[18] In addition, Vikram et al., (2003) concluded that non-obese Indians with a BMI lower than 25 kg/m^2 and normal waist circumference had higher cardiovascular risk compared to obese Indians.[13] The relationship between socio-economic factors and diet has been examined on the basis of food and nutrient intake.[4] Persons from socio-economically disadvantaged backgrounds with a detrimental food intake tendency leads to higher rates of chronic disease.[3] Low BMI and the association with mortality have often been explained as being due to confounders like smoking or a pre-existing illness.[9] However, studies that control for confounders still found a J-shaped relationship.[9,13,15,16] Probably low BMI may contribute to the high incidence of CVD mortality within developing countries.

Whether low BMI is associated with CVD and risk in an African population remains unclear. Therefore the aim of this study was to investigate the possible associations of low BMI with markers of cardiovascular function in Africans.

METHODS

Study design

This sub-study of the larger PURE (Prospective Urban and Rural Epidemiology) study is a cross-sectional prospective cohort study in which the health transition in urban and rural subjects was investigated.

Participants and experimental protocol

The study was performed in the North-West Province of South Africa where a total of 2 010 Africans were randomly recruited from a rural and urban setting during the year of 2005. The head of each household gave signed consent. If a person refused or was not at home, the next house randomly selected was utilized. Participants within our sub-study, were selected. They have an apparently low socio-economic status (SES) with an average daily income of R25.80. From the data obtained, a selection of possible subjects older than 35 years of age with no reported chronic diseases of lifestyle was made. Participants were mobilized from their communities by the research team and moved to the research locality arriving at 07:30. All measurements were done in the morning. All subjects were informed about the objectives and procedures of the study prior to participation. Trained field workers assisted and were available to provide information in the participants' language of preference (Setswana-speaking).

The exclusion criteria for this sub-study was participants aged 65 years and older, a history of tuberculosis (TB) or human immunodeficiency virus (HIV) infected, an ear temperature greater than 37°C, blood donors and individuals vaccinated in the previous three months, reducing the overall group to less than 1000 participants. HIV status was determined with the First Response (PMC Medical, India) rapid HIV card test using whole blood. If tested positive, the test was repeated with the Pareeshak (BHAT Bio-tech India) card test. For this sub-study these subjects were further sub-divided into two groups. The first group consisted of Africans with a low BMI smaller or equal to 20 kg/m^2 (Men; N= 152, women; N= 94) whilst the second group consisted of Africans with a normal BMI larger than 20 kg/m^2 and smaller or equal to 25 kg/m^2 (Men; N= 100, women; N= 150). The remaining participants had BMI's larger than 25kg/m^2 and were only used to illustrate the J-curve effect in overweight and obese subjects compared to the normal and low BMI subjects (figure 2.1-2.3).

Ethical considerations

An informed consent form was signed by all the participants prior to the commencement of measurements. Permission for the execution of this study was obtained from the provincial Department of Health, the local authorities, as well as the tribal Chief from the specific rural area. The study protocol complies with the Declaration of Helsinki[19] as revised in 2008 and was approved by the Ethics Review Board of the North-West University, Potchefstroom, South Africa.

Questionnaires

The participants were interviewed using structured demographic, socio-economic and lifestyle questionnaires developed and standardized for the international PURE study.[20] Lifestyle data included self-reported current tobacco use, alcohol intake as well as medical history.

Anthropometric measurements

Anthropometric measurements were done by registered biokineticists. Standardized procedures were used to measure the height (Invicta Stadiometer, IP 1465, Leicester, UK), weight (Precision Health Scale, A & D Company, Tokyo, Japan), and hip- and waist circumference of each participant (Holtain unstretchable metal tape) with the guidelines as indicated by Marfell-Jones (2005).[21]

Cardiovascular measurements

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were obtained with the validated OMRON HEM-757 device (London, UK). The difference between SBP and DBP was used for pulse pressure (PP). Two blood pressure measurements were performed on the right arm (brachial artery), with a 5 minute rest period between the two measurements, from which the last value was used while the participants were seated upright and relaxed. The Carotid-radial pulse wave velocity (c-r PWV) was measured. This noninvasive measurement of arterial stiffness, (Mattace-Raso, 2004:112) was determined on the left side between the carotid-radial arteries of each participant with the Complior SP device (Artech-Medical, Pantin, France).

Blood and serum samples

After the blood was drawn from the antebrachial vein using a sterile winged infusion set and syringes by a registered nurse, the cardiovascular measurements were done. Serum was prepared according to appropriate methods and stored at -80°C in the laboratory. In the remote areas serum was stored under dry ice (no longer than five days) until it could be transported to the laboratory facility.

Biochemical analyses

Quantitative determinations of the total cholesterol (TC), high density lipoprotein cholesterol (HDL-Cholesterol), triglyceride (TG), gamma-glutamyl transferase (GGT) and high sensitivity C-reactive protein (hs-CRP) were targeted from the serum samples and measured utilizing a Sequential Multiple Analyzer Computer (SMAC) Konelab20i™ auto-analyzer (Thermo Fisher Scientific Oy, Vantaa, Finland).

Data analyses

Data analyses were performed using the Statistica 10 software.[22] Normal distributions of the variables were determined with the Shapiro-Wilk's analyses while T-tests were used to determine significant differences between independent groups and reported as arithmetic mean ± standard deviation (SD). The Chi square statistical test was used to determine proportions. Subsequently, one way ANCOVA's, followed with the least square means test, were used to determine BMI group differences independent of age, smoking and alcohol consumption and reported mean with 95% confidence interval (CI). Pearson correlations were performed as well as partial correlations. Partial correlations, which were adjusted for age, smoking and alcohol consumption, determined associations between the BMI and cardiovascular variables. Linear multiple stepwise regression analyses in covariates determined associations between BMI and cardiovascular variables, stratified for each gender and BMI group. Significant values were noted as $p \leq 0.05$. Figures 2.1-2.3 were determined by calculating the average value of a specific endpoint for each BMI value expressed as a whole number.

RESULTS

Descriptive characteristics (table 1.1-1.2)

The descriptive characteristics were presented of the African men and women stratified in low and normal BMI groups. Mean values indicated that African men and women had no significant age differences between low and normal BMI groups. Anthropometric measurements showed that the BMI mean values for African men with low and normal BMI were 17.9 ± SD 1.41 kg/m^2 and 21.8 ± SD 1.27 kg/m^2 respectively. The BMI mean values for African women with low and normal BMI were 17.7 ± SD 1.75 kg/m^2 and 22.7 ± SD 1.37 kg/m^2 respectively. The mean values for the African men with low BMI (table 1.1) for cardiovascular variables indicated higher DBP (88.0 ± SD 13.4 mmHg) reaching pre-hypertensive status,[23,24] MAP (103.8 ± SD 14.4 mmHg), HR and c-r PWV (12.6 ± SD 2.47 m/s) compared to the normal BMI group; DBP (84.2 ± SD 12.2 mmHg), MAP (100.0 ± SD 13.2 mmHg) and c-r PWV (11.6 ± SD 2.00 m/s). The African women with low BMI (table 1.2) only had a significant higher c-r PWV (11.3 ± SD 2.43 m/s) compared to the normal BMI group (10.6 ± SD 2.10 m/s). Biochemical analyses indicated significant higher cholesterol and TG values for the African men with normal BMI (table 1.1) compared to the low BMI group. In addition to this outcome, HDL-Cholesterol for African women with low BMI (table 1.2) was higher compared to the women with normal BMI. Lifestyle factors showed that 74% (p= 0.011) of the African men with low BMI were smoking and 70% (p= 0.062) were consuming alcohol whereas 59% (p= 0.011) of the African men with normal BMI were smoking and 59% (p= 0.062) were consuming alcohol. African women with low BMI showed that 67% (p= 0.028) were smoking and 47% (p= 0.046) were consuming alcohol whereas 53% (p= 0.028) of the African women with normal BMI were smoking and 34% (p= 0.046) were consuming alcohol.

Analyses of covariance (ANCOVA) (table 2)

In African men (adjusted for age, smoking and alcohol consumption, PWV was additionally adjusted for MAP and HR), we revealed that DBP (88.0 with CI [86.0-90.0] mmHg) and c-r PWV (12.5 with CI [12.1-12.9] m/s) remained significantly higher in the low BMI group compared to the normal BMI group; DBP (84.2 with CI [81.8-86.6] mmHg) and c-r PWV (11.7 with CI [11.3-12.2] m/s). African women with low BMI also sustained a significantly higher value for c-r PWV (11.3 with CI [10.8-11.7] m/s) compared to the normal BMI group (10.7 with CI [10.3-11.0] m/s).

Pearson and partial correlations (table 3.1-3.2)

In African men with low BMI, BMI correlated negatively with c-r PWV (r= -0.204; p= 0.012 and r= -0.200; p= 0.020 for Pearson and partial correlations respectively). GGT showed a similar partial correlation of r= -0.181; p= 0.034 in African men with low BMI. HDL-Cholesterol correlated significantly within the low BMI group (r= -0.167; p= 0.045). The combined low- and normal BMI group for African women (table 3.2) indicated a partial correlation of r= -0.162; p= 0.017 for c-r PWV and BMI. CRP for African women with low BMI had an un-adjusted correlation with BMI of r= -0.381; p= <0.001 and an adjusted correlation with BMI of r= -0.344; p=0.001.

Figure 1 illustrates DBP and c-r PWV as a function of low BMI in African men and women. A negative correlation is evident between BMI and c-r PWV in both African men (r= -0.28; p<0.001) and women (r= -0.18; p=0.008). In addition to this tendency we can further notice in figure 2.1-2.3 where the variables are adjusted for age, smoking and alcohol that DBP, PWV and GGT tend to illustrate a typical J-curve pattern, particularly in the African men.

Linear multiple stepwise regression analyses of African men showed a tendency that c-r PWV were negatively influenced by a low BMI (Adjusted R^2= 0.113, b*= -0.246, p= <0.001).

Table 1.1 Descriptive characteristics of African men with low and normal body mass index

Variables	**Low BMI (BMI ≤20) N= 152**	**Normal BMI (20< BMI ≤25) N= 100**	**P-value**
Age (years)	47.9 ± 8.06	49.7 ± 7.3	0.078
Anthropometric measurements			
Body mass index (kg/m²)	**17.9 ± 1.41**	**21.8 ± 1.27**	**<0.001**
Waist circumference (cm)	**69.8 ± 5.55**	**78.9 ± 4.97**	**<0.001**
Hip circumference (cm)	**81.8 ± 4.34**	**89.2 ± 3.97**	**<0.001**
Height (cm)	1.67 ± 0.07	1.68 ± 0.07	0.312
Weight (kg)	**50.0 ± 5.73**	**61.4 ± 6.10**	**<0.001**
Cardiovascular variables			
Systolic blood pressure (mmHg)	135.5 ± 19.5	131.7 ± 18.3	0.122
Diastolic blood pressure (mmHg)	**88.0 ± 13.4**	**84.2 ± 12.2**	**0.022**
Mean arterial pressure (mmHg)	**103.8 ± 14.4**	**100.0 ± 13.2**	**0.035**
Pulse pressure (mmHg)	47.5 ± 13.4	47.5 ± 11.2	0.979
Heart rate (bpm)	**71.4 ± 18.2**	**65.8 ± 13.9**	**0.009**
Carotid-radial pulse wave velocity (m/s)	**12.6 ± 2.47**	**11.6 ± 2.00**	**0.001**
Biochemical analyses			
Gamma-glutamyl transferase (mmol/ℓ)	130.6 ± 162.8	162.2 ± 457.7	0.453
hs C-reactive protein (mg/ℓ)	2.67 ± 5.51	1.79 ± 4.54	0.068
Cholesterol (mmol/ℓ)	**4.82 ± 1.41**	**5.12 ± 1.26**	**0.036**
HDL-cholesterol (mmol/ℓ)	1.83 ± 0.68	1.67 ± 0.67	0.090
Triglycerides (mmol/ℓ)	**0.99 ± 0.38**	**1.30 ± 1.06**	**0.002**
Lifestyle factors			
Smoking N (%)	**113 (74.3)**	**59 (59.0)**	**0.011**
Alcohol N (%)	107 (70.4)	59 (59.0)	0.062

Data presented as arithmetic mean ± standard deviation (SD). Where lifestyle factors are presented as N (%).

Numbers in bold represent statistical significance at $p \leq 0.05$. BMI, body mass index (kg/m²); hs, high sensitive; HDL, high density lipoprotein; N, number of participants.

Table 1.2 Descriptive characteristics of African women with low and normal body mass index

Variables	**Low BMI (BMI ≤20) N= 94**	**Normal BMI (20< BMI ≤25) N= 150**	**P-value**
Age (years)	47.8 ± 7.15	48.9 ± 7.77	0.269
Anthropometric measurements			
Body mass index (kg/m²)	**17.7 ± 1.75**	**22.7 ± 1.37**	**<0.001**
Waist circumference (cm)	**64.3 ± 4.20**	**74.3 ± 5.72**	**<0.001**
Hip circumference (cm)	**82.5 ± 4.95**	**94.4 ± 6.40**	**<0.001**
Height (cm)	1.57 ± 0.07	1.58 ± 0.07	0.188
Weight (kg)	**43.5 ± 5.41**	**56.6 ± 5.72**	**<0.001**
Cardiovascular variables			
Systolic blood pressure (mmHg)	126.8 ± 21.1	127.0 ± 20.8	0.944
Diastolic blood pressure (mmHg)	85.9 ± 13.7	85.6 ± 14.4	0.888
Mean arterial pressure (mmHg)	99.5 ± 15.6	99.4 ± 16.1	0.958
Pulse pressure (mmHg)	41.0 ± 11.8	41.4 ± 10.3	0.751
Heart rate (bpm)	77.6 ± 18.7	75.4 ± 14.8	0.296
Carotid-radial pulse wave velocity (m/s)	**11.3 ± 2.43**	**10.6 ± 2.10**	**0.026**
Biochemical analyses			
Gamma-glutamyl transferase (mmol/ℓ)	91.9 ± 161.4	96.9 ± 172.2	0.824
hs C-reactive protein (mg/ℓ)	1.67 ± 5.02	1.81 ± 3.76	0.670
Cholesterol (mmol/ℓ)	5.10 ± 1.46	5.17 ± 1.36	0.715
HDL-cholesterol (mmol/ℓ)	**1.85 ± 0.77**	**1.62 ± 0.63**	**0.011**
Triglycerides (mmol/ℓ)	1.17 ± 0.61	1.32 ± 0.77	0.137
Lifestyle factors			
Smoking N (%)	**63 (67.0)**	**78 (52.7)**	**0.028**
Alcohol N (%)	**44 (46.8)**	**51 (34.0)**	**0.046**

Data presented as arithmetic mean ± standard deviation (SD). Where lifestyle factors are presented as N (%). Numbers in bold represent statistical significance at $p \leq 0.05$. BMI, body mass index (kg/m²); hs, high sensitive; HDL, high density lipoprotein; N, number of participants.

Table 2 Adjusted variables of Africans with low and normal body mass index

	Low BMI (BMI ≤20)	**Normal BMI (20< BMI ≤25)**	
	Men		
Variables	**N= 152**	**N= 100**	**P-value**
Cardiovascular variables			
Systolic blood pressure (mmHg)	135.7 (132.8-138.5)	131.5 (128.0-135.0)	0.074
Diastolic blood pressure (mmHg)	**88.0 (86.0-90.0)**	**84.2 (81.8-86.6)**	**0.019**
Carotid-radial pulse wave velocity (m/s)	**12.5 (12.1-12.9)**	**11.7 (11.3-12.2)**	**0.011**
Biochemical analyses			
Cholesterol (mmol/ℓ)	4.85 (4.63-5.07)	5.17 (4.89-5.45)	0.081
HDL-cholesterol (mmol/ℓ)	1.82 (1.71-1.93)	1.68 (1.54-1.81)	0.110
Triglycerides (mmol/ℓ)	**0.99 (0.86-1.11)**	**1.31 (1.16-1.46)**	**0.001**
	Women		
	N= 94	**N= 150**	
Cardiovascular variables			
Systolic blood pressure (mmHg)	126.6 (122.5-130.7)	127.5 (124.2-130.8)	0.730
Diastolic blood pressure (mmHg)	85.5 (82.7-88.3)	86.0 (83.8-88.2)	0.791
Carotid-radial pulse wave velocity (m/s)	**11.3 (10.8-11.7)**	**10.7 (10.3-11.0)**	**0.046**
Biochemical analyses			
Cholesterol (mmol/ℓ)	5.12 (4.83-5.41)	5.16 (4.91-5.38)	0.848
HDL-cholesterol (mmol/ℓ)	**1.84 (1.71-1.97)**	**1.63 (1.53-1.74)**	**0.018**
Triglycerides (mmol/ℓ)	1.17 (1.03-1.31)	1.32 (1.20-1.43)	0.115

Mean ± 95% confidence interval (CI). Adjusted for age, smoking and alcohol. Where PWV was additionally adjusted for MAP and HR. Numbers in bold represent statistical significance at $p \leq 0.05$. BMI, body mass index (kg/m²); HDL, high density lipoprotein; PWV, pulse wave velocity; MAP, mean arterial pressure; HR, heart rate; N, number of participants.

Table 3.1 Correlations of variables within African men with low, normal and combined body mass index

	Low BMI (BMI ≤20)		**Normal BMI (20< BMI ≤25)**		**Low and normal BMI (BMI ≤25)**	
Variables	**Pearson**	**Partial**	**Pearson**	**Partial**	**Pearson**	**Partial**
Cardiovascular variables						
Systolic blood pressure (mmHg)	r= 0.141	r= 0.156	r= 0.061	r= 0.030	r= -0.015	r= -0.016
	p= 0.083	p= 0.069	p= 0.548	p= 0.777	p= 0.817	p= 0.806
Diastolic blood pressure (mmHg)	r= -0.029	r= -0.025	r= 0.047	r= 0.048	r= -0.119	r= -0.114
	p= 0.723	p= 0.767	p= 0.645	p= 0.655	p= 0.059	p= 0.085
Carotid-radial pulse wave velocity (m/s)	**r= -0.204**	**r= -0.200**	r= -0.172	**r= -0.228**	**r= -0.279**	**r= -0.240**
	p= 0.012	**p= 0.020**	p= 0.093	**p= 0.041**	**p= <0.001**	**p= <0.001**
Biochemical analyses						
Gamma-glutamyl transferase (mmol/ℓ)	**r= -0.182**	**r= -0.181**	r= -0.123	r= -0.123	r= -0.032	r= -0.015
	p= 0.031	**p= 0.034**	p= 0.236	p= 0.244	p= 0.633	p= 0.825
hs C-reactive protein (mg/ℓ)	r= -0.024	r= -0.021	r= 0.100	r= 0.109	r= -0.086	r= -0.063
	p= 0.778	p= 0.812	p= 0.339	p= 0.304	p= 0.189	p= 0.340
Cholesterol (mmol/ℓ)	r= 0.061	r= 0.061	r= 0.055	r= 0.033	**r= 0.145**	**r= 0.129**
	p= 0.471	p= 0.475	p= 0.601	p= 0.758	**p= 0.026**	**p= 0.050**
HDL-cholesterol (mmol/ℓ)	**r= -0.167**	r= -0.168	**r= -0.315**	**r= -0.283**	**r= -0.217**	**r= -0.201**
	p= 0.045	p= 0.490	**p= 0.002**	**p= 0.007**	**p= 0.001**	**p= 0.002**
Triglycerides (mmol/ℓ)	**r= 0.166**	r= 0.174	r= 0.158	r= 0.143	**r= 0.248**	**r= 0.250**
	p= 0.049	p= 0.400	p= 0.129	p= 0.176	**p= <0.001**	**p= <0.001**

Partial correlations were adjusted for age, smoking and alcohol. Where PWV was additionally adjusted for MAP and HR. Numbers in bold represent statistical significance at $p \leq 0.05$. BMI, body mass index (kg/m²); hs, high sensitive; HDL, high density lipoprotein; PWV, pulse wave velocity; MAP, mean arterial pressure; HR, heart rate.

Table 3.2 Correlations of variables within African women with low, normal and combined body mass index

	Low BMI (BMI ≤20)		**Normal BMI (20< BMI ≤25)**		**Low and normal BMI (BMI ≤25)**	
Variables	**Pearson**	**Partial**	**Pearson**	**Partial**	**Pearson**	**Partial**
Cardiovascular variables						
Systolic blood pressure (mmHg)	r= 0.091	r= 0.179	r= 0.046	r= 0.054	r= 0.039	r= 0.069
	p= 0.381	p= 0.098	p= 0.575	p= 0.527	p= 0.548	p= 0.300
Diastolic blood pressure (mmHg)	r= 0.043	r= 0.112	r= 0.001	r= 0.017	r= 0.002	r= 0.041
	p= 0.684	p= 0.302	p= 0.991	p= 0.841	p= 0.974	p= 0.536
Carotid-radial pulse wave velocity (m/s)	r= -0.035	r= -0.042	r= -0.157	r= -0.153	**r= -0.176**	**r= -0.162**
	p= 0.743	p= 0.708	p= 0.065	p= 0.079	**p= 0.007**	**p= 0.017**
Biochemical analyses						
Gamma-glutamyl transferase (mmol/ℓ)	**r= -0.187**	r= -0.172	r= 0.008	r= 0.045	r= -0.026	r= 0.036
	p= 0.077	p= 0.112	p= 0.929	p= 0.601	p= 0.698	p= 0.584
hs C-reactive protein (mg/ℓ)	**r= -0.381**	**r= -0.344**	r= 0.055	r= 0.053	r= -0.056	r= -0.044
	p= <0.001	**p= 0.001**	p= 0.515	p= 0.533	p= 0.392	p= 0.512
Cholesterol (mmol/ℓ)	r= 0.153	r= 0.170	**r= 0.179**	**r= 0.177**	r= 0.108	r= 0.109
	p= 0.149	p= 0.114	**p= 0.032**	**p= 0.038**	p= 0.099	p= 0.101
HDL-cholesterol (mmol/ℓ)	r= -0.005	r= 0.024	**r= -0.173**	r= -0.155	**r= -0.188**	**r= -0.165**
	p= 0.996	p= 0.828	**p= 0.038**	p= 0.069	**p= 0.004**	**p= 0.013**
Triglycerides (mmol/ℓ)	r= 0.171	**r= 0.271**	**r= 0.190**	**r= 0.196**	**r= 0.177**	**r= 0.201**
	p= 0.107	**p= 0.011**	**p= 0.024**	**p= 0.021**	**p= 0.007**	**p= 0.002**

Partial correlations were adjusted for age, smoking and alcohol. Where PWV was additionally adjusted for MAP and HR. Numbers in bold represent statistical significance at $p \leq 0.05$. BMI, body mass index (kg/m²); hs, high sensitive; HDL, high density lipoprotein; PWV, pulse wave velocity; MAP, mean arterial pressure; HR, heart rate.

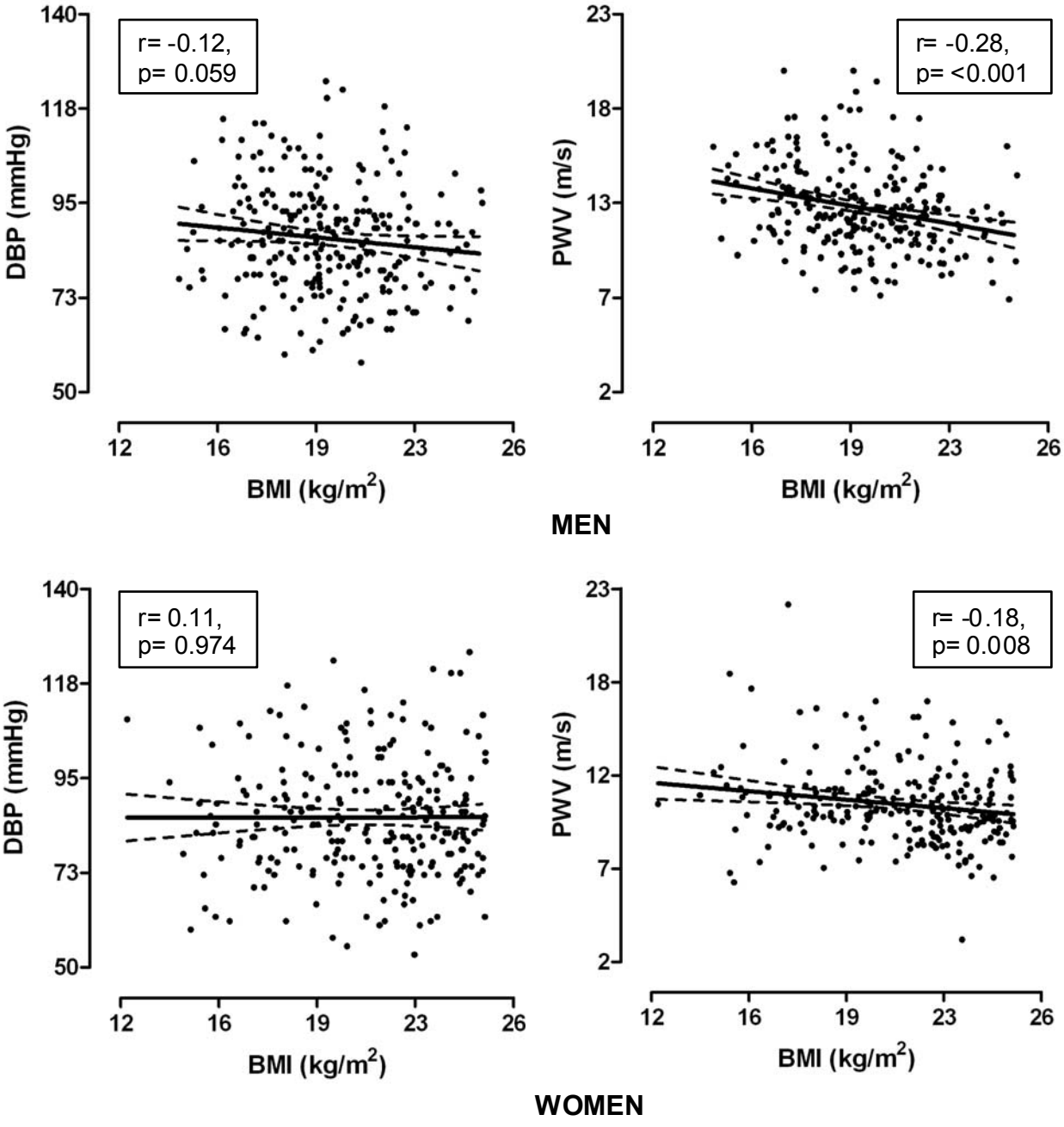

Figure 1 Diastolic blood pressure (DBP) and carotid-radial pulse wave velocity (c-r PWV) as a function of body mass index (BMI) in African men and women.

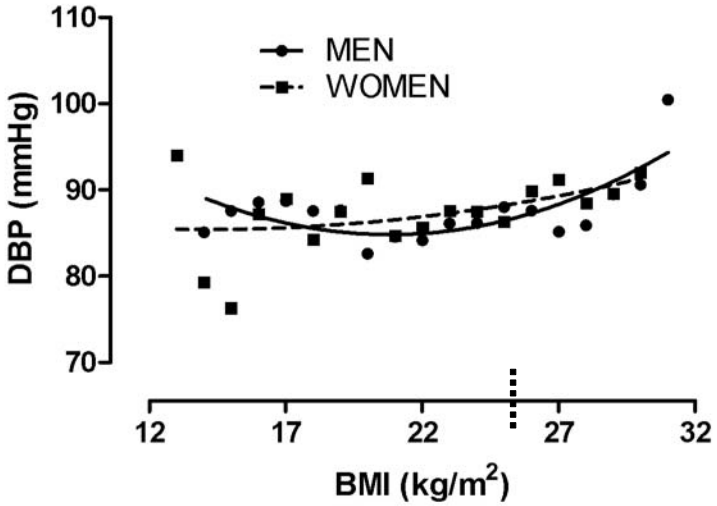

Figure 2.1 Diastolic blood pressure (DBP) as a function of body mass index (BMI). Adjusted for age, smoking and alcohol. Dotted line on the x-axis indicates the borderline (25 kg/m^2) between normal BMI and overweight BMI.

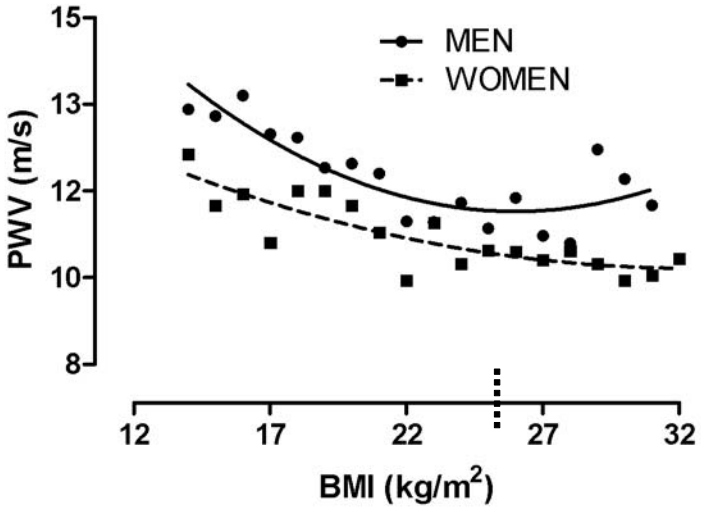

Figure 2.2 Carotid-radial pulse wave velocity (c-r PWV) as a function of body mass index (BMI). Adjusted for age, smoking and alcohol. Dotted line on the x-axis indicates the borderline (25 kg/m^2) between normal BMI and overweight BMI.

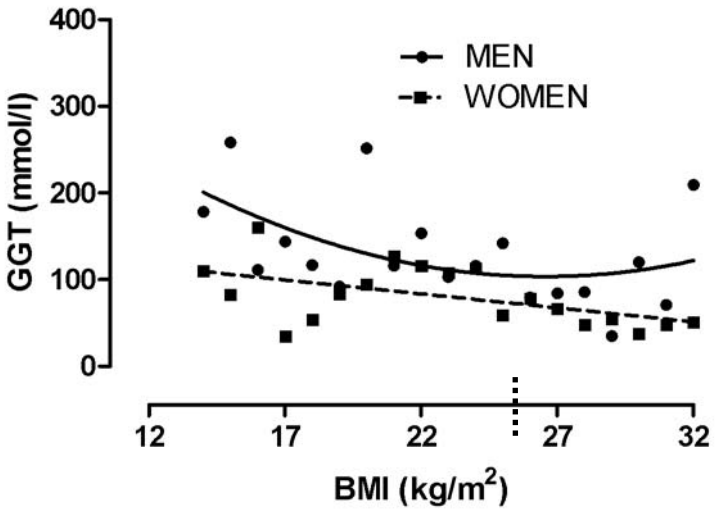

Figure 2.3 Gamma-glutamyl transferase (GGT) as a function of body mass index (BMI). Adjusted for age, smoking and alcohol. Dotted line on the x-axis indicates the borderline (25 kg/m^2) between normal BMI and overweight BMI.

DISCUSSION

This sub-study of the prospective cohort study (PURE) was conducted to determine the associations of low BMI with variables of cardiovascular function in Africans.

Our results indicated that c-r PWV is significantly and negatively associated with BMI in African men (table 3.1). In the African women (table 3.2), this association tended to be lacking in both low and normal BMI groups except for the low- and normal BMI combined group. However, in figure 1 (unadjusted), this negatively associated trend can be noticed between BMI and PWV in both African men and women. In addition to this tendency we further noticed that DBP, PWV and GGT against BMI particularly in African men illustrated a typical J-curve pattern where the variables were adjusted for age, smoking and alcohol intake (figure 2.1-2.3).

Arterial stiffness is an independent predictor of adverse cardiovascular events, including mortality.[25] Schutte et al., (2010) indicated that arteries stiffen with advanced age, even in the absence of vascular disease.[26] An increased arterial stiffness is reflected by an increase in PWV, which is largest in the elastic aorta.[26] Even though most emphasis is placed on the functioning of central arteries like the aorta, the clinical relevance of the peripheral muscular arteries (radialis) has also increasingly been recognized.[26] C-r PWV is therefore a marker for CVD. SBP and DBP were higher in African men with low BMI compared to the normal BMI which could be an indication of stiffened arteries (table 1.1), as well as an increase in peripheral vascular resistance generated by narrowing and stiffening of the resistance arteries and arterioles, as mentioned before.[26] Hence accentuating the importance of PWV as a risk marker for CVD. In our results the c-r PWV against BMI for African men revealed a prominent J-curve in figure 2.2.

According to Calle (1999), literature examining the relation between body weight and mortality supports the hypothesis of a curvilinear relation, in which the CVD risk is increased among low and high BMI. [9,13,17,18]

Opposing studies criticize that many of the studies that found an increased cardiovascular disease risk to be associated with low BMI have been failed to

exclude smokers and people with coexisting illness.[27] In a prospective study conducted in the U.S.A. the relationship between BMI and mortality from all causes differed according to smoking status and the presence or absence of a history of CVD.[27] Low BMI was most strongly associated with an increased risk of mortality among current or former smokers.[27] We have adjusted for smoking and alcohol consumption and excluded HIV infected participants from this study. After we adjusted the results, the negative association between CVD risk markers like c-r PWV and DBP with low BMI still existed especially in the African men. C-r PWV was additionally adjusted for MAP and HR and still this negative association persisted.

Lifestyle factors like smoking and alcohol consumption were high in the low BMI group (74.3% and 70.4% respectively). These detrimental behavioral lifestyle factors of individuals within low socio-economic conditions have a harmful effect on the cardiovascular system and overall health.[1,4] According to van Rooyen et al. (2000), these behavioral lifestyle changes are associated with hypertension in Africans, with unhealthy dietary habits and tobacco and alcohol use.[5] High alcohol consumption is detectable with serum GGT and is one of the most suitable biomarkers obtainable for identifying alcohol abuse in most populations.[28] According to Pisa (2010), increased alcohol consumption in Africans is associated with higher HDL-Cholesterol levels and increased blood pressure values.[28] Increased HDL-Cholesterol and blood pressure was noticeable for African men (table 1.1). We have adjusted GGT for alcohol consumption and we still found a significant negative GGT correlation in African men with low BMI ($r= -0.181$; $p= 0.034$). The GGT values can be noticed with a similar J-curve pattern as PWV and DBP (see figure 2.3).

In accordance with these findings, literature mentioned that serum GGT has conventionally been used as a marker of alcohol intake and as a non-specific marker of liver function. GGT is increasingly regarded as a marker of CVD and the conditions associated with CVD such as oxidative stress, leading to the reduced bioavailability of nitric oxide.[28-31] Furthermore Wannamethee (2008) indicated that GGT contributed to PWV in a prospective study of 6997 men aged 40-59 with no history of CVD or diabetes.[31] Whether high alcohol consumption or GGT is responsible for this harmful effects in African men remain uncertain and it could have an added negative influence on the stiffness and vascular damage contributing to

CVD.[31,32] These associations suggest that c-r PWV (arterial stiffness), DBP (pre-hypertension) and GGT (oxidative stress) in African men and in a lesser extent in African women play a possible role in associating negative cardiovascular function with low BMI, supporting the J-curve theory.

Our study must be further interpreted within the context of its limitations. In this study causality could not be inferred. We also need to compare data of Africans with data of Caucasians and recent measurements with additional focus on target organ damage in other organs. Lastly, for this study the carotid-radialis PWV was measured instead of the carotid-femoralis PWV.

In conclusion, a detrimental effect of low BMI is evident on cardiovascular function in Africans even after excluding participants with known chronic disease and adjusted for age, smoking and alcohol consumption. If BMI decreases from the optimum value to lower values, a J-curve between BMI and cardiovascular variables is evident suggesting a higher risk of developing CVD and detrimental cardiovascular function associated with low BMI.[7,14]

C-r PWV, DBP and GGT significantly higher in African men with low BMI whereas the key J-curve was indicated in the c-r PWV, thus supporting the theory that stiffening of the arteries are evident in Africans with a low BMI. Low BMI may contribute to the high prevalence of CVD mortality within low income countries and therefore increase the risk for CVD.

ACKNOWLEDGEMENTS

The author acknowledged the contributions of the PURE team members and participants. Dr S Yusuf and the PURE project office staff at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, ON, Canada. This study was financially supported by the National Research Foundation South Africa, North-West University, Potchefstroom and the Metabolic Syndrome Institute.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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CHAPTER THREE

Conclusion and recommendations

3.1. Conclusion

According to the results, SBP and DBP for the African men with low BMI displayed a pre-hypertensive nature although the African women with low BMI were normotensive. Africans with low BMI, after adjusted for age, smoking and alcohol use, have a higher risk for CVD as a result of their higher c-r PWV. We also found negative correlation values for c-r PWV among African men with low, normal and combined BMI. Additionally, the correlations for GGT of African men with low, normal and combined BMI had a strong negative value. DBP, c-r PWV and GGT independently promote the J-curve theory, which suggests that there is a detrimental effect of low BMI on cardiovascular function in Africans. This could imply stiffened arteries, suggesting that the African men with low BMI have an increased risk for endothelial dysfunction and subclinical atherosclerosis.

The hypothesis that there is a detrimental effect of low BMI on variables of cardiovascular function in Africans is accepted. A detrimental effect of low BMI is evident on cardiovascular function in Africans with increased c-r PWV, DBP and GGT even after excluding participants with known chronic disease and adjusted for age, smoking and alcohol consumption. If BMI decreases from the optimum value to lower values, a J-curve is evident suggesting higher prevalence of CVD and detrimental cardiovascular function associated with low BMI.

3.2. Recommendations

The following recommendations are proposed for future studies:

- Use of a different study other than a prospective cohort study to infer causality.
- Target organ damage in other organs should also be investigated.
- Compare data of Africans and the effect of low BMI on the cardiovascular function with Caucasians and up-to-date measurements.
- The carotid-femoralis PWV should rather be measured than the c-r PWV because the carotid-femoralis PWV is the Golden standard for pulse wave velocity measurement.