TEMPORAL CHANGES IN THE CARDIOMETABOLIC DISEASE RISK PROFILE OF THE BELLVILLE SOUTH MIXED-ANCESTRY COMMUNITY BETWEEN 2008/09 AND 2014/16

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Thesis Presented for the Degree of

DOCTOR OF PHILOSOPHY

in the Department of Medicine

UNIVERSITY OF CAPE TOWN

2021

University of Cape Town

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- Davids SF, Matsha TE, Peer N, Erasmus RT, Kengne AP. Changes in Obesity Phenotype Distribution in Mixed-ancestry South Africans in Cape Town Between 2008/09 and 2014/16. Frontiers in endocrinology. 2019 Nov 6; 10:753
- Davids SF, Matsha TE, Peer N, Erasmus RT, Kengne AP. The 7-year change in the prevalence of insulin resistance, inflammatory biomarkers, and their determinants in an Urban South African Population. Journal of diabetes research. 2020 May 22;2020.

Signature: Date: 03/01/2022

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Declaration

This thesis is submitted to the University of Cape Town in fulfilment of the requirement for the degree of Doctor of Philosophy (PhD) in Medicine, Faculty of Health Sciences. The work presented in this thesis is original unless indicated in the text and has not, either in full or in part, been submitted for another degree at this or any other institution. The contents of this thesis are entirely the work of the candidate. In the case of multi-authored published papers, the candidate was the lead author. The contribution of the candidate toward these publications is described in the preface to the thesis.

Signature: Date: 03/01/2022

Acknowledgements

I wish to thank:

- The Almighty for His guidance and strength through this journey
- Professor André Pascal Kengne (Supervisor): Thank you for allowing me to be a student under your guidance. Your invaluable support and insight have allowed me to complete my thesis, while also allowing me to forge a career path that I absolutely love.
- Professor Tandi Edith Matsha (Co-supervisor and boss): Thank you for being an inspiration and mentor not only through this PhD journey, but also in my working career. Your invaluable guidance and support has truly been instrumental.
- Professor Nasheeta Peer (Co-supervisor): Words is not enough to say how grateful and appreciative I am for your support, guidance, encouragement, and mentorship. Your help and advice came at a time when I needed it most and has allowed me to push through and complete my thesis.
- Professor Rajiv Timothy Erasmus (Co-author): for your input into the manuscripts and for allowing me to include these manuscripts as part of my thesis
- Dr Gloudina Hon (Project Manager): Your encouragement and mentorship have not only helped me in my PhD journey but also in my working career.
- Soraya Chalklen (Lab assistant): for your assistance on the Vascular and Metabolic Health (VMH) study and for being a part of our dynamic team.
- Dr Shanel Raghubeer (Colleague): for your support, friendship, and encouragement.
- To all my colleagues and fellow students at the SAMRC/CPUT Cardiometabolic Health Research Unit, thank you for all the encouragements, laughs and moral support.
- The participants of the Bellville South Study and VMH study, without you this would not have been possible
- Cape Peninsula University of Technology, The South African National Research Foundation (SANRF) and South African Medical Research Council (SAMRC) for funding of these research projects.

Dedication

“Seek knowledge from the cradle to the grave.”

Prophet Muhammad (Peace Be Upon Him)

For my late Grandparents:
Ismail and Gadija Davids and Gamat Armien and Aysa Doutie;
Parents:
Mogamat Phaldie Davids and Fatoma Doutie;
and Siblings:
Luqman and Amirah Davids

Abstract

Background/purpose: The burden of cardiovascular disease (CVD) is growing rapidly and has shifted from high-income countries to low-middle income countries, including South Africa. In the South African Mixed-ancestry population, there is a dearth of trend studies examining the changes in cardiometabolic risk factors and their behavioural, socio-demographic, and lifestyle determinants. This thesis aimed to determine the temporal changes between 2008/09 and 2014/16 in (1) absolute blood pressure levels and hypertension prevalence; (2) distribution and change in obesity or body size phenotypes; and (3) the prevalence of insulin resistance (IR), inflammatory biomarkers, and their determinants.

Methodology: Participants, aged ≥20 years, residing in Bellville South and Belhar, Cape Town, were recruited in two independent cross-sectional surveys conducted during 2008/09 (N=928) and 2014/16 (N=1969). Data were obtained through questionnaires, clinical measurements (anthropometric measurements and BP), and biochemical assessments (oral glucose tolerance tests, lipid profile, and sub-clinical inflammation markers). Obesity phenotype was defined using a combination of body mass index (BMI) categories and abnormal cardiometabolic status. The latter was defined as the presence of ≥ 2 cardiometabolic risk factors. Indices used to assess IR included: insulin fasting, HOMA-IR, QUICKI, McAuley and Matsuda. Biomarkers defining sub-clinical inflammation included Ultra-Sensitive-C-Reactive Protein (us-CRP) and gamma-glutamyl transferase (gamma GT).

Statistical packages used for data analysis were Statistica v.13 (TIBCO Software Inc., 2017) and SPSS v.25 (IBM Corp, 2011). Measures of central tendencies and dispersion characteristics are reported to summarize survey data. The crude and age-standardised prevalence of hypertension were compared across years. With regards to obesity phenotype, IR, and sub-clinical inflammation, change in the distribution was investigated using interaction tests across the years of study. Linear and logistic regression analyses adjusted for year of study, age, and gender, were applied for all three studies.

Results: Participants were older in 2008/09 (54.3 years) compared to 2014/16 (49.6 years), the majority (>75%) of whom were female. Mean systolic blood pressure increased from 124 to 136 mmHg and mean diastolic blood pressure from 75 to 85 mmHg over the 7-year period. The prevalence of newly-detected hypertension increased from 11.6% to 24.8% and remained significant after adjusting for confounding variables. Importantly, there was a shift in the peak prevalence of hypertension from older ages (≥ 70 years) in 2008/09 to younger individuals (40-49 years) in 2014/16.

The BMI distribution between 2008/09 vs 2014/16 improved significantly with decreases in overweight (27.4% vs 23.6%) and obese (45.3% vs 42.2%) participants (p=0.001). However, across all BMI categories in both metabolic healthy and abnormal participants, anthropometric and biochemical measurements, and glucose and lipid profiles linearly increased (all $p \leq 0.018$ for linear trends).

Over the 7-year period, there was an increase in the prevalence of sub-clinical inflammation: us-CRP (54.7% vs 57.1%) and gamma-GT (29.6% vs 33.4%). Furthermore, multivariable analyses revealed that obesity levels, glycated haemoglobin, and fasting insulin levels were prominent risk factors associated with increased IR or subclinical inflammation, after adjusting for confounding variables.

Conclusion: A significant increase in hypertension prevalence was uncovered with a rightward shift in absolute BP. The majority of these increases were amongst newly-detected hypertension, suggesting a non-optimal detection of the disease. Therefore, increased awareness and screening drives for hypertension detection is crucial to reduce the prevalence of hypertension in this population group. Complications and nominal costs related to severity of hypertension must be incorporated on a greater scale than is currently practised in order to manage and prevent CVD development. A significant proportion of normal weight participants presented with metabolic abnormalities, while a substantial percentage of obese participants presented as metabolically healthy. Additional research is required to improve risk stratification for obesity phenotypes. Additionally, sub-clinical inflammation increased over the seven-year period, and was linked to strong predictors of CVDs, i.e., IR and metabolic syndrome components. Therefore, before substantial changes in CVD are observed in the population, monitoring the pathophysiological development of sub-clinical

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List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
AUDIT	Alcohol Use Disorder Identification Test Questionnaire
BMI	Body Mass Index
BRFSS	Behavioural Risk Factor Surveillance System
CAGE	Cut Annoyed Guilty And Eye
CARES	Cardiac Arrest Registry To Enhance Survival
CHWs	Community health care workers
CVD	Cardiovascular disease
DALYs	Disability-Adjusted Life Years
DBP	Diastolic Blood Pressure
DEXA	Dual Energy X-Ray Absorptiometry
DHS	Demographic And Health Survey
DoH	Department of Health
ED	Endothelial Dysfunction
FCAC	Framework Convention On Alcohol Control
gamma GT	Gamma Glutamyl Transferase
GLUT4	Glucose transporter type 4
HDL-C	High-density lipoprotein Cholesterol
HICs	High-Income Countries
HIV	Human Immunodeficiency Virus
HOMA-IR	Homeostatic model assessment of insulin resistance
IDF	International Diabetes Federation
IHD	Ischaemic Heart Disease
IL-6	Interleukin
IR	Insulin Resistance
KG	Kilogram
LDL-C	Low-Density Lipoprotein Cholesterol
LMICs	Low-Middle Income Countries
M^2	Metre squared
MEASURE DHS	Monitoring And Evaluation To Assess And Use Results Demographic And Health Survey
MAO	Obese and Metabolically Abnormal
MHO	Obese and Metabolically Healthy
NCDR	National Cardiovascular Data Registry
NCDs	Non-Communicable Diseases
NHANES	National Health And Nutrition Examination Survey
NWMA	Normal Weight and Metabolically Abnormal
NWMH	Normal Weight and Metabolically Healthy
OGTT	Oral Glucose Tolerance Test

OvMA	Overweight and Metabolically Abnormal
OvMH	Overweight and Metabolically Healthy
QUICKI	Quantitative Insulin-Sensitivity Check Index
SADHS	South African Demographic And Health Surveys
SBP	Systolic Blood Pressure
SSA	sub-Saharan Africa
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TG	Triglycerides
TNFα	Tumor Necrosis Factor Alpha
us-CRP	Ultra-Sensitive-C-Reactive Protein
WC	Waist circumference
WHO	World Health Organisation
WHO FCTC	World Health Organisation Framework Convention On Tobacco Control
YLD	Years Lived With Disability

Preface

Chapter 1: Literature review on burden and changing trends of cardiovascular disease

Chapter 2: Overview of methodology for the study of cardiovascular disease trends in a South African population

Chapter 3: Motivation for study, aims and objectives

Chapter 4: Increase in blood pressure over a 7-year period in a Mixed-ancestry South African population

Chapter 5: Changes in Obesity Phenotype Distribution in Mixed-ancestry South Africans in Cape Town Between 2008/09 and 2014/16

Chapter 6: The 7-year change in the prevalence of insulin resistance, inflammatory biomarkers and their determinants in an urban South African population

Chapter 7: Conclusion and perspective of key findings of the thesis including recommendations and strength and limitations of the study

Candidate's contribution

The primary studies entitled, "The Bellville South Study" and "the Vascular Metabolic Health study", contributed to the analyses presented in this thesis. The candidate was involved in the fieldwork where she assisted with recruitment, clinical assessments, training of staff, etc.

The manuscripts included in this thesis, i.e., the three original research manuscripts, the candidate is the lead author. Under the guidance of her supervisors, the candidate prepared the dataset for analyses, conducted the analyses and drafted the manuscripts. For the published papers, the candidate addressed the comments of journal editors and reviewers and submitted the revised manuscripts for publication.

Chapter 1-Literature Review

1.1 Introduction

Non-Communicable Diseases (NCDs) include cardiovascular disease (CVD), cancers, diabetes mellitus, chronic respiratory diseases and mental health disorders, among other conditions. According to the World Health Organisation (WHO), NCDs are a leading cause of death worldwide responsible for more than 60% of disability-adjusted life years (DALYs), 70% of deaths and more than 80% of years lived with disability (YLD) [1,2]. The seriousness of the problem led to the WHO in 2013 launching the Global Action Plan for the Prevention and Control of Non-communicable Diseases. The plan recommended policies to reduce NCD-related premature mortality by 25% by 2025 [3]. The global action plan focuses on strengthening health services and public policy to prevent and manage the four major NCDs (CVD, cancer, diabetes mellitus, and chronic respiratory diseases), and their four main health-related risky behaviours of diet, physical activity, tobacco use, and excessive alcohol intake.

The literature review will address four areas of CVD, namely: the surveillance and monitoring, an overview of the current burden and trends, the epidemiological transition and its influences, and the risk factors that contribute to CVD.

1.2 Surveillance and monitoring of cardiometabolic diseases

Public health surveillance is defined as the systematic and continuous collection, analysis and interpretation of data that track health events, risk factors, determinants and outcomes at a population level [4,5]. These interpretations are then used by policy makers to aid in the planning, implementation and assessment of public health strategies. Surveillance systems can then further measure the effectiveness of the strategies or interventions and allow for adaptations to be introduced.

The first such system developed was for infectious disease with the aim of timeously detecting disease outbreaks, determining individuals at the greatest risk for contracting the disease, and controlling the disease from spreading. This type of system was first found in 3180 BC, in the time of Pharaoh Mempses. Then, public surveillance was designed to control infectious diseases in which the “great pestilence” had taken place [6,7]. While surveillance began for control of infectious disease, this has now been extended to surveillance of NCDs.

With a growing NCD burden demonstrated in the early 20th century, in 1968, the 21st World Health Assembly, recommended that surveillance on NCDs be used to aid in understanding their patterns [8]. As a result, various organisations designed methods for the surveillance of NCDs, which included numerous surveys in the United States. These include the following surveys: Behavioural Risk Factor Surveillance System (BRFSS), and National Health and Nutrition Examination Survey (NHANES), registries: Cardiac Arrest Registry to Enhance Survival (CARES), and the National Cardiovascular Data Registry (NCDR) and cohort studies (the Framingham Heart Study) [9–13].

These systems allowed for the (i) tracking ; (ii) monitoring; and (iii) promotion of health, associated with NCD risk factors [14]. For example, such surveillance has shown that the largest proportion of mortality associated with NCDs occur in low- and middle-income countries (LMICs) and in communities with a lower socio-economic status residing in high income countries (HICs) [15]. Surveillance data has further highlighted that, despite NCDs being considered as diseases affecting the old, a large proportion of all NCD deaths (41.7%) were premature deaths, i.e. occurring in those under the age of 70 [16]. The availability of such information has enabled governments to identify the burden of disease and thereby optimally allocate funds and resources to targeting risk factors associated with NCDs, thus allowing for the control of this growing epidemic.

Currently, the Monitoring and Evaluation to Assess and Use Results Demographic and Health Survey (MEASURE DHS) is being used in LMICs across the globe [17,18]. Although the MEASURE DHS did not initially include the surveillance of NCDs, they have been gradually expanding this by incorporating aspects of the STEPwise surveys [19], which is a survey that was specifically designed by the WHO to target NCDs. These surveys aim to understand and advance population and health trends in the region. From the data collected, countries are able to implement policies, develop programmes and monitor the population health. For example, in South Africa, the prevalence of tobacco use decreased between 1998 and 2016. This was observed in the South African Demographic and Health Surveys (SADHS) conducted across these two time points. These surveys enabled the South African Department of Health to monitor and evaluate the effectiveness of various smoking policies and legislation which had been implemented [20–22].

Today, many countries have implemented some sort of surveillance system i.e. governmental records of birth, death etc, census surveys, MEASURE DHS etc. However, there have been numerous challenges surrounding the maintenance of such programmes, particularly in LMICs. These challenges include limited financial resources and laboratory services; lack of coordination, communication systems and reporting tools; and inadequate training of health care personnel and administrative staff [15,23–29].

1.3 Overview of the current burden and changing trends of cardiovascular disease

As defined by the WHO and the American Heart Association, CVDs are a group of disorders of the heart and blood vessels [30,31]. These diseases comprise eleven aetiologies which include: ischaemic heart disease, stroke, hypertensive heart disease, cardiomyopathy and myocarditis, atrial fibrillation and flutter, rheumatic heart disease, non-rheumatic valvular heart disease, aortic aneurysm, endocarditis, peripheral artery disease, and other cardiovascular and circulatory diseases [30,31].

The contribution of CVDs to the global burden of disease has progressed over time. CVDs have emerged as the leading contributor to the burden of disease globally, primarily due to the improved control of infectious diseases and changes in lifestyle. Even in LMICs, as determined by the World Bank, particularly in Africa, where it was thought that CVDs were uncommon, they now contribute substantially to the disease burden [32–34]. The CVD burden, which was initially concentrated in HICs, has shifted to LMICs over time. Although CVDs have remained the leading cause of mortality and morbidity in HICs, LMICs are following suit, with some regions having higher numbers than those of HICs.

With the indication that the main CVDs are Ischaemic Heart Disease (IHD) and stroke, this literature review will therefore focus on these two conditions only.

1.3.1 Prevalence and incidence

The Global Burden of Disease study, in 2019, estimated that 523 million people had CVD globally with 393 million DALYs, and 34.4 million YLD recorded [35]. This higher burden of CVDs mainly incurred by LMICs and has been forecast to grow enormously in future, specifically those on the African continent [36–39]. In 2019, the prevalence

of CVDs was substantially higher in LMICs compared with HICs (LMICs: 363 million vs. HICs: 133 million) [35].

There is a dearth of data on IHD and stroke incidence and prevalence in Africa, which is due to the absence of well-structured registries for IHD and stroke, a focus on infectious diseases and a false belief in the scarcity of CVDs on the continent [40]. This is also true for South Africa, one of the most developed countries on the continent [41]. Most IHD and stroke studies in Africa are hospital-based, which precludes population-based estimates of the incidence and prevalence of these conditions [42]. Nevertheless, although incidence and prevalence could not be determined, hospital admissions for stroke and IHD have been increasingly reported. For example, hospital admissions for stroke increased between 1986 and 2010 from 30.7 to 181 per 100,000 amongst numerous African countries [43–47]. Similarly, IHD was once rare in Africa [48–51] with on average 6 IHD patients admitted to the main referral hospital in Zimbabwe between 1988 and 1993 [51], and an average of 49 IHD patients admitted to the main public referral hospital in Johannesburg, South Africa between 1992 and 1994 [52]. However, these numbers have increased substantially as demonstrated by the IHD admissions to the latter hospital in Johannesburg where, in 2006 alone, 165 IHD patients were admitted [53]. The dramatic increase in IHD over a 14-year period at the same hospital highlights the increasing CVD burden in the region.

To overcome the lack of population-based data, the Global Burden of Disease study used models to globally determine prevalence and incidence trends of stroke and IHD. In 2019, the Global Burden of Disease study reported that LMICs had a higher incidence of stroke (LMIC 9.67 million vs HIC 1.9 million) and IHD (LMIC: 7.3 million vs HIC:4.1 million) compared to HIC [54]. In 2019, the incidence of IHD and strokes accounts for 434 853 and 448 576 of the SSA population, respectively [55].

Due to limited data on trend studies in Africa, a crucial gap has been formed, which prevents the true extent of CVD on the continent from being established to enable governments to implement optimal evidence based health policies and strategies [56].

1.3.2 Mortality

Global estimates indicate that CVDs are the leading cause of death, responsible for an estimated 18.6 million deaths in 2019 [35]. The leading CVDs globally are IHD and stroke, which account for 84.5% of all CVD deaths [35]. Currently, 80% of all CVD

deaths occur in LMICs, with 40% being premature deaths [57]. Unlike in HICs, CVD mortality in LMICs occurs mainly in younger working-age individuals and impact sustainable socioeconomic development and poverty alleviation. [42,58–61].

Furthermore, CVD mortality increased globally between 1990 and 2019 by 53.8%[54], including in sub-Saharan Africa (SSA), which had shown a 59% increase in CVDs deaths over the same period [54]. Indeed, it has been over two decades since the WHO reported that CVDs had become the second most common cause of death after infectious diseases in LMICs, including in SSA [36]. Notably, LMICs have three times higher mortality due to CVD than HICs (LMICs: 14.2 million vs HICs: 3.5 million) [54]. From the study, absolute deaths due to CVDs between 1990 and 2019 increased in LMICs from 8.0 million to 14.2 million, while HICs reported similar values over the two-period (3.6 million to 3.5 million), respectively [54].

South Africa is at the forefront of the CVD epidemic on the African continent. In South Africa, CVD mortality is the second most common cause of death [62]. Notably, in 2019, at 15.85%, the second leading cause of death in South Africa was CVDs, after HIV/AIDS, with IHD and stroke accounting for 5.84% and 5.71% of deaths, respectively [55]. Between 1990 and 2000, the growth of CVD mortality in South Africa was 84.1%, between 2000 and 2010 it was 7.6%; while between 2010 and 2019, there was a decrease of 2.3%. The reason for the recent decline may be improved access to advanced care for CVDs. South Africa is the only SSA country with CVD care facilities, which are on par with international recommendations [63].

1.4 Drivers of the burden of cardiovascular disease

Key drivers have been associated with the increase in burden of CVDs. These drivers include social determinants, behavioural risk factors, and cardiometabolic risk factors, as indicated by the WHO, see figure 1 [64,65].

Using the analogy of a stream, these three drivers could be labelled as upstream, midstream and downstream. Social determinants or upstream drivers are factors which shape society, i.e., by globalisation, urbanisation, growing ageing populations, etc. These social determinants in turn impact population behavioural characteristics and are the midstream drivers. These factors include the changes in dietary behaviours due to easier access to various food products, decreased physical activity influenced by more sedentary and less active work and living environments, and easy

access to tobacco and alcohol. The last phase of the stream, downstream, is the cardiometabolic risk factors. These include obesity, hypertension, diabetes and dyslipidaemia, which are influenced by the upstream and midstream drivers. The behavioural and cardiometabolic risk factors directly contribute to the onset of CVDs.

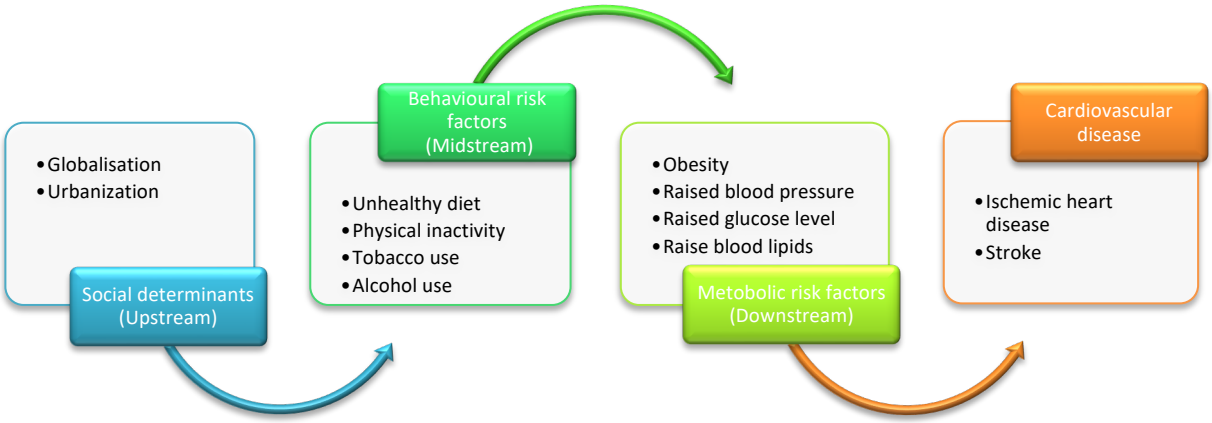


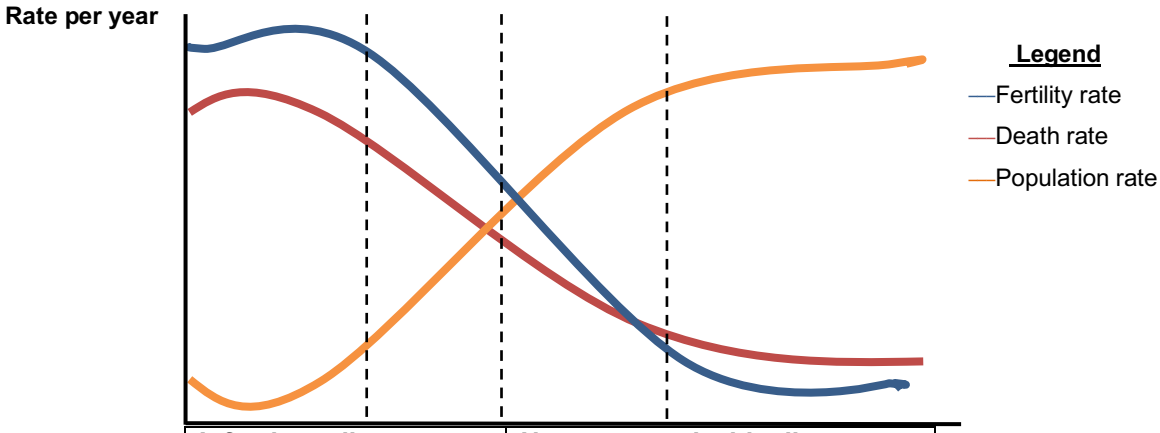
Figure 1.1. *Risk factor associated with CVD*

Source: World Health Organisation. (2013). A Global Brief on Hypertension: Silent Killer. Geneva: WHO Press. [65]

These drivers, which play a pivotal role in the onset of CVDs, influence the demographic and epidemiological transitions. These social determinants, such as improvements to infrastructure, sanitation and access to health care, are used to explain the transitional concepts that influence the changing burden from infectious disease to non-communicable disease including that of CVD patterns over time.

1.4.1 Demographic and epidemiological transition and the influencing factors

One of the most popularised concepts to explain the emergence and changing CVD patterns is the epidemiological transition. In 1971, Omran [66] proposed the epidemiological transition theory to explain the changing patterns in the population and health dynamics in the United States since the beginning of the 19th century. The epidemiological transition occurs when a country shifts from high mortality due to infectious diseases and low NCD deaths to higher NCD and lower infectious disease mortality [67]. The stages for the demographic and epidemiological transition is as follows (figure 2) [66]:



	Infectious disease		Non-communicable disease	
Stages of transition	***Stage 1*** The age of pestilence and Famine	***Stage 2*** Age of receding pandemic	***Stage 3*** The age of degenerative and man-made disease	***Stage 4*** Delayed degenerative diseases
Average life expectancy (years)	35	50	60	>70
% of CVD deaths	5-15	15-35	>35	<50 (Started to decrease after stage 3)
Countries currently in stage	SSA, parts of all regions except HICs	Southern Latin America, South Asia, Oceania	Central and Eastern Europe, Central Asia, North Africa and Middle East	HICs

Figure 1.2. *Stages of the epidemiological transitions*

Source: Adapted from Omran [66], The Global Burden of Disease Study [54]

Stage 1, the pestilence and feminine stage: the fertility and mortality rates are high, mainly due to high infection rates and malnutrition. Stage 2, the receding pandemic stage: the health care systems in countries develop with decreases in infant mortality rates while fertility rates remain high. Stage 3, the degenerative and man-made disease stage: both fertility and mortality rates decrease and is attributed to enhanced lifestyle and access to birth control. Stage 4, the delayed degenerative diseases stage: both fertility and mortality rates decline and plateau with CVDs and cancers the main cause of morbidity and mortality.

The epidemiological transition enables a better understanding of the changing disease patterns with an increase in the burden of CVDs in a country [68]. The factors contributing to the epidemiological transition include globalisation, urbanisation and population ageing, and their underlying socioeconomic, cultural, political and environmental influences [69]. The influences of globalisation and urbanisation in LMICs have been rapid, occurring over the past few decades, compared with HICs where the impact was felt over a few centuries [36].

1.4.2 Social determinants and drivers

Social determinants, or the upstream drivers, as mentioned above, are circumstances that shape an individual or population through economic and social conditions. As per the WHO [70], there are six main social determinants, namely: globalisation, urbanisation, income, education, housing and population ageing. Globalisation and urbanisation, which incorporate income, access and quality of education, which will be discussed in this section.

1.4.2.1 Globalisation

The first notion of globalisation comes from the primitive time in which people would move and settle in new places worldwide. However, modern-day globalisation is defined as the increased connection and reliance between people and countries [71]. With improvements in technology, the impact of globalisation has been marked and increasing in many parts of the world, especially in LMICs.

With globalisation now reaching five continents of the globe, countries in Africa that were considered underdeveloped have been able to reap the benefits of the changing world of trade and access to technology, education and health care previously difficult to come by. Numerous countries in Africa have seen an increase in economic development related to both local and international trading.

With globalisation being a double edge sword, i.e. free trade amongst countries has had substantial benefits with industry, while at the same time having major health implications on populations including the substantial contribution to the rapid increase in CVDs [72]. Globalisation leads to negative changes in behaviour including increases in unhealthy dietary habits, and the uptake of alcohol and tobacco use [73]. For example, national policies allowing for the entrance of multinational alcohol

conglomerates into countries has led to the availability of cheaper alcohol and the increase of alcohol consumption [74]. This was demonstrated in Lesotho, in which alcohol consumption increased 10-fold between 1970 and 1996 following the introduction of laws to encourage foreign direct investment in the country between 1967 and 1970 [75–77]. Consequently, South African Breweries (SAB), the second largest brewery globally, entered the local alcohol market between 1978-1982 [78]. This led to the increased marketing of cheaper and more accessible alcohol in the country which contributed to the marked rise in alcohol consumption. In this manner, globalisation is influencing the uptake of unhealthy lifestyle behaviours, with these high-risk behaviours that were previously limited or non-existent in African countries, now on the rise. They contribute substantially to the increase in CVDs on the continent. It is therefore government's responsibility to protect its populations from the negative impacts of globalisation through legislation, etc. Therefore, a balance between free trade agreements and the growing industrialisation pressures is important, especially in LMIC. For example, in HIC, policies have been developed to counterbalance industries such as the manufacturing, trade, and marketing of tobacco, alcohol and unhealthy foods. In contrast, numerous LMICs, particularly in Africa, have limited or no regulations and/or policies in place for the marketing, formulation, taxation, etc. of these products. Among the African countries that have implemented legislation to control the uptake of these unhealthy products is South Africa. These include legislation to reduce trans-fats in foods, limit the quantity of sugar in sugar-sweetened beverages, and measures to curb tobacco smoking. The latter includes prohibiting advertising and sponsorships by tobacco companies, smoke-free public and work spaces, taxes on tobacco products, etc [79].

1.4.2.2 Urbanisation

According to the United Nations Department of Economic and Social Affairs, urbanisation is the movement of relative populations from rural to urban areas, with urban areas being built up regions that have high population density compared to rural areas [80].

The migration from rural to urban areas has been increasing rapidly, particularly in LMICs, with people searching for employment, and economic upward mobility [81]. However, migration also negatively impacts on health, which includes the uptake of

unhealthy behaviour and lifestyle choices, that promote the development of CVD. For example, in Tanzania, migration from rural to urban areas led to a substantial reduction of vigorous physical activity from 63.7% to 42.7% in males and 32.2% to 11.6% in females over 1-year period. Furthermore, there were increases in both alcohol use (males from 25.0% to 36.8%; females from 23.4% to 29.7%) and tobacco use (males, from 16.2% to 23.5%; no female data) over the same period. Additionally, increases were reported in the average consumption of saturated fats, carbohydrates, red meats and soft drinks, which contributed to weight gain, and increases in waist circumference and total cholesterol (TC) levels [82]. This reiterates the negative effects of urbanization on migrants' lifestyle and health.

In 2018, the United Nations estimated that 55% of the global population currently reside in urban areas; however, this is set to grow to an estimated 68% in 2050, of which 90% will be in Asian and African countries [81]. With this increasing urbanisation, particularly in LMICs, the CVD burden is also set to rise due to the influence of urbanisation on the uptake of unhealthy lifestyles. Consequently, with a projected increase in these behavioural risk factors, earlier onset CVDs is predicted in LMICs, particularly in China where urbanisation is estimated to double by 2050 [80].

In order to improve the adverse health effects as a result of urbanisation and globalisation, government needs to counter-balance this with improved strategies and policies, as described in the previous section under Globalisation. Further, governments need to improve infrastructure such as the development of bicycle lanes and pavements in urban areas to encourage physical activity, while at the same time creating safe green spaces for physical activity to be conducted close to residential areas. The World Heart Federation addressed these issues, as possible tools for reduction of the incidence / prevalence of CVDs [83].

1.4.3 Behavioural risk factors

Unhealthy diet, physical inactivity, tobacco use and alcohol use are the behavioural risk factors that contribute to the development of cardiovascular and cardiometabolic diseases. The World Health Organisation (WHO) indicated that changing these behaviours will reduce the risk for the development of cardiovascular and cardiometabolic diseases [84].

1.4.3.1 Unhealthy diets

Globalisation and urbanisation enable access to diverse food products, be it healthy or unhealthy [85]. Rapid globalisation and urbanisation in LMICs, unlike HIC where these occurred over several decades, have led to the uptake of unhealthy diets that have contributed to the development of CVDs over a relatively shorter period. Global populations have adapted rapidly to westernized diets, which are high in sodium, saturated and trans-fats, carbohydrates and sugar-sweetened products, and low in fruit and vegetables. These diets create nutritional imbalances allowing for the onset of cardiometabolic risk factors associated with CVD. In 2017, an estimated 11 million people died due to dietary-related illnesses of which CVD was the leading cause [86]. For this thesis, we will focus on three dietary patterns, namely [1] high sodium intake [2] energy-dense high-caloric foods and [3] low fruit and vegetable intake. All three dietary patterns are known to contribute to the development of CVDs [64].

1.4.3.1.1 Changing dietary patterns and their clinical consequences

High sodium *intake*

The WHO has recommended that on average an individual should consume less than 5 g of salt per day [87]. However, in South Africa, the daily consumption of sodium is 7.2 g [88]. Contributors to high salt intake include the consumption of high levels of salt-rich processed food, salty snacks, breads, margarines, stock and soups. In South Africa, bread which is part of the staple diet, comprises the main source of the daily sodium intake, i.e. 25-40% [89]. The excess sodium in diet has been linked to elevated blood pressure levels and, with continuous high sodium intake, individuals could develop salt-sensitive hypertension [90]

Energy-dense high-caloric diets

Energy dense high-caloric food products are those that usually are high in simple sugars or carbohydrates, and saturated or trans-fats. These include fast foods, fried foods, highly processed foods, sugar-sweetened beverages, etc.

Daily dietary recommendations suggest intakes of 25-35% fats [91], and 55% carbohydrates [92] with an average of 25 g of sugar [93]. However, total daily dietary intake in South Africans consists of between 17-35% fats with a high proportion from unhealthy saturated fats, and 47-69% carbohydrates with between 32-82 g sugar [94].

The high intake of saturated fats, carbohydrates and sugar with excess caloric consumption leads to the onset of dyslipidaemia, particularly high triglycerides, obesity and elevated insulin levels which is a precursor of type 2 diabetes [95–97]. Over time, excess sugar contributes to stiffening of the arteries and subsequent heart disease and stroke [98].

Low intake of fruits and vegetables

According to the World Health Organisation, in order to reduce the risk of non-communicable disease, a minimum 400 g per day of at least five portions of fruit and vegetables is required [99]. However, this intake in LMICs is less than the recommended daily allocation [99]. For example, in South Africa, the average daily intake of fruits and vegetable is 200 g per day [100]. Low intake of fruits and vegetables leads, not only to nutritional deficiencies, but has also been associated with the onset of hypertension [101,102], dyslipidaemia, diabetes [103,104], and certain types of cancers [105]. Fruit and vegetables are high in potassium and fibre. The former contributes to lower blood pressure levels and reduced hypertension prevalence [106–109]. High dietary fibre, among other benefits, reduces cholesterol build-up thereby preventing dyslipidaemia [110,111].

1.4.3.1.2 Strategies to improve diet

Given that the current environment is more conducive to unhealthy dietary behaviours, population level interventions are required to create an environment where the healthier options are the easier choices at an individual level. Seeing that population level strategies are required to regulate the intake of unhealthy diets; many countries have implemented policies and legislations to curb the uptake of unhealthy foods. These include awareness campaigns, subsidies on healthy food options and higher taxes on unhealthy food items, etc. Governments have implemented national awareness campaigns, strategies and policies to reduce the influence of unhealthy food [112,113].

However, governments face resistance from the food industry which adopts various strategies to deflect negative publicity from their products and refute claims of unhealthy links to their products. This makes implementation of policies difficult due to the contradictory studies done by industry. For example, the link between obesity and

sugar has been downplayed by the food industry, and physical inactivity falsely blamed as the primary contributor to the obesity epidemic [114]. Notably, strategies, initiatives and policies to enable the uptake of healthier diets need to include government departments outside the health sector such as agriculture, trade and industry, transportation, etc. Therefore, key stakeholders and leaders in government are required to drive these strategies, initiatives and policies that cut across all sectors. This may then allow for cultural and environment changes to occur, thereby making the healthier option the easier choice.

Reduction of high sodium intake through reformulation, education, and taxation

In 2021 it was reported that 96 countries globally had strategies to reduce the amount of salt their populations consumed [115]. These countries were mainly in Europe, North America and Western Pacific Region. According to Trieu et al [116] and Santos et al. [115], many countries were able to reduce salt by using multifaceted programmes such as: reformulating recipes with the aid of industry, developing sodium targets for food products, awareness campaigns on the risk of too much salt, front-of packaging labelling, governments implementing tax on high-salt products and using public institutions to deliver interventions. For example, in South Korea [117], where salt intake was double the daily recommended limit, the government implemented a successful initiative called the “Less Salt Campaign” between 2007 and 2010. This included five steps, namely: (1) awareness campaigns to change individuals’ consumption behaviour; (2) increase low-salt foods at places of work and school; (3) increase low-salt foods at restaurants; (4) processed food manufacturers could voluntarily reformulate the recipes so that products have less salt; and (5) formulation of low salt recipes for home cooking. This multicomponent intervention was able to successfully reduce dietary salt by 23.7% in 4 years in South Korea.

In Africa, three countries have shown either to be planning salt reduction initiatives (Ethiopia and Nigeria) or have implemented an initiative (South Africa) [115,118]. In South Africa, legislation and policies to improve population diet by reducing salt in foods was developed in 2013, and implemented from 2016 with full effect by 2019 [115]. As such, industry had complied with the regulations by reducing the salt content in bread, fat spreads, breakfast cereals, snacks etc by 2019 [119]. Early evidence

suggests that this initiative has been effective in reducing the salt intake of the South African population [120].

Reducing energy-dense high-caloric diet food products by reformulation of food products, education, and taxation

Various countries, globally, have implemented policies to reduce energy-dense high-caloric diets, i.e., by means of taxes on sugar-sweetened beverages and legislation to reduce the amount of trans-fats in food products. The " sin tax" on sugar-sweetened beverages has been implemented in various countries, including those in Africa such as Mauritius, St Helena, Seychelles and South Africa, to name a few [114]. These countries have various ways in which the tax was implement i.e. either by sugar content or the volume. For example, the South African government has implemented tax on sugar quantity i.e. if manufacturers use above the recommended level, a tax is imposed for each 4 gram per 100ml [121]. The reduction of sugar in sugary-beverages has been demonstrated to reduce levels of obesity [122].

Similarly, the implementation of trans-fats legislation in South Africa in 2011, stated that food items could not exceed 2g per 100g of trans-fat [123]. Furthermore, nutritional information needed to be included on all packaging so that consumers are made aware of the nutritional contents [123]. However, this may not always be easy for consumers to understand or to determine which are the healthier food options; visual images are preferable. A better and easier system proffered has been the traffic light system on the front-of-packaging as implemented in Australia and the United Kingdom [123]. The traffic-light system (red, yellow, green) enables individuals to easily select the more nutritious option [124,125], which is easier for people with lower literacy levels. In South Africa, the Heart and Stroke Foundation uses a symbol i.e. a white heart, knife and fork inside of a red circle to indicate that the product is a healthier option and approved as part of their meal plans [126].

Increasing fruits and vegetable intake by government subsidisation, education and incentivization

Countries, globally, have not made a concerted effort in improving the availability and accessibility of fruits and vegetables to the poor; in certain regions these items are currently too expensive for the poor to purchase [124,125]. Although taxes on fruits

and vegetables vary globally, i.e. they are either exempt, reduced or taxed, governments would need to introduce subsidies as an aid to encourage the purchase of these items as a cheap alternative to unhealthy food items [127]. Of the few countries that have exempted tax on fruits and vegetables is South Africa. With regards to subsidies, Australia is at the forefront of encouraging its population to eat fruits and vegetables by reimbursing consumers for the purchase of these products. For example, for every 100g of fruit or vegetables purchased, the consumer would be reimbursed a certain amount [128]. Similarly, in South Africa, a private medical aid scheme has developed a programme for its members which offers up to 25% back on purchases of healthier food options including fresh fruits and vegetables [129].

Other measures to increase the affordability of fruit and vegetables may include governments subsidising the transportation, etc. of fruits and vegetables with this cost saving translating into cheaper prices for consumers. For example, transport subsidies provided by the Indian government has eliminated the middle-man allowing local consumers to purchase directly from the farmers making it easier to access and at an affordable price [130]. Additionally, governments could run awareness campaigns to promote the intake of fruit and vegetables via national television and newspapers highlighting the health benefits these items including improvements in blood pressure levels and prevention of cancers, among other benefits.

1.4.3.2 Physical inactivity

Following industrialisation, mechanisation and urbanisation, there has been a widespread uptake of motorised transportation, a shift towards greater reward for more sedentary occupations and the development of technologies for leisure time activities, among other changes [131,132]. For example, with the advancement of technology, both adults and children prefer to play video games and watch television compared to being outdoors or doing physical activity in their leisure time [133,134]. Consequently, physical activity has been on a downward spiral and sedentary behaviours on the rise with this reduced activity contributing to poor health including both poor physical and/or mental well-being.

1.4.3.2.1 Prevalence and trends

The WHO defines the minimum aerobics physical activity per week required for health as: [1] 150 minutes of moderate-intensity activity; [2] 75 minutes of vigorous-intensity activity; or [3] an equivalent combination of moderate to vigorous aerobics physical activity [135]. This recommendation by the WHO is currently not being met by a large proportion of the global population. In 2016, it was estimated that 1.4 billion of the adult global population were physically inactive with the largest burden in HICs [136,137]. The prevalence of physical inactivity in low income countries was almost half that of HICs (low income: 16% vs HICs: 37%), an indication of differential development in these regions [136,138]. This higher percentage of physical inactivity in HICs is likely linked to greater industrialisation and mechanisation and the associated changes mentioned above compared with low income countries where more physically active lifestyles generally prevail [84,138,139].

As for trends, it was reported that between 2001 and 2016 physical inactivity had plateaued. This was likely a result of improved physical activity levels in China, the most populous country globally, after implementation of policies at national levels to promote activity. This has likely led to increases in leisure time physical activity in China [136,138,140].

Generally, women were less active than men (2001: females: 31.5% vs males: 25.5% and 2016: females: 31.7% vs males: 23.4%) [138]. This may be associated with males tending to have more strenuous occupations compared to females who tend to have less physically exerting occupations [141]. Additionally, sociocultural values and perceptions may deter women from participating in physically active lifestyles. This was determined in various studies, for example, Indian females partaking in physical activity and wearing active wear, were considered as losing their Indian heritage [142]; while a group of Mexican females stated by participating in physical activity, the community saw them as being selfish and neglecting their family responsibilities [143]; and in the United Arab Emirates are outdoor activities where discouraged as a result of the hot climate, females did not partake easily in physical activity due to lack of culturally sensitive facilities [144].

In South Africa, it is has been reported that 57.4% of individuals were not physically active (14.8% and 27.8% were moderate and vigorously active, respectively) [145]. These high levels of physical inactivity may be linked to numerous factors such as

high levels of crime making it unsafe to walk as a means of transport, infrastructure not conducive for walking or cycling, not enough parks and recreational spaces in townships, a sociocultural environment that promotes inactivity, etc. [146–151].

1.4.3.2.2 Health consequences

The lack of physical activity has been linked to increases in poor health and the development of chronic diseases including obesity, hypertension, diabetes, dyslipidaemia, CVD, cancers and depression, just to name a few [152–160].

In 2009, physical inactivity was the fourth leading risk factor for global mortality, according to the WHO, after high systolic blood pressure, tobacco use and high fasting blood glucose [161]. Further, physical inactivity was also listed among the top 10 leading behavioural risk factors contributing to DALYs in the Global Burden of Disease study [138]. As a result of physical inactivity and sedentary lifestyles, individuals increase their risk of developing NCDs and all-cause mortality. For example, in 2012 it was reported, that globally, approximately 7% of diabetes and 6% of coronary heart disease could have been avoided if a minimum of 30 minutes of daily moderate physical activity were met [160]. Similarly, a Tanzanian study found that when the level of physical activity decreased from 63.7% to 42.7% in males and 32.2% to 11.6% in females, over 1-year period, weight (males: from 58.8 kg to 61.1 kg and females: from 61.8 kg to 64.1 kg) and waist circumference (males: from 77.3 cm to 79.2 cm and females: from 83.3 cm to 85.5 cm) increased [82]. This demonstrates the importance of regular physical activity in maintaining optimal health. Furthermore, the WHO estimated that around 5 million deaths due to inactivity could be prevented if a minimum 30 minutes moderate daily physical activity is achieved [162]. In two similar studies, it was reported that physical inactivity likely increases the risk of all-cause mortality between 45-54% [163,164].

1.4.3.2.3 Measuring physical activity

The gold standard to measure physical activity is known as the doubly labelled water method, where isotope traces, i.e. high levels of hydrogen (^{2}H) and oxygen (^{18}O) in water, are ingested. Levels of carbon dioxide, which are released during periods of exertion or physical activity, is measured in the blood, urine, or saliva, to determine total energy expenditure [165,166]. However, this test's drawback is that it is highly

expensive, time-constraining, a burden to the participant, and the inability to capture qualitative data [166,167]. Due to these shortcomings, numerous other techniques have been developed to measure physical activity either by way of a questionnaire, diaries/logs or use of devices.

Majority of epidemiological studies measure physical activity using validated self-reported questionnaires such as the Global Physical Activity Questionnaire or the International Physical Activity Questionnaire [168,169]; however, these are prone to recall bias. More recently, devices, such as accelerometers [170–173], and pedometers [174–176] have been used. Although these are objective measures to monitor physical activity, the costs of such devices are high and a major concern limiting their use in epidemiological studies.

1.4.3.2.4 Strategies to increase physical activity

In the WHO Sustainable Development Goals, increasing the number of physically active people globally by 2030 was reported among the primary goals [84]. The WHO "Global action plan on physical activity 2018–2030: more active people for a healthier world" developed four main objectives. These objectives required (1) the development of a physically active society; (2) creating environments for physical activity; (3) create programmes for individual to become more active; and (4) governments to develop systems to increase physical activity [137].

Some of these strategies have been implemented in various forms by several countries to increase physical activity. For example, China has used the WHO global action plan on physical activity to encourage leisure time activities. This was done by developing recreational parks as a way to encourage outdoor lifestyle and activities [140,177]. It has been reported that majority of park users are adults, of which over 50% use the areas to do moderate-to-vigorous physical activity such as dancing and tai chi [177]. This has translated into greater physical activity levels in the country [177].

On the other hand, in South Africa, a private medical aid scheme has developed incentive programmes to reward members who are physically active. These include tracking members physical activity via their fitness devices and apps and rewarding the member accordingly [178], and encouraging participation in fun runs [179]. However, these programmes are limited to members of this medical scheme and does

not extend to the poor majority. Governments need to introduce strategies and programmes to proactively encourage the uptake of physical activity in their populations.

1.4.3.3 Tobacco use

Tobacco use is defined as the use of tobacco products in various forms, i.e., either smoked (such as cigarettes, hand-rolled, cigars, pipes, etc), smokeless (such as chewing tobacco leaves), water pipes, and more recently, electronic cigarettes. Notably, the use of any tobacco product is potentially addictive, with even one cigarette being considered harmful to an individual's health [84,180,181].

1.4.3.3.1 Prevalence and trends

According to the Global Burden of Disease study, in 2019, it was estimated that 1.14 billion individuals were current smokers worldwide, of which 80% resided in LMICs. This total number of smokers had increased substantially between 1990 and 2019 from 0.99 billion to 1.14 billion [182]. By gender, it was reported that 32.7% of males and 6.6% of females were current smokers, with the highest number of male smokers residing in LMICs, while female smokers resided predominantly in HICs [182]. Although the percentage of female smokers is lower in LMICs, this is increasing as more females are becoming independent due to entering the job market and having more disposable income.

Eight of the top ten highest smoking countries are from LMICs; the highest is China which accounts for 30% (341 million) of all global smokers [182]. Smoking trends in LMICs have been increasing, while these have plateaued in HICs [183]. The latter is likely the result of litigations against tobacco companies in HICs because of tobacco related morbidity and mortality, which has been accompanied by stricter regulations and interventions in these regions [184].The upward smoking trajectory in LMICs is likely related to interference in government strategies to curb tobacco use by the tobacco industry and their aggressive and subversive marketing of tobacco products in the region. Consequently, tobacco control policies implemented by governments are falling short with measures such as tobacco excise taxes being too low, etc. [183].

1.4.3.3.2 Health consequences

Tobacco use is responsible for 36 adverse health outcomes with the most common being lung cancer, CVD, chronic respiratory disease, chronic obstructive pulmonary disease, peripheral vascular disease and congenital disorders in pregnant women who smoke [84,181,183,185–189]. With tobacco use being one of the most preventable causes of premature death, cessation of tobacco products is considered the most effective way to reduce premature death. Quitting smoking at any point can improve health and thereby increase the life expectancy of individuals [183]. Although e-cigarettes have not been long on the market and the adverse health effects have not yet been clearly established, the aerosols that are given off have already been linked to the development of cancers, CVD, and lung disorders to name a few [190].

1.4.3.3.3 Mortality

In 2019, the Global Burden of Disease study reported that tobacco use was the second leading risk factor for mortality responsible for an estimated 7.7 million global deaths [55,182]. Of these deaths, the majority were males (6.2 million) compared to females (1.5 million) [182]. Notably, LMICs reported an estimated 6.0 million deaths, in 2019, compared to 1.7 million in HICs [182]. It was further reported that of the tobacco attributable adverse health outcomes, the most deaths were due to IHD (1.7 million), chronic obstructive pulmonary disease (1.6 million), tracheal, bronchus, lung cancers (1.3 million) and stroke (0.93 million) [182]. Interestingly, deaths attributed to tobacco used varied depending on the region; for example, in HICs, the leading cause of death was lung cancer, while in southeast Asia, east Asia and Oceania it was chronic obstructive pulmonary disease [182].

1.4.3.3.4 Second-hand smoke

The WHO suggests that second-hand smoke exposure is extremely harmful to non-smokers [181]. Globally it was estimated that one-fifth of males and one-third of females are exposed to second-hand smoke, be it as a result of smoke from cigarettes or other forms of tobacco products. In 2019, it was estimated that 1.3 million people had died as a result of second-hand smoke [54]. Many of these second-hand smoking-associated deaths were related to CVD, with the main aetiologies being IHD (397,419) and stroke (201,054) [54]. Second-hand smoke exposure is most common in LMICs,

specifically in the Asian regions such as Indonesia and Pakistan [183]. In these Asian regions, a large proportion of the population are smokers as a result of cultural influences. However, the harmful effects associated with second-hand smoke is not adequately publicised, with minimal awareness and intervention programmes developed to combat this in these regions [191–193].

Furthermore, second-hand smoke has similar adverse effects on non-smokers and smokers. Sufficient evidence has shown that second-hand smoke exposure can cause infants sudden death syndrome and children can develop lung illnesses such as asthma and impaired lung function, and middle ear disease, among other diseases [183,194–197]. Similarly, it was reported that adults exposed to second-hand smoke could develop respiratory diseases, CVD, cancer and pregnant females could deliver preterm [183,194–197].

1.4.3.3.5 Strategies to control Tobacco use

The control of tobacco is a critical element in reducing the tobacco-attributable disease burden in populations [198]. In response to the growing tobacco epidemic as a result of globalisation, the WHO drafted an evidence-based treaty, WHO Framework Convention on Tobacco Control (WHO FCTC), in 2003 as a guideline to control tobacco use globally. In 2020, 182 countries had ratified the treaty, of which 168 were signatories [199]. The key strategies of the treaty include increasing excise taxes on tobacco products to the appropriate level; governments creating smoke-free environments; the regulation of tobacco products which is to disclose its contents and emissions; packaging should indicate health warnings; banning of tobacco advertisements, promotion and sponsorships; control illicit trade; develop awareness campaigns to educate the public on negative health effects of tobacco; and create cessation programmes for current users of tobacco products [200].

Although numerous countries have signed the WHO FCTC, enacting and implementation of such strategies in LMICs is limited. For example, in Africa, although 44 out of 54 countries have signed the WHO FCTC, the willingness to enact the tobacco control legislation has been met with various hurdles. These include minimal capacity and knowledge base in the home countries on tobacco control strategies with the tobacco industry subsequently being able to successfully subvert attempts to legislate tobacco use. These include the promulgation of misinformation, and

influencing policies to aid their agenda instead of contributing to decreasing tobacco use [201–203]. For example, Namibia took 20 years to enact legislation as a result of staff constraints and interference of the tobacco industry. For instance, the latter had misinformed the Namibian government on the process to ratify the FCTC. The limited legal expertise within the Ministry to verify the tobacco industry claims led to delays in the ratification [204]. Additionally, there is also a lack of implementation after legislation has been passed. For example, in Kenya, although tobacco control legislation has been enacted, there is a lack of enforcement at the ground level [205] due to lack of training and funding to promote the legislation, i.e. these laws are not enforced by the police nor by civil society, which would change the population culture in not accepting smoking in public spaces. In contrast, in South Africa , the government in conjunction with the media and civil society enforced various legislation to create a new mind set for the population, i.e. not accepting smoking in public spaces, no sales of tobacco to those under the age of 18, etc. [206].

Nevertheless, some LMICs including Mauritius, Uganda and South Africa, are reported to be at the forefront of the implementation of the WHO FCTC. They have successfully implemented various measures such as introducing excise taxes, banning the advertisement of tobacco products, having smoke-free policies and environments, and displaying graphic warning labels on the packaging of tobacco products, among others [207–209]. The Mauritian and Ugandan governments have implemented the WHO FCTC guidelines; however, not all measures implemented were as per the recommendation. For example, both have sixty to seventy percent of the tobacco packaging covered with a graphic health warning, and banning the mislabelling on packaging such as using “light” or “low tar”, in keeping with the WHO FCTC recommendations. However, with regards to the excise tax, while Mauritius had implemented 84% excise tax of the retail price in accordance with the recommended excise tax of 70% or more, Uganda had only implement a 40% excise tax, which is well below this level [210–212].

Interestingly, South Africa implemented an excise tax on tobacco since the 1970s; however, the tobacco industry was working with government in setting these prices [213]. Consequently, the excise tax on tobacco products decreased by 70 cents between 1970 and 1990. In 1993, South Africa first implemented legislation on tobacco control, with an amendment in 1999 in which health warnings regarding smoking were

introduced on packaging, restriction on sales of tobacco products to those under the age of 16, prohibiting of advertisement, vending machine restrictions and smoking was prohibited in public spaces, be it places of employment, restaurants, public transport, etc. [214,215].

Despite WHO FCTC recommendation of excise tax on tobacco products to be at least 70% of the retail price, in South Africa this is considerably lower with excise tax being only 55% of the retail price of tobacco products in 2019 [216,217]. Additionally, with the implementation of excise tax, there needs to be a firm control on the illicit tobacco industry, else the excise tax will fall short of what it was intended to achieve i.e., decrease tobacco use in the country.

Since the year 2000, there have been numerous amendments to this act in South Africa, in that some of the WHO FCTC strategies were implemented further. These included the increase of the minimum age of sales of tobacco products from 16 to 18 years, to name a few [79,214,218]. There have been other amendments to the Tobacco Control Act further strengthening control measures in South Africa. The most recent amendment proposed was in 2018 which includes the regulation of e-cigarettes as a tobacco product, among other initiatives to tighten tobacco control [219].

Although countries globally have implemented numerous legislations, and although all are not optimal, these legislations have, however, had a direct impact on the prevalence of smokers. For example, the SADHS reported a decrease in the prevalence of smokers between 1998 and 2016, i.e. in both males (1998: 42% vs 2016: 37%) and females (1998: 11% vs 2016: 7%) [21,22]. Nevertheless, considering that a substantial proportion of individuals still smoke in South Africa and worldwide, more needs to be done with greater implementation and adherence to the recommendations of the WHO FCTC in countries globally.

1.4.3.4 Alcohol use

Over the centuries, alcohol use has formed part of various cultures throughout the world [220,221]. However, alcohol misuse and abuse contribute to ill-health and disease and socioeconomic burden. With alcohol use being described as a substance that affects the brain and nervous system thereby altering an individual's mental state, the abuse of this substance is concerning and therefore should be controlled or avoided to preserve health and life [222]. The WHO stated that the impact of alcohol

consumption is dependent on two factors, namely: the total alcohol consumed and the pattern of consumption [222].

1.4.3.4.1 Prevalence and trends

In 2016, approximately 2.3 billion people consumed alcohol globally, of which Europe (59.9%), Americas (54.1%), and Western Pacific regions (53.8%) had the highest percentage of people consuming alcohol [220]. The high consumption levels could be due to a variety of reasons, for example in Europe, alcohol consumption is a sociocultural norm, with individuals opting to have one glass of wine or beer with dinner each day [223]. However, in recent years the prevalence of binge drinking has increase in Europe particularly amongst the younger generation, who are known to drink more at social gathering i.e. while watching club soccer at pubs, etc. [224,225]. This harmful pattern has become a concern for governments as excessive alcohol use increases the social and health related consequences [226–228].

In contrast, the Middle East and Africa regions had reported the lowest prevalence of persons consuming alcohol (2.9% and 32.2%) and the highest prevalence of lifetime abstainers (94.9% and 57.5%) [220]. The high percentage of lifetime abstainers may be attributable to the diverse cultures and religions in the region that prohibit the use of alcohol [229–231].

In Africa, despite the much lower proportion of alcohol use compared with Europeans, the alcohol consumed per capita is the second highest (18.4 litres) globally after Europe (21.2 litres) [220]. With only one-third of Africans consuming alcohol, it can be extrapolated that the actual alcohol consumption per drinker is likely much higher. Therefore, it may be deduced that individuals in these populations who drink do not usually consume alcohol in moderation, but rather drink excessively e.g. binge drink [232–235].

In South Africa, the 2016 SADHS indicated that 26% of females and 61% of males, 15 years and older are current drinkers [21]. Interestingly, in South Africa, of those who drank alcohol, 3% of females and 16% of males are reported to be binge drinkers, which is concerning because of the high rates of adverse consequences attributable to excessive alcohol use in the country [21]. The situation is unlikely to improve since policies to control alcohol in South Africa are somewhat non-existent and highlight the urgent need for effective alcohol control measures in the country [236].

1.4.3.4.2 Clinical consequences

Alcohol misuse is harmful because it impairs an individual's cognitive, psychological, physiological and behavioural abilities [237–239]. This in turn leads to numerous consequences which not only affect the user of alcohol but also their families, friends and even strangers in that there is an increase in social problems such as domestic abuse and motor vehicle accidents. Together with social consequences, the misuse of alcohol has been linked to over 200 diseases including CVD, malignant neoplasms, hypertension, type 2 diabetes mellitus (T2DM), alcohol use disorder, and digestive disorders, to name a few [220,222,240,241]. In a meta-analysis it was described that heavy drinkers (≥5 drinks per single occasion at least once a month) had a 1.5- to 2-fold increased risk of developing IHD [242]. Furthermore, the WHO reported that current drinkers in the African region had increased from 29.8% in 2010 to 32.2% in 2016 [220,221]. This increase in alcohol consumption was mirrored in the increasing alcohol attributed DALYs indicators (2010: 5.3% to 2016: 5.6%) and deaths (2010: 4.6% to 2016: 4.9%) in the African region [54]. Furthermore, the 2019 Global Burden of Disease study highlighted that alcohol attributed DALYs and deaths were listed amongst the top 10 leading behavioural risk factors globally and in Africa [55].

1.4.3.4.3 Mortality

In 2016, alcohol use was found to be the seventh leading cause of premature death and disability, worldwide. The Global Burden of Disease study estimated that approximately 2.8 million people died as a result of alcohol related deaths, of which the majority were males [243]. Of these deaths, the majority were from LMICs (1.7 million) in comparison to HICs (532,390) [54]. This was substantial higher than the figure reported in 1990 for LMICs (1.1 million) but only slightly higher for HICs (484,390) [54]. This highlights that, over the last 2-3 decades, while alcohol related mortality has plateaued in HICs, it is increasing in LMICs.

According to the WHO, the three leading causes of alcohol related deaths are digestive diseases (8.3 per 100,000), CVDs (7.4 per 100,000) and cancers (4.8 per 100,000) [220]. Globally, 11.4 per 100,000 individuals die due to injuries as a result of alcohol, with the highest being in the Africa region (17.1 per 100,000) and the lowest in North Africa and the Middle East (0.6 per 100,000) [220]. In South Africa, in 2015,

alcohol was a significant contributor to mortality; it was the ninth leading risk factor for mortality, accounting for 11.8% of the overall deaths [55,236].

1.4.3.4.4 Measuring alcohol consumption and misuse

In order to assess an individual's alcohol related dependency, a recollection interview between a clinician and patient needs to be conducted for a clinical diagnoses [244]. Biochemical markers could also be used to confirm excessive drinking; however, abnormal liver function tests are not specific for alcohol use [245].

Although clinical diagnoses of alcohol use disorders are optimal, they are however time-consuming and costly, and not feasible for epidemiological studies. Therefore, simpler self-administered questionnaires have been developed to determine problematic or harmful drinking patterns. These include the Alcohol Use Disorder Identification Test questionnaire (AUDIT) [246], and the CAGE questionnaire, an acronym that uses four questions to determine alcohol misuse, [247], as a way to assess the risk and harm alcohol poses to an individual's health.

1.4.3.4.5 Alcohol control

In order to control alcohol use, policies need to be implemented to reduce the use of alcohol. In 2007, a call for the development of a Framework Convention on Alcohol Control (FCAC) similar to that of the FCTC was made since alcohol contributed to as many deaths as that of tobacco at the time (alcohol: 4% vs tobacco: 4.1%)[55]. However, the achievements in controlling tobacco use, with the utilisation of international law, have not been replicated to curb excessive alcohol intake with little done to support developing a FCAC [248] .

In 2010, the WHO developed the Global Strategy to Reduce the Harmful Use of Alcohol, which was endorsed by the World Health Assembly [249], while the Regional Committee of African regions endorsed the Regional Strategies to Reduce Alcohol Use on the African continent [250]. Both these strategies included having a written national policy; excise tax; legal age limit for alcohol use; restrictions of availability of alcohol i.e., specific times of day for sale; national maximum legal blood alcohol limit when driving a motor vehicle; regulations on alcohol advertisement, promotion, and sponsorships; health warnings on alcohol advertisement and containers; and government support at a community level.

Some countries have taken these strategies seriously as a way to curb alcohol use. For example, the Russian government had successfully reduced alcohol consumption in their country by implement numerous policies. These include increasing the price of alcohol, limiting the availability to purchase alcohol i.e. no sales between 11pm and 8am, no alcohol consumption in public places and changing the minimum drinking age from 18 to 21 years. Following the implementation of these measures, Russia was able to reduce the average alcohol consumption from 17.1 litres in 2006 to 11.1 litres in 2016 [251]. This highlights the potential of effective alcohol control measures to decrease alcohol use in a country.

In a study of 46 countries in Africa, 84% had implemented an excise tax on the price of alcohol; however, these were not considered adequate since a number of them had not adjusted for inflation [252]. Similarly, 70% of countries had no legal regulations for alcohol advertisement, 19% did not have a minimum legal purchase age for on-premise sales, while 26% had no alcohol policy for off-premise sales [252].

In South Africa, little has been done to curb and prevent the misuse of alcohol, with minimal effective policies regarding the availability of alcohol and drink-driving countermeasures [252]. The few strategies that have been implemented in the country are not considered adequate to deter misuse of alcohol. For example, the average excise tax in South Africa is estimated to be between 15% and 45%, depending on the type of alcohol product purchased [253]. This excise tax is considered extremely low given that an average bottle of beer in South Africa costs approximately $1.68 versus that of Qatar which is $11.26 [254–257]. Similarly, although there are written warning labels on containers, these are considered inadequate given that graphic labels are more effective in deterring individuals from drinking [258,259]. Moreover, alcohol advertisements are not prohibited nor effectively regulated. They falsely convey an association of consuming alcohol with happiness, wealth, success, glamour and high status [260,261]. The failure and ineffectiveness of current alcohol control measures are reflected in the increase in alcohol use in males (58% vs 61%) between 1998 and 2016, while being stable but high amongst females (26%) [21,22]. Notably, almost half (43%) of all current drinkers are problem drinkers, the majority of which are males [262]. This highlights the need for effective alcohol control policies in South Africa and globally to address the problem of excessive alcohol intake.

1.4.4 Cardiometabolic risk factors

The four behavioural risk factors described above, i.e., diet, physical activity, tobacco and alcohol use, contribute to the onset of cardiometabolic diseases and CVDs. In conjunction with these behavioural risk factors, cardiometabolic diseases also significant contributors to the development of CVDs of IHD and stroke and will be described in this section. These cardiometabolic risk factors include obesity, hypertension, T2DM and dyslipidaemia.

1.4.4.1 Obesity

1.4.4.1.1 Definition, health consequences and mortality

Obesity, according to the WHO is defined as an excess or abnormal fat accumulation in the body, which results from an imbalance between the intake of energy-rich foods and energy expenditure [263–265]. In 2013, obesity was classified by the International Statistical Classification of Diseases as a chronic disease in its own right because of the adverse health consequences associated with this condition [248,266]. Obesity contributes to numerous medical conditions including CVDs such as coronary artery disease and stroke, and their risk factors of T2DM, hypertension and dyslipidaemia [264,267–275]. Lavie et al. [276] reported that a one unit increase in body mass index (BMI) contributes to a 4% and 6% increase in the risk of developing IHD and stroke, respectively. Further, the odds of developing hypertension or T2DM in the presence of obesity is 3.5-7-fold greater [271,277]. Similarly, obesity increases the risk of developing dyslipidaemia with approximately 60-70% of obese individuals having the condition [278].

Further, obesity contributes to various cancers such as kidney, liver, ovarian and breast cancers [275]. Obesity also causes mechanical problems such as movement disabilities associated with the excess weight which adversely affects daily activities such as standing-up, walking, moving, etc. It is also associated with severe arthritis, impairment of musculoskeletal system and chronic back pain, etc. [279,280].

In 2019, according to the Global Burden of Disease Study, high BMI (≥25 kg/m^2) was the fifth leading risk factor contributing to mortality globally. An estimated 5.0 million deaths are attributed to obesity related causes annually, of which 3.2 million were due to CVDs [281]. Mortality due to high BMI increased in both HICs and LMICs between

1990 (HICs: 807,303 and LMICs: 1.3 million) and 2019 (HICs: 1.1 million and LMICs: 3.7 million), with approximately two-thirds of these deaths related to CVD [55].
In South Africa, the Global Burden of Disease study established that high BMI was the third leading risk factor for mortality in 2019, after unsafe sex and high Systolic Blood Pressure (SBP) [55]. Mortality due to a high BMI more than doubled in South Africa between 1990 (21,013) and 2019 (55,365) with 75% of these deaths attributed to CVD and diabetes [55].

1.4.4.1.2 Predisposing factors

Globalisation, urbanisation, and mechanisation has been increasing globally since the mid-20th century and have led to the development of an obesogenic environment with easy access to unhealthy foods and changes in the built environment contributing to decreases in activity levels [282]. This has been discussed in detail in sections 1.4.4.1 and 1.4.4.2 above. These changes in lifestyles, exacerbated by the obesogenic environment, with the uptake of unhealthy diets and decreases in physical activity have contributed to the high and rising levels of obesity globally [283–285].
Additionally, the uptake of obesity is influenced by sociocultural beliefs in numerous populations, which plays a key role in the continuation, development and uptake of obesity. For example, the African culture considers obese females to be more voluptuous, healthy, attractive, and able to bear children, while those who are either underweight or normal-weight, are considered less attractive and linked to having various diseases including HIV/AIDS [286,287].

1.4.4.1.3 Prevalence and trends

In 2016, the WHO reported that approximately 1.9 billion adults globally were either overweight or obese [265,288]. The overall prevalence of overweight/obesity (BMI ≥25 kg/m^2) was 39.1% in 2016, of which both females (39.7%) and males (38.5%) had similar prevalence [289]. However, gender differences in overweight/obesity exist across different regions. For example, in Europe overweight/obesity rates were higher in males (66.0%) compared to females (58.8%), while in Africa the opposite is true i.e. females have a higher BMI ≥25 kg/m^2 than their male counterparts (females: 34.8% vs males: 20.4%) [289].

The global prevalence of obesity has almost doubled between 1975 and 2016, from 20.2% to 39.1% [289]. Although HICs had reported the highest prevalence of obesity with a 2-fold increase between 1975 and 2016, LMICs reported a 2.5 fold increase representing a more rapid uptake of the disease in these regions [289]. Similar to HICs, the uptake of obesity in LMICs is due to changing lifestyle patterns linked to globalisation, urbanisation, high energy dense diets, lack of physical activity, etc. In Africa, the prevalence of overweight/obesity has increased substantially from 12.0% in 1975 to 36.8% in 2016 [289,290]. In some African countries obesity levels are comparable to those in HICs, for example, in Libya (65.7%) and Egypt (61.9%) [289]. South Africa has one of the highest rates of overweight/obesity globally, particularly in females. In 2016, prevalence of BMI ≥25 kg/m^2 was 51.9% with higher rates in females (64.0%) compared with males (38.6%) [289]. These rates have doubled over the last four decades from 24.9% in 1975 (females: 35.3% and males: 14.3%) [289].

1.4.4.1.4 Measurement of obesity

The most accurate test to determine obesity is the Dual Energy X-ray Absorptiometry (DEXA) [291,292]. However, this is not optimal for routine assessments and epidemiological studies because they are expensive, time-consuming and impractical, making them difficult to use in clinical settings or research purposes [293]. The most cost-effective, quick and easy techniques to determine adiposity are proxy measures. These include BMI, a measure of generalised adiposity, calculated as an individual's weight (in kilograms) divided by height (in meters squared) [294,295]. Measurements of body fat distribution and central obesity, i.e. waist circumference and related measures such as waist-to-hip ratio and waist-to-height ratio, are more closely linked to the development of cardiometabolic diseases [296]. This is because the latter estimates visceral obesity, which is a crucial risk factor for cardiometabolic diseases.

1.4.4.1.5 Strategies for the management, prevention and lifestyle modification of obesity

In the early 1990s the WHO reported that the obesity levels had reached epidemic proportions. This created an urgent need to address the epidemic, by using a multifaceted approach to manage, prevent and reduce obesity. In 2014, the Global Status Report on NCDs described strategies to address obesity at population and

individual levels [84]. These relate to improving diets by promoting the uptake of healthy diets through policies at the population level as discussed in Section 1.4.4.1.2, and increasing physical activity as described in Section 1.4.4.2.4.

Although diet and physical activity are the primary recourse for reducing weight, individuals with psychosocial issues, relating to weight gain, may benefit from counselling to control their weight; i.e. understanding triggers for unhealthy eating would aid in weight reduction [297]. Another approach for morbidly obese individuals could be surgery [298]. For example, bariatric surgery may be usually considered when all other options have been exhausted. Nevertheless, the uptake of healthy diets and increased physical activity are still the cornerstone to maintain an optimal weight even in individuals undergoing bariatric surgery [299].

1.4.4.2 Hypertension

1.4.4.2.1 Definition, measurement and health consequences

Hypertension, commonly known as high blood pressure, is defined as systolic and/or diastolic blood pressure ≥ 140/90 mmHg or being on antihypertensive medication [65]. Most hypertension is primary hypertension or idiopathic, but may also be secondary to other medical conditions, such as renal failure, pheochromocytoma, renovascular disease, aldosteronism, etc [300]. For this thesis we will focus on primary or idiopathic hypertension.

Blood pressure is measured by auscultation using a stethoscope and mercury-tube sphygmomanometer on the arm of an individual [301] or, more recently, by using a semi-automated blood pressure machine. The latter is used in epidemiological studies and can be easily used at home for self-monitoring due to the ease of use [302–304].

The clinical consequences of hypertension include macrovascular and microvascular complications. Macrovascular clinical consequences arising from untreated or uncontrolled hypertension include IHD, stroke and heart failure [305–307]. Microvascular complications include retinopathy and nephropathy and renal failure, etc, [308]. Hyperglycaemia and diabetes exacerbate these complications. For example by reducing blood pressure level the risk of death due to IHD and stroke reduces by 40% and 42%, respectively [309].

1.4.4.2.2 Predisposing factors

The development of essential hypertension is complex and includes genetic and other non-modifiable factors such as age, family history, etc. and modifiable risk factors [65]. Modifiable risk factors for hypertension include obesity, unhealthy diets, physical inactivity, and alcohol use. These include a high salt and caloric diets, decrease intake of fruits and vegetables, excessive alcohol use, and low physical activity levels [65,310–315]. These have been discussed further in sections 1.4.4.1, 1.4.4.2, 1.4.4.3 and 1.4.4.4. Additionally, psychosocial risk factors also contribute to the development of hypertension [316]. Stress stimulate physiological responses which lead to the development of hypertension [317,318].

1.4.4.2.3 Prevalence and trends

In 2015, hypertension prevalence in adults ≥ 18 years of age was estimated to be 22.1% with a slight male preponderance (males: 24.1% vs. females: 20.1%) [319]. This was evident from the global average mean SBP where males had a higher average SBP compared to females (males: 127.0 mmHg vs. females: 122.3 mmHg) [320]. Hypertension affects more adults in LMICs compared with HICs; two-thirds in LMICs vs. one-fifth in HICs [319]. The Global Burden of Disease study reported that the absolute number of adults with hypertension had substantially increased between 1975 and 2015, from 594 million to 1.13 billion [321]. This increase was largely attributed to LMICs where there had been an increase in aging populations and population growth [321]. Interestingly, trend studies demonstrate this more clearly where the mean SBP decreased substantially in HICs between 1975 and 2015, while increasing in LMICs. These increases in LMICs, are mainly from Central and Eastern Europe, south Asia and SSA [321] .

In 2015, the WHO Africa region had the highest hypertension prevalence at 27.4%, which had increased slightly since 1975 from 26.5% [319]. The hypertension prevalence in 2015, was similar between females and males (females: 27.7% vs males: 26.8%) [319]. In South Africa, the overall hypertension prevalence was 46% and 44% amongst females and males in 2016 [21]. This had nearly doubled since 1998 from 25% in females and 23% in males [22].

1.4.4.2.4 Mortality

Globally, the leading risk factor contributing to mortality in 2019 was high SBP, with an estimated 10.8 million deaths reported [55]. These deaths attributable to high SBP were linked mainly to CVD, diabetes and kidney disease [55]. Mortality attributable to high SBP varied substantially by region with the higher burden in LMICs (8.5 million) compared with HICs (1.9 million) [55]. The absolute number of deaths attributed to high SBP increased in LMICs while decreasing in HICs, between 1990 and 2019 [55]. In 2019, high SBP accounted for 11.8% of total deaths in Africa and was the third leading risk factor for mortality [55]. Mortality attributable to high SBP in Africa increased between 1990 and 2019, from 517,225 to 1,054,072, which was an approximate doubling of the number of deaths attributable to high SBP [55].

In 2019, high SBP was the second leading risk factor contributing to mortality in South Africa [55]. The number of deaths attributable to high SBP in South Africa has increased more than 2-fold between 1990 (29,648) and 2019 (61,473) [55]. About 9% of total deaths were due to high SBP in South Africa [322].

1.4.4.2.5 Management of hypertension

For the adequate management of hypertension, there needs to be high rates of awareness, treatment and control of hypertension. Failure to achieve adequate hypertension management places a considerable burden on households, particularly those who are poverty-stricken, given that uncontrolled blood pressure could lead to subsequent premature morbidity and mortality [323,324]. In LMICs, only one-third of individuals with hypertension were aware of their hypertension status in 2010. This was considerably lower than the two-thirds reported in HICs regions [325]. Additionally, treatment among those who were aware of their hypertension status, was quite disparate between the regions, with less than one-third (29.0%) on treatment in LMICs compared with 55.6% in HICs [325]. Furthermore, the control of hypertension, amongst those on treatment, in LMICs is very low, with only 7.7% controlled on treatment. Hypertension control is more than 3-fold higher in HIC regions at 28.4%; however, this is still suboptimal [325].

In SSA, the awareness, treatment and control of hypertension was in keeping with other LMICs. In a meta-analysis, the awareness (11-47%), treatment (10-32%) and control (0.4-16.8%) of hypertension in SSA was amongst the worst in LMICs [326]. In

South Africa, management of hypertension was indicated to be better than other LMIC regions. In a paper using the South African 2011 census data, awareness of hypertension was higher in females (29%) compared to males (18%). Interestingly, of those aware of their hypertension status over 80%, in both genders, were on treatment for the disease but less than on-third had control of the disease [327].

Together with appropriate medical management, a healthy lifestyle is required for optimal hypertension care [326]. These lifestyle modifications include decreases in salt intake, increase fruits and vegetables intake, optimal weight management and physical activity [65,325]. These have been discussed in sections 1.4.4.1.2 and 1.4.4.2.4.

Even though cost-effective treatment for hypertension is available, management remains poor globally, and particularly in Africa [325,328]. The determinants of hypertension management are multifactorial and include the healthcare system, healthcare providers and patient factors [329]. Currently, multiple shortcomings exist, particularly in LMICs leading to suboptimal care. For instance, the healthcare system challenges include overcrowded healthcare facilities, limited functioning equipment and inconsistent supply of cost-effective medication to patients, among other barriers [330]. This is compounded by insufficient and inadequately trained healthcare workers to provide hypertension care [329–331]. Patient factors include limited knowledge on hypertension leading to defaults on treatment, and time and cost constraints preventing regular attendance for hypertension management [330].

In order to improve hypertension management, all determinants need to be addressed. Among the measures that may be implemented to alleviate the burden on both the healthcare facilities and providers is task-shifting, i.e. shifting tasks from higher level to lower level healthcare workers [330]. For instance, nurses and community healthcare workers could manage uncomplicated hypertension, while physicians treat more serious cases [332,333]. This would assist to reduce overburdened healthcare system and reduce waiting periods for patients at clinics. Further, community health care workers could provide patient education to improve adherence to care.

1.4.4.3 Diabetes

1.4.4.3.1 Definition, measurement and health consequences

According to the International Diabetes Federation (IDF), diabetes is a metabolic disorder characterised by chronic hyperglycaemia because of defects in insulin secretion, insulin action or both [332,333]. Diabetes may be classifies as type 1 diabetes mellitus, T2DM or gestational diabetes, among other causes [334]. The predominant form of diabetes being studied is T2DM, which is the focus of this thesis. The gold standard to diagnose diabetes is the oral glucose tolerance test (OGTT) [334]. Fasting blood glucose levels ≥ 7mmol/L and/or 2-hour blood glucose levels ≥ 11.1 mmol/L are diagnostic of diabetes.

Diabetes contributes substantially to morbidity and premature death worldwide. These include microvascular complications which affect the kidney (nephropathy), retina (retinopathy) and vascular endothelium (neuropathy) [334]. Macrovascular complications in people with diabetes are associated with the large blood vessels and contribute to the onset of CVD such as IHD, stroke and peripheral vascular disease [335–339]. According to the IDF, in the presence of diabetes, the risk of developing any type of CVD is 32%, IHD 21% and stroke 7.6% [337–341]. Individuals with diabetes also have a 2-to-4 fold higher all-cause mortality compared to non-diabetes [334].

1.4.4.3.2 Predisposing factors

Predisposing factors associated with the onset of T2DM include both non-modifiable (age, gender, family history and ethnicity) and modifiable (obesity, unhealthy diet, and physical inactivity) risk factors [342]. By adjusting the modifiable risk factors, studies have demonstrated a decrease in the onset of diabetes. For example, the IDF indicated that across four studies, in which lifestyle modification was implemented, the relative risk reduction of diabetes was between 38.0-67.4% depending on the duration of study [343–346].

1.4.4.3.3 Prevalence and trends

In 2019, the IDF estimated that the global prevalence of diabetes, amongst adults aged 20 to 79 years, was 9.3% (463 million people) [347]. This prevalence has increased from 8.3% (366 million) in 2011 [348]. Furthermore, the prevalence of

diabetes in LMICs and HICs increased between 2011 (LMICs: 8.6% vs HICs: 7.9%) and 2019 (LMICs: 9.5% vs HICs: 10.4%) [347,348]. The prevalence of diabetes was similar by gender (females: 9.0% vs males: 9.6%) [347,348]. In Africa, the estimated prevalence of diabetes, in 2019, was 3.9%. This corresponds to an estimated 19.4 million people as per the IDF [347]. This has increased from 2.4% (7.1 million) in 2001 [347]. In South Africa, an estimated 4.6 million people between the ages of 20-79 years of age had diabetes in 2019 [349]. These numbers have more than doubled from 1.9 million in 2011 [348].

1.4.4.3.4 Mortality

The global deaths from all-cause in people with diabetes aged 20-79 year was 11.3% in 2019, which corresponds to 4.2 million deaths [349]. By sex, more females died due to diabetes compared to their male counterparts (females: 2.3 million vs males: 1.9 million) [347]. Despite Africa not having the highest overall mortality due to diabetes globally, the region had the highest proportion of premature deaths (73.1%), among those under the age of 60 years [347]. In comparison, in Europe, where the overall number of deaths was similar to that of Africa, the proportion of premature deaths was the lowest globally at 31.4%, which was less than half that of Africa [347].

The premature deaths are the result of uncontrolled diabetes which is highest in Africa. The implications of the premature deaths also has an impact on a countries' economic growth due to reductions in the work force and loss of income among bread winners leading to increases in poverty [347].

In South Africa, Statistics South Africa approximated that diabetes was the second leading overall cause of mortality in the country, contributing to 26,879 deaths in 2018 [350]. Diabetes was the number one underlying cause of death amongst females, while it was the fourth leading underlying cause of death amongst males [350]. This was in keeping with the rest of Africa where mortality was 1.8 times higher in females compared to their male counterparts [350].

1.4.4.3.5 Management of diabetes

Effective management of diabetes relies on awareness, treatment and control of the disease in order to have optimally controlled glucose levels [347]. In 2019, the IDF approximated that 1 in 2 adults with diabetes was unaware of their condition, globally.

The highest proportion of unawareness was in LMICs (52.1%) compared with HICs regions (38.3%) [347]. Furthermore, SSA reported the highest proportions of unaware individuals globally (59.7%) [347]. These high rates of undiagnosed diabetes are likely attributable to deficiencies in healthcare facilities, healthcare providers and patient factors. The factors contributing to poor diabetes management are likely similar as those for hypertension, which have been discussed in section 4.5.2.5.

The proportion of individuals with diabetes on treatment was between 29.6-56.0% across LMICs, including those in SSA, as indicated in the PURE study, with HICs regions having the highest proportion, i.e. 74.0% [351]. These treatments are considered to be cost effective; however, poorer households were unable to afford these medications, particularly in LMICs, as they pay out of pocket for their diabetic medication [347,351]. For instance, an estimated 13.8% of people with known diabetes globally are unable to afford diabetic oral medication, while a further 36.7% are unable to afford insulin [347,351]. This in turn leads to poor control of glucose levels and thus increases the onset of serve diabetic complications in individuals.

Regular testing of glucose levels is required for diabetes control. However, about 47% of individual with diabetes in SSA reported that they had not tested their glycaemic levels in a 12-month period [352]. This is of concern and could be attributed to factors such as the lack of healthcare facilities, healthcare providers or individuals becoming complacent due to not understanding the severity of the disease nor its complications. Therefore, patient education on appropriate diets and adequate physical activity to optimise glucose control is crucial. Improvements required for healthier lifestyles have been described in sections 1.4.4.1, 1.4.4.2, 1.4.4.3 and 1.4.4.4.

1.4.4.4 Dyslipidaemia

1.4.4.4.1 Definition and health consequences

The presence of abnormal blood concentrations of either TC, Low-Density Lipoprotein Cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), or Triglycerides (TG), is defined as dyslipidaemia [353]. Each dyslipidaemia component confers an independent risk for CVDs, which is independent of each other, and should therefore be evaluated separately. For example, while higher LDL-C and TG confer a greater risk for CVD, higher HDL-C is protective. Therefore, it is important to assess the

individual dyslipidaemia components rather than only assessing the composite indicator which is TC [354].

Dyslipidaemia may be hereditary, due to secondary causes such as nephrotic syndrome and hypothyroidism, or could be related to poor diets and inadequate physical activity levels [353]. Dyslipidaemia is an important risk factor in the development of atherosclerosis leading to CVDs [355–358]. As reported in the INTERHEART study, abnormal lipid levels were one of the greatest risk factors associated with the onset of IHD [353,359]. Dyslipidaemia is also closely linked with hypertension and diabetes and their presence accelerates the risk of developing CVD.

1.4.4.4.2 Predisposing factors

Risk factors associated with the onset of TC include poor diets, physical inactivity and genetics [360]. In regards to diet, a high level of trans fat and high-calorie diet has been associated with dyslipidaemia and the onset of endothelial dysfunction [361–365].

1.4.4.4.3 Prevalence and trends

At a global level, data on the prevalence of elevated LDL-C, the lipid component that is the target for treatment, is limited, with more information available on elevated TC. In 2008, the WHO reported that the prevalence of elevated TC was 39% amongst adults [364,365]. The average TC level had remained constant over a 10 years period, 2008 :4.6 mmol/L vs 2018: 4.5 mmol/L [366]. In 2008, HICs had reported the highest prevalence of TC across all income groups [366]. The mean TC in LMICs was lower than that of HICs regions [2008: (LMICs: 4.6 mmol/L vs HICs: 5.0 mmol/L)] [366]. Mean TC levels have remained constant in LMICs over a 10-year period, while HICs reported a slight decrease [2018 (LMICs: 4.5 mmol/L vs HICs: 4.8 mmol/L)][366].

In a meta-analysis conducted in 2018, the overall prevalence of dyslipidaemia in Africa was 29.7% for elevated TC (cut-off criteria: ≥5 mmol/L), 18.5% for elevated LDL-C (cut-off criteria: ≥3.3 mmol/L), 38.6% for low HDL-C (cut-off criteria: <1.0mml/L) and 26.0% for TG (cut-off criteria: ≥1.7 mmol/L) [367]. In South Africa, the CRIBSA study indicated that TC, in age groups 25 -64 years increased from 1990 (19.3%) to 2008/09 (23.3%) using a cut-off of >5.0 mmol/l [368]. Interestingly, although this had increased slightly, the overall prevalence of LDL-C (cut-off >3.0mmol/L) had more than doubled

over this period, i.e. 1990: 17.0% to 2008/09: 40.7% [368]. The disproportionate lower increase is TC is likely a reflection of the high prevalence of low HDL-C with a cut-off <1.2mmol/l (1990: 33.5% vs 2008/09 : 61.7%) [368]

1.4.4.4.4 Mortality

In 2019, high LDL-C was the 7th leading risk factor for mortality, and had contributed 7.8% of the total cause of deaths globally [368]. Between 1990 and 2019, there had been an increase in the total number of deaths attributed to elevated LDL-C, i.e. from 3.0 million to 4.3 million, respectively [366]. Of those who had died, 41.4% was attributed to IHD while 9.4% was due to stroke [55]. LMICs, on the other hand, had reported the highest number of deaths attributed to elevated LDL-C, in comparison to HICs, in 2019 (LMICs: 3.4 million vs HICs: 862,050) [55]. Since 1990, the number of deaths attributable to high LDL-C in LMICs had almost doubled, whilst HICs reported a decline over the same period (LMICs: 1.8 million vs HICs: 1.2 million) [55].

In further analysis it was determined that, although Africa had the lowest number of deaths attributed to LDL-C in 2019 globally, the percentage of LDL-C attributable mortality had increased over a 30 year period , from 2.1% (166,309 in 1990) to 3.81% (340,811 in 2019) [55]. These increases could be due to globalization occurring in Africa, which has aided in the rapid expansion of urban areas and adoption of an unhealthy lifestyle.

In 2000, 4.6% of all deaths were attributed to high cholesterol in South Africa, which was the 7th leading risk factor of underlying causes of death [369]. The Global Burden of Disease study estimated that the percentage of overall deaths attributed to elevated LDL-C, in South Africa, was 2.82% in 2019, which had changed minimally since 1990 (2.48%)[55].

1.4.4.4.5 Management of dyslipidaemia

The management of dyslipidaemia is considered to be fairly recent in comparison to other diseases such as hypertension and diabetes. Nevertheless, the principles of management remain the same, i.e., having effective awareness, treatment and control of the disease.

In general population studies in SSA, there has been a lack of data on dyslipidaemia and its management given that majority of studies that do focus on dyslipidaemia

management is in relation to diseases such as hypertension and diabetes [370–372]. This is due to those individuals having regular contact with healthcare facilities and providers in relation to the management of their other diseases. Interestingly, even though these individuals have access to healthcare services, the prescription and use of dyslipidaemia treatment is indicated to be low [370–372]. For instance, in a Ghanaian localised study it was indicated that the prescription of statins was low, with 1 in 6 individuals with diabetes and 1 in 7 who had a stroke were indicated to be on treatment [372]. While in South Africa, in two separate studies, the awareness (urban: 2.6% and rural: 1.1%), treatment (urban: 2.7% and rural: 0.7%), and control (urban:1.5% and rural: none given) was extremely low, although this is indicated to be slightly better than the rest of SSA [368,373].

When comparing this to the management of wealthier countries, the management of dyslipidaemia, while not optimal, is much better, with approximately 1 in 5 individuals being aware of their status (females:17% and males: 19%), whilst just under 50% were on treatment (females: 44% and males: 45%), and almost two-thirds of individual reported to have control ,with a TC ≤ 6.5mmol/l [374].

1.5 Conclusion

There is a high and rising burden of CVD which includes obesity, hypertension, diabetes and dyslipidaemia, particularly in Africa. This is influenced by levels of unhealthy lifestyle behaviours relating to unmodifiable and modifiable risk factors. Therefore, monitoring the influence and development of social determinants, i.e. globalisation and urbanisation, on the uptake of unhealthy lifestyle behaviours, i.e. unhealthy diet, physical inactivity, tobacco and alcohol use, and the subsequent development of cardiometabolic risk, i.e. obesity, hypertension, diabetes and dyslipidaemia, is critical in order to curb their harmful effects. Such information is needed for the formulation of health services and policy solutions to prevent further deterioration of the health of the population and may furthermore be used to extrapolate to other countries, communities and ethnicities.

This literature highlights the increasing trends of the burden of CVD risk factors in South Africa, with data from the national 1998, 2003 and 2016 SADHS [21,375,376]. However, these may not reflect trends at the local level, i.e. in specific population or

minority groups, who are not Black African. This includes the Mixed-ancestry population from the Western Cape who have different exposures to CVD risk factors due to different cultural beliefs which influence their lifestyle behaviours. As a result, the CVD risk factors and trends in the Mixed-ancestry population in the Western Cape may not mimic those of the major the South African population group and therefore warrants exploration in greater detail.

1.6 References

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Chapter 2- Overview of the Methods for the study of cardiovascular disease trends in a South African population

2.1 Introduction

The project made use of two cross-sectional studies conducted in the same population seven years apart. Survey one, called the Bellville South Study was conducted in 2008/2009 while survey two, named the Vascular and Metabolic Health Study (VMH), commenced in 2014/2016.

2.2 Study population

South Africa has a diverse landscape with regards to ethnicity. Under the apartheid government, the South African population was classified into four ethnic groups, namely, Mixed-ancestry, Black, Caucasian, and Indian/Asian. According to the Population Registration Act of 1950, proclamation No.123, a Mixed-ancestry individual was defined as a person who was neither Caucasian nor Black, or were from the Khoisan, Bantu or other aboriginal ethnicities of South Africa [1,2]. According to the South African census of 2011, the South African population constituted 79.2% blacks, 8.9% Mixed-ancestry, 8.9% Caucasian, and 2.5% Indian/Asian [3].

However, the population groups are not evenly distributed around the country. For example, most of the Mixed-ancestry population is concentrated in the Western Cape province of South Africa, of which Cape Town is the capital city. Of the 4 million residents in Cape Town, the Mixed-ancestry population comprises of the highest proportion (47.5%), followed by blacks (35.7%) and then Caucasians (16.0%).

During apartheid, the government had passed a law called ‘The Group Areas Act of 1950’ in which people were forced to reside in specific areas based on ethnicity. Suburbs such as Bellville South and Belhar in Cape Town were exclusively allocated to the Mixed-ancestry communities, see diagram 3.

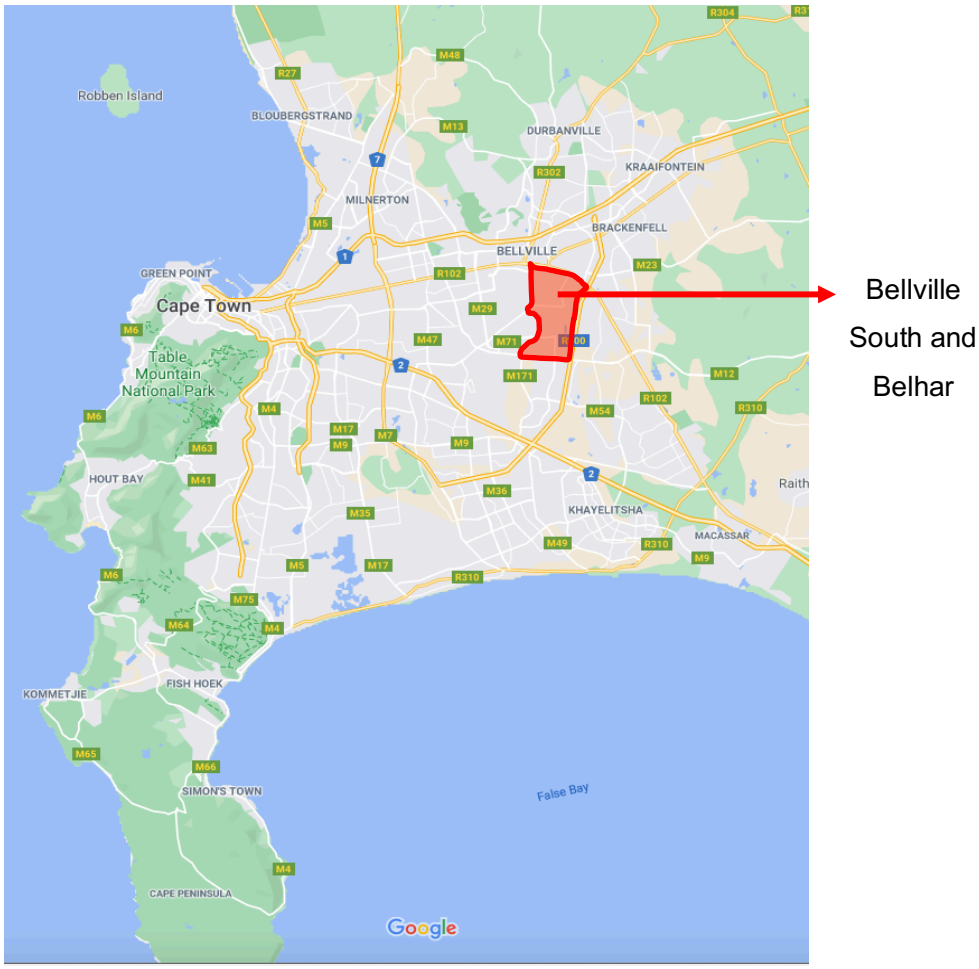

Figure 2.1. Map of Cape Town, South Africa (red highlight is Bellville South and Belhar)

Source: Google maps (2020), https://www.google.com/maps/@-34.0860378,18.5589428,10.75z

2.3 Study design and sampling procedure

According to the 2011 census, Bellville South and Belhar were defined as urban areas, with almost 90% of the residents being of Mixed-ancestry decent, with various professions, and socio-economic statuses [4,5]. For both surveys, all streets in the Bellville South area were included for recruitment; however, the same participants were not recruited in both surveys. The neighbouring suburb of Belhar, which has similar characteristics as Bellville South area, was only included in survey two.

Financial and logistical constraints dictated the sample sizes of both studies, which were derived using convenient sampling methods. Fieldworkers visited the area and worked systematically using the area map as a guide. Each street and house were visited during the recruitment phase, except those which were considered to be

dangerous i.e., known for gang violence etc. Fieldworkers visited the areas on multiple occasions to raise awareness of the studies and provide ample opportunities for residents to participate in the surveys.

All individuals who met the inclusion criteria were invited to participate in the surveys. For this thesis all participants over the age of 20 years were included from both surveys, as it was the common minimum age across both surveys and allowed for comparison. However, the minimum age of each survey was different due to the criteria set out by the principal investigator of each of the surveys (i.e., survey one: ≥18 years and survey two: ≥20 years). Therefore, the final number of participants included in this thesis in survey one was 928, while in survey two there was 1969.

2.4 Recruitment and marketing

The team for both surveys consisted of 1) fieldworkers, who had a minimum matriculation qualification; 2) qualified nurses from the community; and 3) a supervisor, who had a minimum of 2 years' experience in laboratory/fieldwork, monitored the performance of the team and was responsible for calibrating equipment according to a standard protocol.

In the first survey, awareness of the study was raised through the local radio station (Radio Tygerberg), community newspaper (The Tygerberger), a public address system (megaphone) on board a truck, and brochures and fliers. Additionally, buy-in was obtained from religious and community leaders. While in the second survey, Fieldworkers went door-to-door distributing fliers to raise awareness of the study and recruit participants. In both surveys, a day before the scheduled appointment, fieldworkers contacted participants reminding them to fast overnight and confirm the pick-up location.

2.5 Study criteria

2.5.1 Inclusion

The eligibility criteria for the purpose of this study which included a comparison of both surveys were (1) persons who identified as being Mixed -ancestry, (2) resided in either Bellville South or Belhar, and (3) ≥20 years of age.

2.5.2 Exclusion

In both surveys, participants were excluded from the survey if, (1) they were very sick (unable to do anything for themselves), and (2) females who were pregnant.

2.5.3 Onsite exclusion criteria

Participants who had not fasted were excluded and invited to revisit the clinic on another day. Participants who weighed less than 40 kg were not allowed to participate due to possible adverse health implications.

2.6 Data Collection

After completion of the consent forms, blood pressures, and fasting blood specimens were taken, followed by the administration of the OGTT for those without self-reported diabetes. Thereafter, the survey questionnaire was administered, anthropometric measurements taken and bloods drawn after a 2-hour period.

2.6.1 Questionnaire

The same questionnaire was used in both surveys and administered in either English or Afrikaans. Data collected included socio-demographic history, behavioural risk factors (smoking and alcohol consumption, physical activity, diet, etc), self-reported medical history (CVD, diabetes mellitus, hypertension, dyslipidaemia, etc), and relevant family medical history. These were adapted from the WHO's STEPwise approach to NCD risk factor surveillance [6]. Further medication history was also obtained by examining the clinic cards as well as the medication that participants brought to the research site.

2.6.2 Clinical measurements

Clinical measurements included height, weight, hip and WC, and BP. Measurements were carried out by fieldworkers who underwent training to standardise all measurements before the commencement of the surveys.

BP measurements were performed using a semi-automatic digital blood pressure monitor (survey one: Rossmax PA, USA and survey two: Omron M6 comfort-preformed cuff BP Monitor, China) in accordance with the WHO guidelines. Following

a 10 minutes rest, blood pressure was taken 3 times at 5-minute intervals [7]. All three readings were recorded, and the lowest BP reading used in the analyses.

Weight was determined on a digital scale, which was calibrated and standardised using the weight of a known mass. Weight measurements were recorded to the nearest 0.1 kilograms and taken with each subject in light clothing and barefoot. Height was recorded in centimetres, to the nearest one decimal point, using a stadiometer. Participants stood on a flat surface at a right angle to the vertical board of the stadiometer. BMI was calculated as weight per metre squared (kg/m2). WC was measured using a non-elastic tape at the level of the narrowest part of the torso midway between the lowest palpable rib and the iliac crest (STEPwise manual). All anthropometric measurements were performed three times, and the average measurements were used for analysis.

2.6.3 Biochemical analyses

Following an overnight fast, all participants, except those with self-reported diabetes, underwent a 75 g oral glucose tolerance test (OGTT) as prescribed by the WHO [8]. Other blood samples collected included glycated haemoglobin (HbA1c) assessed by High Performance Liquid Chromatography (BioRad Variant Turbo, BioRad, Hercules, CA, USA); serum insulin by a paramagnetic particle chemiluminescence assay (Beckman DXI, Beckman Coulter, South Africa); serum cotinine by Competitive Chemiluminescent (Immulite 2000, Siemens, Munich, Germany); plasma glucose by enzymatic hexokinase method (Beckman AU, Beckman Coulter, Brea, CA, USA); TC; HDL-C by enzymatic immunoinhibition – end point (Beckman AU, Beckman Coulter, Brea, CA, USA); TG by glycerol phosphate oxidase-peroxidase, end point (Beckman AU, Beckman Coulter, Brea, CA, USA); LDL-C by enzymatic selective protection – end point (Beckman AU, Beckman Coulter, Brea, CA, USA) or calculated using Friedewald's formula in survey one; ultra-sensitive- C-Reactive Protein (us-CRP) by Latex Particle Immunoturbidimetry (Beckman AU, Beckman Coulter, Brea, CA, USA); Serum creatinine by the modified Jaffe-Kinetic method (Beckman AU, Beckman Coulter, Brea, CA, USA); and gamma Glutamyl Transferase (gamma GT) by IFCC-Rate (Beckman AU, Beckman Coulter, Brea, CA, USA). Blood samples were transported daily in an ice-pack box for processing at an ISO 15189 accredited Pathology practice (PathCare Reference Laboratory, Cape Town, South Africa).

2.7 Definitions

2.7.1 Adiposity

The BMI classification as per the WHO were as follow: <18.5 kg/m2 is classified as underweight, between 18.5 and 24.9 kg/m2 as normal weight, between 25 and 29.9 kg/m2 as overweight and ≥30 kg/m2 as obese [9].

As per Matsha et al [10], in the Mixed-ancestry population, raised WC was defined as ≥ 90cm for both females and males.

2.7.2 Hypertension

Hypertension is defined as SBP equal to or above 140 mmHg and/or DBP equal to or above 90 mmHg or on hypertension medication [11,12]

2.7.3 Dysglycaemia

Categories of glucose tolerance were defined by applying the 1998 WHO criteria [13]. Diabetes is defined as a fasting plasma glucose level ≥7.0 mmol/L and/or a 2-hour post-OGTT plasma glucose level ≥11.1 mmol/L, or self-reported on diabetes medication. Prediabetes included impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG). IGT was defined as having a fasting plasma glucose <7.0mmol/l and a post 2-h glucose between 7.8 mmol/l and 11.1 mmol/l. IFG was defined as fasting plasma glucose between 6.1 and 6.9 mmol/l and, if measure, a post 2-h glucose <7.8mmol/l.

2.7.4 Dyslipidaemia

Dyslipidaemia is defined as an abnormality of any of the following: TC ≥ 5.0 mmol/l, HDL-C < 1.2 mmol/l, LDL-C ≥3.0 mmol/l or TG ≥1.7 mmol/l [14,15]. In survey one LDL-C was determined using the Friedwald's formula i.e. LDL-C (mmol/L) = TC (mmol/L) − HDL-C (mmol/L − TG (mmol/L)/2.2[16], while LDL-C was measured in survey two.

2.7.5 Insulin resistance

Insulin resistance (IR) was calculated using five indices: the 75th percentile of fasting insulin, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [17] as well as the 25th percentile QUICKI [18], McAuley index [19] and Matsuda index [20]. The 75th or 25th percentiles were derived from the first survey and the same cut-

off points applied to the two survey populations. Using percentiles specific to each of the sample would lead to differing cut-off points and no change in IR prevalence over time.

2.7.6 Inflammation

Sub-clinical inflammation was assessed using two biomarkers: the us-CRP and gamma GT. The cut-point defining sub-clinical inflammation for us-CRP was >3mg/L [21,22] and for gamma GT it was ≥ 38 IU/L [23]

2.7.7 Obesity phenotypes

Obesity phenotype is defined when using BMI in conjunction with cardiometabolic risk factors in order to determine categories of metabolic health. Currently, there is no uniform criteria for obesity phenotype [24–27]; however, some of the JIS metabolic syndrome criteria [28] was used as cardiometabolic risk factors for this survey which included: Hypertension: BP ≥140 mmHg and/or ≥90mmg or on hypertension treatment [11,12]; (2) HOMA-IR cut off at the 90th percentile; (3) HDL-C i.e., male ≤1.0 mmol/l and female ≤1.30 mmol/l; (4) TG >1.7 mmol/l; and (5) Fasting glucose ≥ 5.6 mmol/l. Metabolically abnormal was defined as two or more cardiometabolic risk factors being abnormal, while one or less was considered metabolically healthy. The obesity phenotype categories were defined as normal weight and metabolically healthy (NWMH), normal weight and metabolically abnormal (NWMA), overweight and metabolically healthy (OvMH), overweight and metabolically abnormal (OvMA), obese and metabolically healthy (MHO), and obese and metabolically abnormal (MAO).

2.8 Statistical analyses

The data was analysed using the statistical program SPSS v.25 (IBM Corp., 2011). Descriptive statistics were used to summarize the data of the sample population. The profile of participants was summarized overall and across major subgroups (age and gender), for each year of the survey. Means and standard deviation and/or medians (25-75th percentiles) described the continuous variables and counts and proportions, the categorical variables. Comparisons across years were done using the student t-test, Analysis of Variance (ANOVA) and non-parametric equivalents for continuous variables including Kruskal-Wallis, while chi-square test for association and

equivalents for categorical variables. Determinants of changes between surveys were investigated using linear and generalized linear regression models for continuous outcomes, and logistic regression models for categorical outcomes. Furthermore, plots of distribution curves were used to investigate time shift in the distribution of key characteristics over time. A p-value <0.05 was used to characterise statistically significant results and adjustment made as appropriate for multiple comparisons.

2.9 Ethical considerations

Survey one received ethical approval from the Cape Peninsula University of Technology Ethics Committee (CPUT/HW-REC 2008/002) whilst survey two was approved by the Research Ethics Committees of the Cape Peninsula University of Technology (CPUT) and Stellenbosch University (respectively, NHREC: REC - 230 408 – 014 and N14/01/003). Additional ethics approval was obtained from the University of Cape Town for this PhD survey (ref: 442/2016).

Written informed consent was obtained from all participants, and the survey was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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Chapter 3- Motivation, aims and objectives

3.1 Motivation for the study

With the Mixed-ancestry community being the second biggest population in South Africa and the largest in the Western Cape, understanding the temporal changes of cardiometabolic diseases in this urban community is important. This will enable government to better target healthcare resources, and develop policies and strategies for effective screening, treatment and management of these diseases.

However, the last regional community-based surveys on the urban Mixed-ancestry population that focused on cardiometabolic diseases risk factors were done in 1985 and 1999 [1,2]. Using data from community-based surveys that are over 20 years old to allocate resources and develop management programmes would be ineffective and inappropriate, given that they do not reflect the current burden of cardiometabolic disease and its risk factors.

Conducting community-based serial surveillance surveys on cardiometabolic disease in the Mixed-ancestry population can potentially highlight healthcare challenges that require greater attention. Such data can inform the allocation of health resources and the development of strategies for the screening and management of cardiometabolic and CVD risk factors. Serial surveillance data will inform better planning, implementation, and evaluation of public health practice.

Considering the changing trends of CVD, which have been shown in the Black African population in the Western Cape [3–5], it is likely that the burden of cardiometabolic diseases and their risk factors in other specific or minority populations, such as the Western Cape Mixed-ancestry population, may have also changed. Studies on cardiometabolic traits in the Western Cape Mixed-ancestry population have not been conducted recently. For example, the last study on hypertension at a community-level in the Western Cape Mixed-ancestry population was done almost four decades ago [6].

3.2 Aims

This study aims to investigate the temporal changes in hypertension, obesity phenotypes, sub-clinical inflammation and IR, and their determinants, between 2008/09 and 2014/16 in the Mixed-ancestry population aged 20 years and older in Cape Town.

3.3 Objectives

The objective of the study was to determine the change in patterns of cardiometabolic diseases and their risk factors between 2008/09 and 2014/16, in the Mixed-ancestry population in Cape Town, South Africa. This was done on history, clinical examination and biochemical assessments by collecting the following information:

1. Self-reported sociodemographic data including medical history of pre-existing cardiometabolic disease and behavioural risk factors
2. Measuring the BP electronically using standardised methodology to determine change in BP levels and hypertension.
3. The measurement of anthropometric profile and obesity by measuring height, weight, WC, hip circumference and calculating BMI.
4. Administering OGTTs and measuring HbA1c to diagnose diabetes
5. Measuring the lipid profile (TC, LDL-C, HDL-C and TG) in fasting serum samples to diagnose dyslipidaemia.
6. Assessing cardiometabolic biomarkers of us-CRP and gamma-GT for sub-clinical inflammation
7. Calculating IR using five known indices (insulin fasting, HOMA-IR, QUICKI, McAuley and Matsuda) commonly used in clinical and epidemiological studies.

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Chapter 4- Manuscript 1

Title: Increase in blood pressure over a 7-year period in a Mixed-ancestry South African population

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Journal: South African Medical Journal

DOI: 10.7196/SAMJ. 2019.v109i7.13663

Abstract

Background. An increase in the prevalence of high blood pressure (BP) has been reported globally and in the South African (SA) population.

Objectives. To investigate temporal changes in absolute BP levels and hypertension prevalence in the Mixed-ancestry South Africans.

Methods. Participants were from two independent cross-sectional surveys conducted during 2008/09 (N=928) and 2014/16 (N=1 969) in Bellville South, Cape Town, SA. Participants' eligibility was based on several criteria, including age >20 years and neither bedridden nor pregnant. Data were obtained by administered questionnaires, clinical measurements (BP and anthropometry) and biochemical assessments (oral glucose tolerance tests and cotinine levels). Known hypertension was based on a self-reported history of doctor-diagnosed hypertension and ongoing treatment. Comparison across years was based on the crude prevalence of hypertension as well as direct age-standardised prevalence, based on the SA 2011 Mixed-ancestry population distribution, in 10-year age increments.

Results. In all, 708 participants (76.3%) in 2008/09 and 1 488 (75.6%) in 2014/16 were female. Between 2008/09 and 2014/16, mean systolic BP increased from 124 to 136 mmHg (absolute mean difference 15 mmHg) and mean diastolic BP from 75 to 85 mmHg (absolute mean difference 9 mmHg) in the overall sample. The prevalence of screen-detected hypertension increased from 11.6% to 24.8%, with a similar increase in males and females, while the prevalence of known cases remained stable. These changes remained significant after adjustment for age and gender.

Conclusions. A rightward shift in absolute BP translated into a significant increase in the prevalence of hypertension over time in this population. The predominant increases in screen-detected hypertension suggest that the deteriorating profile was not matched by efforts to detect and manage individuals with higher-than-optimal BP levels.

Keywords: Blood pressure, hypertension, screen-detected hypertension, age, Mixed-ancestry, South Africa

Background

Hypertension is the most prevalent non-communicable disease (NCD) risk factor estimated to affect two in five adults globally, and responsible for approximately 9.4 million deaths each year [1]. The highest hypertension prevalence, at 46%, is in the World Health Organization's (WHO) Africa region where it is frequently undiagnosed [1,2]. This is of concern because of the severe complications associated with raised blood pressure (BP). These include cardiovascular diseases (CVDs) such as strokes and heart attacks, kidney failure, cognitive impairment and blindness [3,4].

Hypertension in South Africa is similarly high to that reported on the rest of the continent; in the 2016 South African Demographic Survey (SADHS) the prevalence was 46% and 44% in ≥15-year-old females and males, respectively [5]. This represents a high and rising burden of hypertension in the country; the prevalence increased 1.8-2-fold in 2016 [5] compared with 1998 when it was 25% in females and 23% in males [6]. The hypertension prevalence in national surveys are generally a reflection of the findings in the Black African population who comprise the majority in the country (80.8%) [7]. The other historically defined South African population groups include Caucasian (8.0%), Indian/Asian (2.5%), and coloured or Mixed-ancestry (8.8%) individuals who have Khoisan, Caucasian, Black and Malay heritage [7], In the 2016 SADHS, Mixed-ancestry females and males had much higher hypertension prevalence (57% and 58%, respectively) compared with their Black African counterparts (females: 44%, males: 41%) [5]. Hypertension in the Mixed-ancestry population was 1.9-fold and 2.2-fold higher in 2016 compared with 1998 where the prevalence was 30% in females and 26% in
males [5, 6].

These findings, from a national study, are not generalizable to specific communities in South Africa because of urban-rural, provincial, population group and other differences. Therefore, these data may not be used to estimate the hypertension prevalence and patterns in the Mixed-ancestry population of Cape Town, where there is a dearth of recent data. Determining accurate hypertension prevalence and patterns at a local level is necessary to optimally and appropriately allocate healthcare resources and develop cost-effective therapeutic strategies and programmes for that

community. Therefore, the aim of this study was to investigate the temporal changes in absolute BP levels and hypertension prevalence from 2008/09 to 2014/16 in the Mixed-ancestry population of Bellville South, a suburb of Cape Town, Western Cape, South Africa.

Methods

Study population and sampling procedure

This study is a comparison of two independent cross-sectional studies conducted in 2008/09 and 2014/16 in the predominately Mixed-ancestry population of the Bellville-South Township. The Mixed-ancestry population, also known as coloured, comprises of 32-43% Khoisan (indigenous South Africans), 20–36% Bantu-speaking African, 21 – 28% European and 9 – 11% Asian ancestry and is unique to South Africa[8].The Bellville-South Township, which refers to an urban area that was underdeveloped, is located in the Northern suburbs of Cape Town South Africa and was founded in the late 1950s.The initial study was conducted in ≥18-year-old and the 2nd study in ≥20-year-old residents using randomized street selection. Trained fieldworkers approached every dwelling in the selected streets and invited all potential participants from each household who fulfilled the inclusion criteria. If there was no answer the recruiters would make a note and then move to the next house, this made it difficult to determine the number of non-responders in both studies. During the 2008/09 survey, 946 subjects were recruited as previously described by Zemlin et al. [9] and during the 2014/16 survey an additional 1989 subjects were recruited. Consenting subjects who were residing in the Bellville-South area, of Mixed-ancestry origin, were ≥20 years of age, neither bed-ridden nor pregnant were included in this study.

Data collection

Trained research personnel administered questionnaires and collected clinical and biochemical measurements at a designated research site. The anthropometry measurements, including weight, height, and hip and waist circumferences were obtained using standardized techniques as prescribed by the WHO [10]. Each measurement was taken thrice and then averaged for the purpose of this study. Registered nurses measured the participants' BPs, using electronic BP monitors; BP readings were taken three times at 3-minute intervals [10], of which the lowest systolic BP (SBP) and corresponding diastolic BP (DBP) readings were used. Participants with

no history of clinically-diagnosed diabetes mellitus underwent a 75-g oral glucose tolerance test (OGTT) as recommended by the WHO [11].

Definitions

Level of education was categorized into two groups, namely, ≤7 years of education (completion of primary school) and >7 years of education (secondary schooling and higher). Body mass index (BMI), calculated as weight in kilograms (kg) divided by height in metre squared (m2) defined normal weight (<25.0 kg/m2); overweight (25.0 kg/m2- 29.99 kg/m2) and obesity ≥30.0 kg/m2. Known hypertension was defined as those who were diagnosed and currently on hypertension medication, while screen-detected hypertension was those who had BP ≥140/90 mmHg. Diabetes diagnosis was defined as fasting plasma glucose ≥7.0 mmol/l and/or a 2-hour post-OGTT plasma glucose ≥11.1 mmol/l, or self-reported on diabetes medication. Pre-diabetes was defined as fasting plasma glucose between 6.1 and 6.9 mmol/l or/and a post 2-hour glucose between 7.8 mmol/l and 11.1 mmol/l [11]. Current tobacco use was defined as cotinine levels >10ng/mL [12, 13]. Alcoholic consumption was self-reported.

Statistical analysis

The software programmes Statistica v.13 (StatSoft, Southern Africa) and SPSS v.24 (IBM Corp, 2011) were used for data analyses. The results are reported as mean, standard deviation, percentages and confidence intervals (CI). The Student's t-test was used to assess the significance of absolute differences in mean BP over time while the chi-square test was used for categorical variables. Crude prevalence of hypertension as well as direct age-standardized prevalence, based on the South African 2011 Mixed-ancestry population distribution, were estimated in 10 year age increments [14]. Multivariable linear regression, adjusted for age, gender and years of study, was assessed the effects of BMI, waist circumference, diabetes status, tobacco and alcohol use, and level of education on absolute BP levels. Equivalent logistic regression models, adjusted for age, gender and year of study, investigated the predictors of hypertension overall (known and screen-detected) and separately for screen-detected hypertension. A p-value <0.05 characterized statistically significant results.

Results

The final sample size for the 2008/09 survey was 928 after excluding participants younger than 20 years of age, five non-consenting individuals and a single participant who withdrew from the study. The final sample size for the 2014/16survey was 1969 after excluding 10 participants each who were not eligible and who withdrew from the study

Differences between participants in 2008/09 and 2014/16

The majority of participants were female in both studies (2008/09: 76.3%, n=708 and 2014/16: 75.6%%, n=1488) (Table 1). In 2014/16, compared with the 2008/09 study, participants were younger (mean age: overall: 49.6 vs. 54.3 years, females: 50.3 vs. 53.7 years and males: 47.4 vs. 56.3 years, all $p<0.001$). The level of education was similar across both surveys (all $p>0.612$), with about two-thirds of participants having completed >7 years of education.

Within the surveys, male vs. female differences were observed for some characteristics, but not consistently across the two surveys, specifically with regards to males being younger in 2014/16 compared to 2008/09 (Table 1). This translated across the males anthropometric and behavioural aspects, with weight, BMI, waist, hip and diabetes status being in lower in 2014/16 compared to 2008/09. Furthermore, although the overall BMI decreased marginally between 2008/09 and 2014/16: 29.9 (7.3) vs. 29.2 (8.0) kg/m2) with a non-significant decrease in females (31.0 vs.30.7 kg/m2; $p=0.349$), BMI decreased significantly in males (26.1 vs.24.6 kg/m2, $p=0.003$). In 2008/09 and 2014/16, the percentage of current alcohol users was similar in the overall groups (27.3% vs. 26.6%) and in females (21.2% vs. 22.3%) but decreased in males: (47.0% vs. 39.5% $p<0.001$). The percentage of current smokers increased in all groups over the 7-year period: 42.5% vs. 49.8% overall, 40.9% vs. 46.2% in females and 47.7% vs. 60.8% in males; (all $p<0.019$).

Differences in BP and hypertension between 2008/09 and 2014/16

The mean BP levels increased between 2008/09 and 2014/16 from 124 mmHg to 136 mmHg for SBP and from 75 mmHg to 85 mmHg for DBP in the overall sample (both $p<0.001$). A similar pattern was observed for males and females (Figures 1 and 2). Between 2008/09 and 2014/16, the greatest increases for SBP were 19 mmHg in

females and 13 mmHg in males, while for DBP these were 12 mmHg and 9 mmHg in males and females, respectively (Figure 1).

The crude and age-standardised hypertension prevalence increased from 48.4% and 30.7%, respectively, in 2008/09 to 59.1% and 45.0% in 2014/16 ($p<0.001$). Of concern, was the high proportion of screen-detected or unknown hypertension, which more than doubled between 2008/09 and 2014/16; the crude prevalence increased from 11.6% to 24.8% and the age-standardized prevalence from 8.3 % to 22.9% (both $p\leq0.003$). The crude screen-detected hypertension by gender increased in both females (11.0% to 23.7%, $p<0.001$) and males (13.6% to 28.3%, $p<0.001$).

In contrast, the prevalence of known hypertension in the overall sample mostly remained stable: 36.7% in 2008/09 vs. 34.3% in 2014/16 for crude prevalence, and 22.4% vs. 22.1% for age-standardized prevalence. However, this concealed a significant decrease in known hypertension prevalence for males from 34.5% to 22.7% ($p=0.013$); there was minimal change for females: 37.4% vs. 38.1% ($p=0.838$) (Table 2). There was evidence of interaction by gender in the change of hypertension prevalence across years (known hypertension: $p=0.030$ for gender*year and screen-detected hypertension: $p<0.001$ for gender*year; Table 2).

Furthermore, when comparing the relation of age with hypertension prevalence, there was a highly significant decrease in the mean age of participants with screen-detected hypertension from 58.6 years (14.5) in 2008/09 to 51.0 years (13.8) in 2014/16 ($p<0.001$). Although the prevalence of screen-detected hypertension increased with age in 2008/09 peaking in the oldest age group (18%), in 2014/16 it peaked in the 40-49 age group (32%), (Figure 3).

Table 1. *Comparison of the characteristics of study participants in 2008/09 and 2014/16 by gender*

	Overall			Female			Male			F v. M 2008/09 *p*-value	F v. M 2014/16 *p*-value
	2008/09 (*N*=928) Mean (SD)	2014/16 (*N*=1 969) Mean (SD)	*p*-value	2008/09 (*N*=708) Mean (SD)	2014/16 (*N*=1 488) Mean (SD)	*p*-value	2008/09 (*N*=220) Mean (SD)	2014/16 (*N*=481) Mean (SD)	*p*-value		
Age (years), mean (SD)	54.3 (14.7)	49.6 (15.2)	<0.001	53.7 (14.4)	50.3 (14.9)	<0.001	56.3 (15.2)	47.4 (15.7)	<0.001	0.022	<0.001
Level of education, *n*/*N* (%)			0.612			0.653			0.856	0.056	0.007
≤7 years	324/920 (35.2)	670/1 956 (34.3)		259/702 (36.9)	531/1 479 (35.9)		65/218 (29.8)	139/477 (29.1)			
>7 years	596/920 (64.8)	1 286/1 956 (65.7)		443/702 (63.1)	948/1 479 (64.1)		153/218 (70.2)	338/477 (70.9)			
Alcohol use, *n*/*N* (%)			<0.001			<0.001			<0.001	<0.001	<0.001
Currently drinking	250/915 (27.3)	519/1 957 (26.6)		148/698 (21.2)	330/1 479 (22.3)		102/217 (47.0)	189/478 (39.5)			
Non-drinker	474/915 (51.8)	1 229/1 957 (62.8)		413/698 (59.2)	1 005/1 479 (68.0)		61/217 (28.1)	224/478 (46.9)			
Past drinker	191/915 (20.9)	209/1 957 (10.6)		137/698 (19.6)	144/1 479 (9.7)		54/217 (24.9)	65/478 (13.6)			
Tobacco use, *n*/*N* (%)			<0.001			0.019			0.001	0.074	<0.001
Smoker	392/923 (42.5)	950/1 909 (49.8)		288/705 (40.9)	666/1 442 (46.2)		104/218 (47.7)	284/467 (60.8)			
Non-smoker	531/923 (57.5)	959/1 909 (50.2)		417/705 (59.1)	776/1 442 (53.8)		114/218 (52.3)	183/467 (39.2)			
Weight (kg)	74.9 (17.9)	74.1 (19.8)	0.308	75.4 (18.1)	75.3 (19.9)	0.942	73.1 (17.1)	70.1 (19.0)	0.053	0.092	<0.001
Height (cm)	158.7 (8.7)	159.7 (8.6)	0.003	156.0 (7.0)	156.7 (6.6)	0.019	167.5 (8.0)	169.0 (7.5)	0.022	<0.001	<0.001
BMI (kg/m^2)	29.9 (7.3)	29.2 (8.0)	0.031	31.0 (7.2)	30.7 (7.9)	0.349	26.1 (6.2)	24.6 (6.4)	0.003	<0.001	<0.001
Waist circumference (cm)	97.1 (14.9)	92.6 (17.1)	<0.001	98.0 (14.7)	94.7 (16.7)	<0.001	94.1 (15.1)	86.1 (16.6)	<0.001	0.001	<0.001
Hip circumference (cm),	109.8 (14.8)	104.5 (16.4)	<0.001	112.7 (14.9)	107.7 (16.2)	<0.001	100.3 (10.0)	94.5 (12.5)	<0.001	<0.001	<0.001
SBP (mmHg)	123.5 (19.2)	136.0 (25.9)	<0.001	122.5 (19.5)	136.3 (25.7)	<0.001	126.6 (18.0)	135.0 (26.5)	<0.001	0.007	0.320
DBP (mmHg)	74.9 (12.5)	85.2 (14.9)	<0.001	74.5 (12.7)	85.8 (14.5)	<0.001	76.3 (11.7)	83.5 (15.8)	<0.001	0.068	<0.001
Pulse rate (bpm)	74.0 (11.7)	72.3 (12.8)	<0.001	74.4 (11.7)	73.4 (12.5)	0.06	72.7 (11.7)	68.9 (13.1)	<0.001	0.057	<0.001
Diabetic status, *n*/*N* (%)			<0.001			<0.001			<0.001	0.622	<0.001
Diabetes	266/925 (28.8)	384/1 960 (19.6)		198/705 (28.1)	310/1 480 (20.9)		68/220 (30.9)	74/480 (15.4)			
Prediabetes	185/925 (20)	298/1 960 (15.2)		145/705 (20.6)	243/1 480 (16.4)		40/220 (18.2)	55/480 (11.5)			
Normal	474/925 (51.2)	1278/1 960 (65.2)		362/705 (51.3)	927/1 480 (62.6)		112/220 (50.9)	351/480 (73.1)			

F v. M = female v. male; SD = standard deviation; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; bpm = beats per minute.

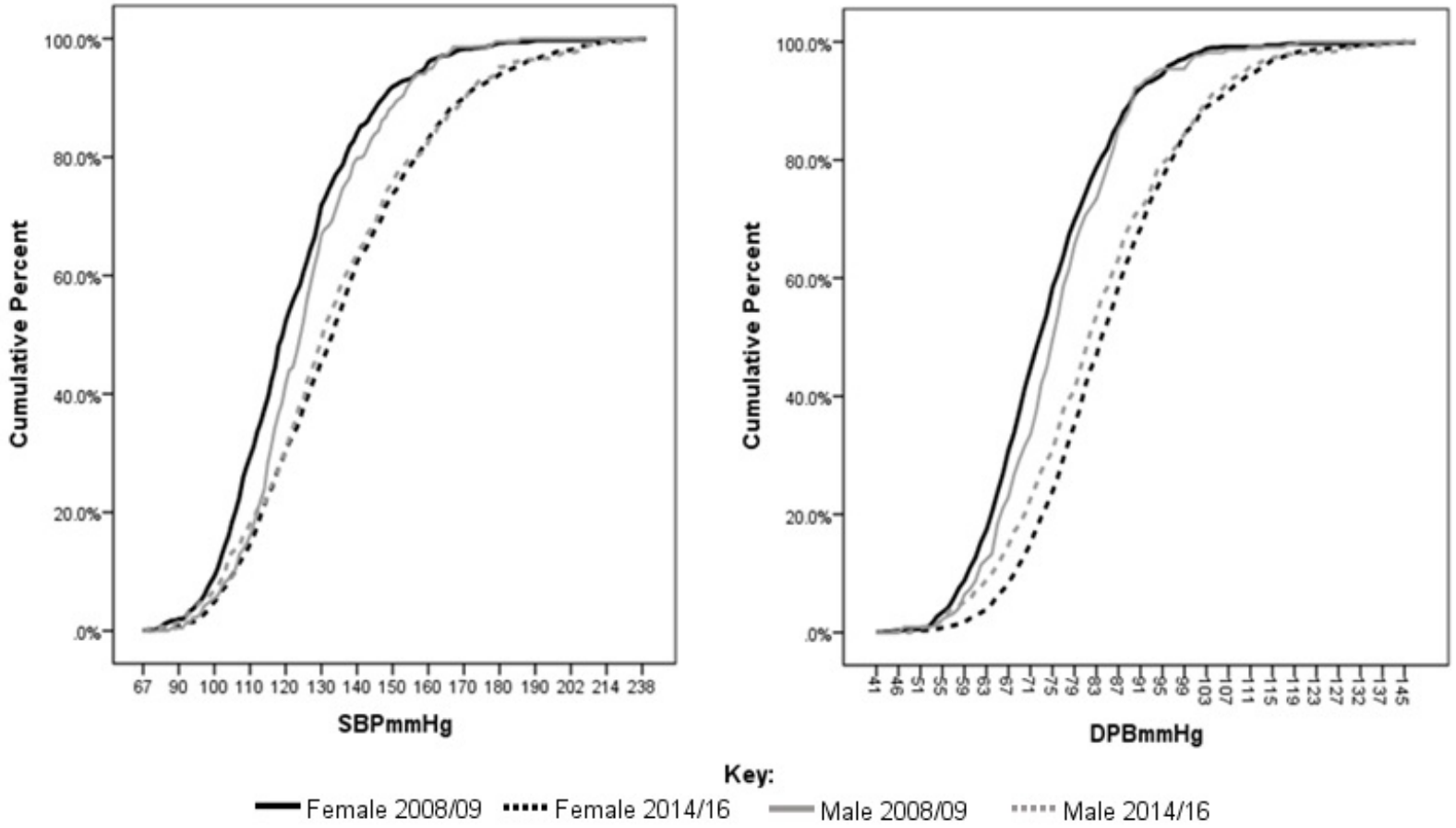

Figure 1. Cumulative distribution of overall hypertension status (normal, known hypertension and screen detected hypertension) by SBP and DBP for 2008/09 and 2014/16. (SBP = systolic blood pressure; DBP = diastolic blood pressure)

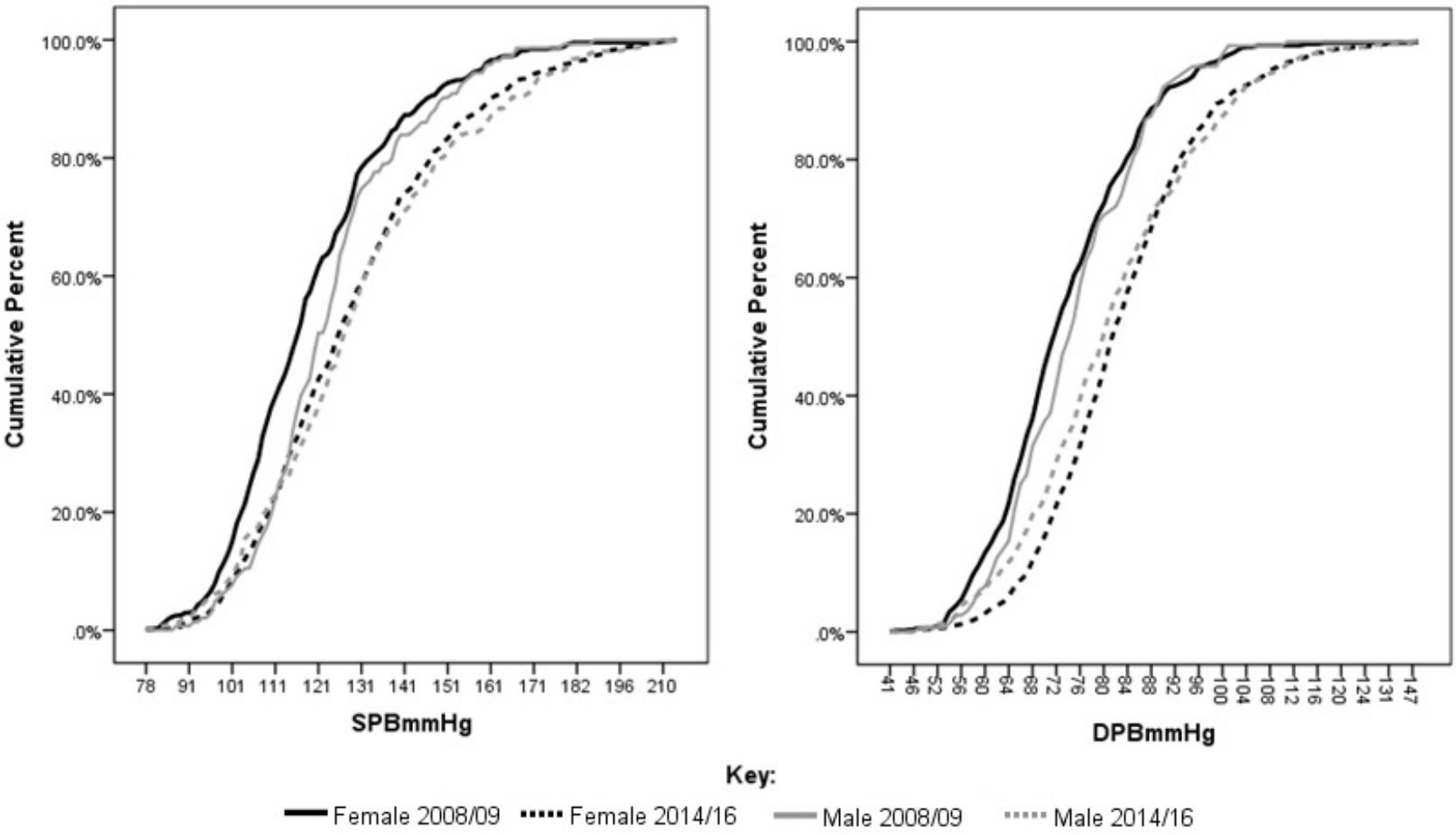
Cumulative Percent
100.0%
80.0%
60.0%
40.0%
20.0%
.0%
78 91 101 111 121 131 141 151 161 171 182 196 210
SPBmmHg
Cumulative Percent
100.0%
80.0%
60.0%
40.0%
20.0%
.0%
41 46 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 112 116 120 124 131 147
DPBmmHg
Key:
Female 2008/09
Female 2014/16
Male 2008/09
Male 2014/16

Figure 2. Cumulative distribution of screen-detected hypertension by SBP and DBP for 2008/09 and 2014/16. (SBP = systolic blood pressure; DBP = diastolic blood pressure)

	Total			Female			Male				
	2008/09 (*N*=928)	**2014/16 (*N*=1 969)**	***p*-value**	**2008/09 (*N*=708)**	**2014/16 (*N*=1 488)**	***p*-value**	**2008/09 (*N*=220)**	**2014/16 (*N*=481)**	***p*-value**	**F v. M 2008/09 *p*-value**	**F v. M 2014/16 *p*-value**
Crude prevalence of hypertension: BP ≥140/90 mmHg and on treatment, % (95% CI)											
Known hypertension	36.7 (33.7 - 40)	34.3 (32.2 - 36.5)	0.380	37.4 (33.9 - 41.1)	38.1 (35.6 - 40.6)	0.838	34.5 (28.4 - 41.3)	22.7 (19 - 26.7)	0.013	<0.001	<0.001
Screen-detected hypertension	11.6 (9.7 - 13.9)	24.8 (22.9 - 26.8)	<0.001	11.0 (8.9 - 13.6)	23.7 (21.5 - 25.9)	<0.001	13.6 (9.5 - 19.1)	28.3 (24.3 - 32.6)	0.007	<0.001	<0.001
Known and screen-detected hypertension	48.4 (45.1 - 51.7)	59.1 (56.9 - 61.3)	0.003	48.4 (44.7 -52.2)	61.8 (59.2 - 64.2)	0.002	48.2 (41.4 - 55)	50.9 (46.4 - 55.5)	0.695	<0.001	<0.001
Age-standardised prevalence of hypertension, % (95% CI)											
Known hypertension	22.4 (22.4 - 22.5)	22.1 (22.0 - 22.1)	<0.001	23.4 (23.3 - 23.5)	25.3 (25.2 - 25.3)	<0.001	21.9 (21.9 - 22)	14.1 (14.1 - 14.2)	<0.001	<0.001	<0.001
Screen-detected hypertension	8.3 (8.2 - 8.3)	22.9 (22.9 - 23.0)	<0.001	8.0 (7.9 - 8.0)	22.5 (22.4 - 22.5)	<0.001	8.2 (8.2 - 8.2)	24.7 (24.6 - 24.8)	<0.001	<0.001	<0.001
Known and screen-detected hypertension	30.7 (30.7 - 30.8)	45.0 (44.9 - 45.0)	<0.001	31.4 (31.3 - 31.4)	47.7 (47.7 - 47.8)	<0.001	30.1 (30 - 30.2)	38.8 (38.8 - 38.9)	<0.001	<0.001	<0.001

F v. M = female v. male; CI = confidence interval.

Table 2. Crude and age-standardised prevalence of hypertension in 2008/09 and 2014/16, by gender and year

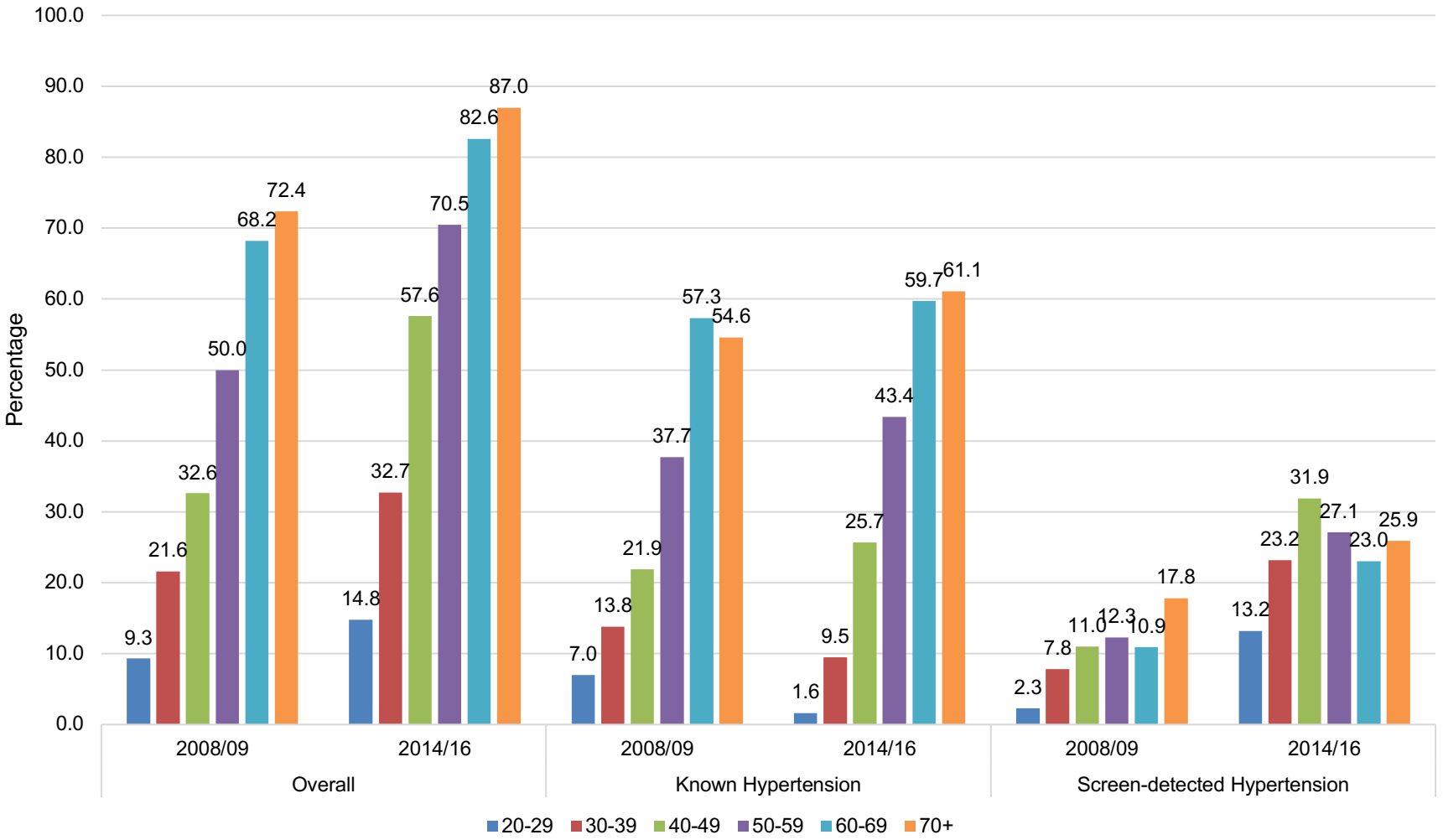

Figure 3. Comparison of the prevalence of hypertension (overall, known and screen detected) between 2008/09 and 2014/16 by age group

Determinants of changes in BP and hypertension

In linear regression model's data of the two surveys was combined and adjusted for age, gender and year of study. The participants in 2014/16 compared with 2008/09 had 15.6 mmHg (95%CI: 13.9-17.4) higher SBP, and 11.1 mmHg (10.0-12.2) higher DBP. Furthermore, age, BMI, waist circumference, diabetes, prediabetes, current smoking, and current alcohol use were associated with both SBP and DBP, while higher education level was inversely associated with SBP (Table 3).

In an expanded multivariable model using a backward selection method of the above variables, age, BMI, abnormal glucose tolerance and current drinkers were associated with both SBP and DBP, while education levels were inversely associated with SBP (Table 4). Furthermore, the model had shown that the year of study, i.e. 2014/16 compared to 2008/09 was associated with higher SBP (16.0 mmHg 95%CI: 14.2-17.7), as well as a higher DBP (11.5 mmHg 95%CI: 10.7-12.9).

In logistic regression models, adjusted for age, gender, and year of study, participants in 2014/16 compared with 2008/09 had almost 3-fold higher odds of hypertension (odd ratio (OR) 2.83; 95%CI: 2.33-3.45). The odds for screen-detected hypertension was 4-fold greater (OR 4.33; 3.29-5.69) (Table 5). Older age, current alcohol use, and overweight and obesity were associated with higher odds of hypertension and screen-detected hypertension (Table 5). Additionally, diabetes was significantly associated with hypertension, while lower education level was related to screen-detected hypertension; the odds for the latter was lower for past drinking vs. no drinking.

Table 3. Age, gender and year of study adjusted linear regression models for determinants of absolute BP levels*

	Model 1: SBP				Model 2: DBP			
		95% CI				95% CI		
	β	**Lower limit**	**Upper limit**	***p*-value**	**β**	**Lower limit**	**Upper limit**	***p*-value**
Year of study	15.6	13.9	17.4	<0.001	11.1	10.0	12.2	<0.001
Gender (male)	1.1	-0.7	3.0	0.233	-0.8	-2.0	0.4	0.180
Age (per 5 years)	3.3	3.1	3.6	<0.001	0.8	0.6	1.0	<0.001
BMI	0.4	0.3	0.6	<0.001	0.4	0.3	0.5	<0.001
Waist circumference	0.2	0.2	0.3	<0.001	0.2	0.2	0.2	<0.001
Diabetes	6.1	4.0	8.2	<0.001	2.3	0.9	3.6	<0.001
Prediabetes	4.4	2.1	6.6	<0.001	2.4	0.9	3.8	<0.001
Current smoking	–1.9	–3.6	–0.2	0.029	–1.6	-2.7	–0.6	<0.001
Secondary level of education or higher	–2.3	–4.1	–0.5	0.012	–1.0	-2.2	0.1	0.090
Current drinking	3.0	1.0	5.0	0.003	2.5	1.2	3.7	<0.001
Past drinking	–2.2	–4.6	0.2	0.081	–0.6	-2.2	0.9	0.420

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; β = beta-coefficient; CI = confidence interval; BMI = body mass index.

*In Table 3, two linear regression models showing the relationship between SBP (model 1) and DBP (model 2) were used with variables known to be associated with high BP. Each model was adjusted for age, gender and year of study. In both models BMI, waist circumference, diabetes, prediabetes, current smoking and current drinking were found to be significant, with level of education only being significant in SBP.

Table 4. Age, gender and year of study adjusted multivariable linear regression models for determinants of absolute BP levels*

	Model 1: SBP				Model 2: DBP			
		95% CI				95% CI		
	β	**Lower limit**	**Upper limit**	***p*-value**	**β**	**Lower limit**	**Upper limit**	***p*-value**
Year of study	16.0	14.2	17.7	<0.001	11.8	10.7	12.9	<0.001
Gender (male)	3.5	1.5	5.4	0.001	0.6	-0.7	1.8	0.37
Age (per 5 years)	2.9	2.6	3.2	<0.001	0.7	0.5	0.9	<0.001
BMI	0.4	0.3	0.6	<0.001	0.2	0.1	0.3	<0.001
Diabetes	4.9	2.8	7.0	<0.001				
Prediabetes	3.1	0.9	5.4	0.006				
Secondary level of education or higher	–2.3	–3.8	–0.8	0.003				
Current drinking	3.0	1.0	5.0	0.003	3.5	2.3	4.7	<0.001

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; β = beta-coefficient; CI = confidence interval; BMI = body mass index.

*In Table 4, a backward elimination linear regression was done. This meant that all variables were used in the model and the variables with the most statistically insignificant decline were deleted, one by one, until a final model was determined with only statistically significant variables. Each model was adjusted for age, gender and year of study. Therefore, in model 1, the variables that indicated significance were BMI, diabetes, prediabetes, education level and current drinking, while model 2 showed BMI and current drinking as the only significant variables.

Table 5. Age, gender and year of study adjusted multivariable linear regression models for determinants of absolute BP levels*

	Overall hypertension (*N*=2 897)		Screen-detected hypertension (*N*=1 852)	
Variables in each model	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Year		<0.001		<0.001
2008/09	1		1	
2014/16	2.83 (2.33 - 3.45)		4.33 (3.29 - 5.69)	
Age (years)		<0.001		<0.001
20 - 29	1		1	
30 - 39	2.46 (1.62 - 3.75)		2.18 (1.37 - 3.48)	
40 - 49	5.65 (3.79 - 8.41)		4.50 (2.89 - 7.02)	
50 - 59	9.55 (6.39 - 14.27)		5.36 (3.40 - 8.44)	
60 - 69	18.27 (11.84 - 28.21)		8.20 (4.95 - 13.60)	
≥70	26.46 (16.31 - 42.93)		14.54 (8.2 - 25.80)	
Gender		0.938		0.110
Female	1		1	
Male	1.01 (0.81 - 1.26)		1.24 (0.95 - 1.63)	
Level of education		0.750		0.040
Primary or lower	1		1	
Secondary or higher	0.75 (0.61 - 0.91)		0.77 (0.60 - 0.99)	
Alcohol use		<0.001		<0.001
Non-drinker	1		1	
Current drinker	1.56 (1.24 - 1.96)		1.81 (1.38 - 2.38)	
Past drinker	0.94 (0.72 - 1.23)		0.58 (0.39 - 0.86)	
Tobacco use		0.870		0.271
Non-smoker	1		1	
Smoker	0.87 (0.71 - 1.05)		0.87 (0.68 - 1.11)	
BMI category		<0.001		<0.001
Normal	1		1	
Overweight	1.52 (1.19 - 1.94)		1.45 (1.07 - 1.96)	
Obese	2.56 (2.02 - 3.24)		2.11 (1.57 - 2.84)	
Diabetic status		<0.001		0.249
Normal	1		1	
Prediabetic	1.17 (0.92 - 1.49)		0.98 (0.72 - 1.34)	
Diabetic	2.40 (1.88 - 3.07)		1.31 (0.94 - 1.82)	

OR = odds ratio; CI = confidence interval; BMI = body mass index.

Discussion

Increases in overall hypertension prevalence over a 7-year period

Results from the current study showed a highly significant increase in overall hypertension prevalence in the Mixed-ancestry population living in Cape Town, South Africa. Results are from two cross-sectional studies conducted in the same community (Bellville-South) and showed 1.5-fold increase in age-standardized hypertension over a 7-year period from 2008/09 (30.7%) to 2014/16 (45.0%). The rise in hypertension prevalence in this community over seven years was similar to that reported by Peer et al for Black Africans in Cape Town over an 18-year period (1.8-fold increase from 21.6% to 38.9%) [3]. This may be a reflection of differential contributors to hypertension in these communities but could probably represent an accelerated uptake of hypertension risk factors over time. Peer et al [3] conducted their comparison between 1990 and 2008/09 while the current comparison was between 2008/09 and 2014/16. Rapid increases in urbanisation over the past decade and the associated uptake of hypertension risk factors may be contributing to a steep non-linear rise in hypertension in Cape Town.

High prevalence of screen-detected hypertension

The high prevalence of screen-detected hypertension (50%) in 2014/16 and the almost 3-fold increase in screen-detected hypertension between 2008/09 and 2014/16 is of concern. It demonstrates the failure of the healthcare system to adequately provide hypertension detection and treatment services in this community. Despite the high and rising hypertension prevalence in the Mixed-ancestry population in Cape Town, the stable prevalence of known hypertension indicates that minimal screening efforts are undertaken in this community. This is unacceptable considering the severity of hypertension-related complications as well as the nominal costs involved, apart from time, when measuring BP. There needs to be an increase in hypertension awareness in this community and a concerted drive by the healthcare sector to promote hypertension screening and to “know your numbers”. This needs to be accompanied by an increase in healthcare resources such as staff and medication to optimally treat the high burden of screen-detected hypertension.

The South African Department of Health (DOH) prioritized the management of NCDs at the South African Summit on the Prevention and Control of NCDs in 2011. One of

the goals was to reduce the prevalence of raised BP by 20% by 2020 [15]. Nevertheless, despite numerous good legislative and policy initiatives formulated by the DOH for the control and management of hypertension over the past two decades, these have unfortunately not translated into successful action as demonstrated by this study findings.

Our results have reflected primarily a significant increase in newly-diagnosed hypertension cases, but with a stable known hypertension prevalence. South African Government has implemented guidelines to increase awareness of NCDs, large proportion of subjects are unaware of their hypertension status which shows clearly that the hypertension epidemic exceeds efforts to detect and therefore treat/control the disease. These reports suggest that hypertension, which has been called the "silent killer disease", by virtue of its nature, that is absence of symptoms in the early stages [16] may need different strategies than those which have been followed so far. Although the South African Government are implementing strategies to control NCDs, in most cases, opportunistic screening at healthcare facilities are still relied on to diagnose hypertension, where, in some instances physical access to healthcare and low socio-economic status is further major challenges in curbing the NCD rates. About two thirds of the Western Cape population lives in the City of Cape Town which results in overburdened public healthcare facilities with long queues and staff shortage [17,18]. Access to private healthcare is only available to those people who are able to afford the facilities or who are on a medical aid, putting a burden on the public system. Therefore, our findings suggest that further strategies are required to bring awareness programmes and screening opportunities that are aimed at reducing and possibly prevent further increases in NCDs, but that this must be accompanied with solutions to the causal effects of the increase in hypertension prevalence.

Shift in peak prevalence from old- to middle-age

In contrast to the 2008/09 findings and global trends in general [16], in 2014/16 hypertension prevalence peaked at a much younger age. This was particularly true for participants with screen-detected hypertension, where the prevalence peaked in 40-49-year-olds in 2014/16 compared with ≥ 70-year-olds in 2008/09. The shift in peak hypertension prevalence by age was unexpected but may be due to earlier, sustained and longer exposures to lifestyle related risk factors than those experienced a decade ago. Hypertension is now affecting the younger working-age population in this

community who are in their prime; a decade ago, it was the older retired members of society who commonly succumbed to hypertension. This has far-reaching social and financial repercussions as breadwinners succumb to uncontrolled hypertension and its complications. The loss of breadwinners who are unable to work rapidly drains household incomes and perpetuates the cycle of poverty.

Similar findings however, have been reported in developing countries such as China and India. Wang et al [19] reported an increa.se in hypertension prevalence in China between 1991 and 2011 of which the greatest increase (68%) was in females aged 35–44 years and similarly Roy et al. [20] had reported that the highest prevalence of change was in the age group 35-44 years between 1991 and 2012 in India. These findings are however, in contrast to reports in general where hypertension has been reported increased mostly due to “an ageing world population” [16] and where a longer life expectancy could be expected to result in an increased exposure to risk factors [16]. It is unclear from the results of the current study why there was a shift in the hypertension peak prevalence to middle-age, but could possibly have been due to changes in the lifestyle and/or environmental surroundings, including working environments. In this regard, South Africa has recently been reclassified as a middle to high income country by the World Bank [21] which could presumably suggest an increase in stress related working conditions, more so than previously. However, this greater burden of disease in younger individuals would influence the burden on the current healthcare system and more importantly affect the economy due the age of individuals attaining the disease being in the prime of their working careers. Therefore, efforts aimed at screening need to be intensified in this age group. Regular screening of raised BP could possibly be effective in monitoring the disease at an early stage and similarly possibly be used by management in managing workloads/responsibilities in stressful work environments.

Risk factors associated with hypertension

The traditional risk factors for hypertension of obesity and alcohol intake were significantly associated with hypertension in this study; this highlights the influence of urbanisation and other environmental factors on the development of the disease. However, smoking was not positively associated with hypertension, similar to that reported in Black Africans in Cape Town [3].

The association of diabetes with hypertension was unsurprising. It underscores the frequent co-existence of these diseases and the need to screen for one in the presence of the other condition. Lifestyle and cultural norm changes such as a decrease in physical activity as has been well reported in modern working environments and similarly changes between male and female traditional habits, such as the increase in the percentage of females reported smoking (also in males) and drinking in the 2014/16 study population are major risk factors for the NCD epidemic in developing countries [22, 23].

Results from the current study showed alcohol consumption positively and smoking inversely associated with the BP, with both SBP and DBP, but the association with smoking becomes non-significant after using back-ward selection in a multivariate selection model, However, the phenomenon of an inverse association between smoking and high BP has also been reported in the 2014 China National Health Survey, where smoking was associated with lower BP, whilst cessation of smoking was linked to increased hypertension [16,24].

The strength of this study is that the two surveys were conducted in the population from the same geographical area using similar procedures. However, the study limitations are as follows: (1) it consisted of only two cross-sectional surveys which prevented a reliable assessment of trends; (2) the second study was not a follow-up but rather a second cross-sectional study collecting new participants from the area (3) there was a low proportion of men included in these studies (24%), a common problem in South African studies[3]; (4) the absence of dietary history pertaining to high salt intake, a contributory factor for the development of hypertension; (5) although hypertension treatment was obtained from participant, control was not examined, and (6) neither was hypertension target organ damage assessed. Therefore, this precluded the evaluation of hypertension control and optimal management across the two surveys.

Conclusion

In conclusion, our findings have shown a rightward shift in absolute BP in the South African Mixed-ancestry population that translated into a significant increase in the prevalence of hypertension, particularly screen-detected cases in both males and females over a seven-year period. The traditional risk factors for hypertension of obesity, diabetes and alcohol intake were significantly associated with hypertension in

this study; highlighting the influence of urbanisation and other environmental factors on the development of the disease.

A concerted drive on hypertension awareness is crucial by the healthcare sector on hypertension status in this population group. The severity of hypertension-related complications as well as the nominal costs involved, necessitates screening for raised BP to be incorporated on a much wider scale than is currently practised, possibly in the working environment as well in order to manage and prevent consequent cardiovascular diseases.

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Chapter 5- Manuscript 2

Title: Changes in Obesity Phenotype Distribution in Mixed-ancestry South Africans in Cape Town Between 2008/09 and 2014/16

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Journal: Frontiers in Endocrinology

DOI: https://doi.org/10.3389/fendo.2019.00753

Abstract

Background: The concept of obesity phenotypes encompasses a different approach to evaluating the relationship between obesity and cardiometabolic diseases. Considering the minimal research on obesity phenotypes in Africa, we investigated these changes from 2008/09 to 2014/16 in the Mixed-ancestry population in Cape Town, South Africa.

Methods: In all, 928 (2008/09) and 1969 (2014/16) ≥20 year old participants were included in two community-based cross-sectional studies. For obesity phenotype classification, a combination of body mass index (BMI) categories and prevalent cardiometabolic disease risk factors were used, with the presence of ≥2 cardiometabolic abnormalities defining abnormal metabolic status. Interaction tests were used to investigate changes in their distribution across the years of study.

Results: Distribution of BMI categories differed significantly between the 2 years; normal weight, overweight and obese: 27.4, 27.4, and 45.3% in 2008/09 vs. 34.2, 23.6, and 42.2% in 2014/16 ($p = 0.001$). There was no differential effect in the distribution of obesity phenotypes pattern across the two time-points (interaction $p = 0.126$). Across BMI categories, levels of cardiometabolic risk factors linearly deteriorated in both metabolically healthy and abnormal participants (all $p \leq 0.018$ for linear trends). Findings were not sensitive to the number of metabolic abnormalities included in the definition of obesity phenotypes.

Conclusions: Our study showed negligible differences in obesity phenotypes over time, but a high burden of metabolic abnormalities among normal weight participants, and a significant proportion of metabolically health obese individuals. Further investigation is needed to improve risk stratification and cost-effective identification of individuals at high risk for cardiometabolic diseases.

Keywords: obesity phenotype, body mass index, cardiometabolic risk factors, trends, Africa

Introduction

In 2011, the World Health Organisation (WHO) reported that obesity had reached epidemic proportions globally, accounting for an estimated 2.8 million deaths annually (1). A further 35.8 million disability-adjusted life-years (DALYs) were attributed to overweight and obesity (1). Even in Africa, over one-quarter of adults ≥20 years of age were estimated to be overweight (2). The adoption of western lifestyles, characterized by energy-rich diets and physical inactivity, is considered to be a key contributor to the high and rising adiposity levels on the continent (3–7). South Africa is among the countries with the highest adiposity levels in Africa with a crude prevalence of 48.3 and 22.8% for overweight and obesity, respectively (8).

Despite the major influence of obesity on the development of cardiovascular diseases worldwide, the impact of obesity on cardiovascular diseases in Africa may not be uniform or comparable to other populations (9). Therefore, the concept of ‘obesity' or ‘body size' phenotype was developed (10) to evaluate the cardiometabolic risk associated with excess body weight (11–15). Unlike the metabolic syndrome, which shares common characteristics with obesity phenotype, the latter has no uniform definition and researchers use their discretion per the population being studied. For the measure of adiposity, many advocate the use of waist circumference (WC) with a focus on visceral adiposity (16, 17). However, Despres et al. (18) proposed that visceral adiposity alone was not sufficient to diagnose obesity. Therefore, body mass index (BMI) maybe more appropriately defined for the obesity phenotype concept since BMI is a stronger predictor of CVD than more accurate measures of adiposity such as percentage of body fat (19). Therefore, using BMI to define the latter, in the current study, we aim to determine the distribution and change in obesity or body size phenotypes between 2008/09 and 2014/16 in an urban South African population.

Materials and Methods

Study Population and Sampling Procedure

Two independent cross-sectional surveys were conducted in the Mixed-ancestry population of the Bellville-South Township in Cape Town in 2008/09 and 2014/16. Recruiters approached each dwelling and invited residents who fulfilled the inclusion criteria to participate in the survey. These included Mixed-ancestry residents aged 18

years and older (2008/09 survey) or 20 years and older (2014/16 survey) who were neither pregnant nor bed-ridden. The 2008/09 survey comprised 946 participants, as previously described (20), while the 2014/16 survey included 1989 participants. For this analysis, participants with missing data, and those who were underweight or <20 years old in the 2008/09 study, were excluded. The final sample consisted of 927 in 2008/09 and 1969 in 2014/16.

Data Collection

Eligible participants attended a designated recruitment site where trained personnel administered questionnaires, including the WHO StepWise questionnaire, (21) and collected clinical and biochemical data. Anthropometry was measured using standardized techniques as recommended by the WHO (21). WC and hip circumference measurements were taken thrice, using a non-elastic measuring tape as per WHO guidelines (21), and averaged for the purposes of this study. Height was measured to the nearest centimeter using a stadiometer. Blood pressure was taken three times at 3-min intervals (21), of which the lowest Systolic Blood Pressure (SBP) and corresponding diastolic blood pressure (DBP) readings were used for analysis.

A 75-g oral glucose tolerance test (OGTT) was administered to determine diabetes mellitus in participants without a history of the condition while known diabetes was self-reported as being previously diagnosed by a doctor (22). Biochemical analyses, using fasting samples, were conducted at an ISO 15189 accredited Pathology practice (PathCare, Reference Laboratory, Cape Town, South Africa). These included plasma glucose; plasma insulin, High-density lipoprotein cholesterol (HDL-C); Low-Density Lipoprotein Cholesterol (LDL-C); Total Cholesterol (TC); triglycerides; ultrasensitive C-Reactive Protein (CRP); and serum creatinine.

Definitions

Level of education was categorized as ≤ 7 years of education (up to completion of primary school) and > 7 years of education (secondary schooling and higher). Current tobacco use was objectively defined as cotinine levels >10 ng/mL (23, 24) while alcohol consumption was self-reported Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/l and/or a 2-h post-OGTT plasma glucose ≥ 11.1 mmol/l or self-

reported and/or on diabetes medication. Pre-diabetes: fasting plasma glucose between 6.1 and 6.9 mmol/l or/and a post 2-h glucose between 7.8 mmol/l and 11.1 mmol/l (22). BMI was calculated as weight in kilograms (kg) divided by height in meter squared (m^2) and classified as normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.99 kg/m^2) and obesity (≥ 30.0 kg/m^2).

Although obesity phenotype and metabolic syndrome share similar characteristics, the two have different approaches in understanding the clustering of cardiometabolic risk factors. Metabolic syndrome has predefined set criteria, with the most recent being the harmonized Joint Interim Statement (JIS) definition (25). In contrast, obesity phenotype currently has no uniform criteria. Per the population being studied, investigators take into consideration a number of cardiometabolic risk factors to categorize participants as “metabolically healthy” or “metabolically abnormal” with further categorization based on obesity status or phenotype (26–29). Obesity phenotypes were defined using body size in combination with certain cardiometabolic risk factors to determine the different categories. For the purpose of this study, the presence of two or more metabolic abnormalities classified participants as metabolically abnormal, while those with one or no metabolic abnormality were considered metabolically health.

The cardiometabolic risk factors used to categorize metabolic status were as follows: (1) SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or on blood pressure lowering medications; (2) elevated Triglycerides (>1.70 mmol/L); (3) low HDL-C (men: <1.0 mmol/L, women: <1.3 mmol/L); (4) high fasting blood glucose level (>5.5 mmol/L) or on hypoglycaemic agents; and (5) insulin resistance diagnosed using the homeostatic model assessment of insulin resistance (HOMA-IR) values above the 90th percentile. In secondary analyses we included a sixth metabolic abnormality: elevated CRP (≥ 3 mg/L).

The BMI and metabolic categories were cross-classified into six obesity sub-phenotypes: (1) normal weight and metabolically healthy (NWMH), (2) normal weight and metabolically abnormal (NWMA), (3) overweight and metabolically healthy

(OvMH), (4) overweight and metabolically abnormal (OvMA), (5) obese and metabolically healthy (MHO), and (6) obese and metabolically abnormal (MAO).

Statistical Analysis

The software's, Statistica v.13 (TIBCO Software Inc. (2017) and SPSS v.25 (IBM Corp, 2011) were used for data analyses. The data was tested for normality using Normal Q-Q Plots. The results for continuous variables are reported as means and standard deviations when normally distributed, medians and 25th and 75th percentiles for skewed variable; while categorical variables are reported as counts and percentages with numbers. For group comparisons, analysis of variance test (ANOVA) and Kruskal Wallis test were used for continuous variables, while the chi-square test was used for categorical variables. The Linear-by-Linear Association (LLA) test (categorical), and Brown-Forsythe Levene test (continuous) were used for linear trends to test the change in metabolic phenotype distribution between the two cross-sectional studies. Two-way and three-way interactions between year of study, BMI and metabolic status in the distribution of participants' characteristics were tested in linear (continuous variables) and logistic (categorical variables) regressions by including in the same model the main effects of the variables to be tested as well as their interaction terms. A p-value <0.05 was used to characterize statistically significant results.

Ethical Approval

Ethical approval for this study was obtained from the University of Cape Town Human Research Ethics Committee (ref: 442/2016) and the Cape Peninsula University of Technology for the 2008/09 and 2014/16 studies (ref. no. CPUT/HW-REC 2008/002 and CPUT/HW-REC 2015/H01). Permission to conduct the surveys was granted by the city and community management. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Results

General Characteristics of the Participants

The general characteristics of participants by survey year are summarized in Table 1. Participants in 2014/16 compared to 2008/09 were younger (49.6 ± 15.2 vs. 54.3 ± 14.7 years, $p < 0.001$), slightly better educated (secondary or higher: 65.7 vs. 64.8%, $p < 0.001$) and had lower BMI levels (29.2 ± 8.0 vs. 29.9 ± 7.3 kg/m2, $p < 0.031$). In 2014/16 vs. 2008/09, participants also had better glycaemic variables i.e. lower levels of fasting glucose [5.0 (range: 4.6–5.6) vs. 5.6 (range: 5.0–6.5)], 2-h glucose [6.1 (range: 4.9–7.6) vs. 6.8 (range: 5.7–8.7)], HbA1c [6.1 (range: 4.9–7.6) vs. 6.8 (range: 5.7–8.7)] and HOMA-IR [5.8 (range: 5.4–6.2) vs. 5.9 (range: 5.5–6.3)] (all $p < 0.043$), and lower LDL-C levels (3.3 ± 1.0 mmol/l vs. 3.7 ± 1.0 mmol/l), all $p \leq 0.043$. However, participants in 2014/16 compared with 2008/09 had higher levels of blood pressure (SBP: 136.0 ± 25.9 vs. 123.5 ± 19.2 mmHg, DBP: 85.8 ± 14.9 vs. 74.9 ± 12.5 mmHg, both <0.001) and CRP (4.1 ± mg/L vs. 3.6 ± mg/L, $p < 0.001$).

Distribution of Body Size phenotypes

The prevalence of normal weight, overweight and obesity was, respectively, 27.4, 27.4, and 45.3% in 2008/09 and 34.2, 23.6, and 42.2% in 2014/16; $p = 0.001$ for the difference in the distribution across years (Table 1). A similar pattern was observed in men and women. In 2008/09, 13.5% of the participants were obese yet metabolically healthy (0 or 1 metabolic abnormality present) while 9.4% had normal weight but were metabolically abnormal (2 or more metabolic abnormalities present) (Figure 1). The distribution of obesity phenotypes in 2014/16 was 25.9% (NWMH), 8.0% (NWMA), 11.3% (OvMH), 12.3% (OvMA), 14.0% (MHO), and 28.5% (MAO). There was no difference in the pattern of distribution of obesity phenotype across the two time-points (interaction $p = 0.126$; Figure 1). In both 2008/09 and 2014/16, the proportion of metabolically unhealthy participants steadily increased across BMI categories (both $p < 0.001$ for linear trends; Figure 1). Within BMI categories, the proportion of metabolically abnormal participants (2008/09 vs. 2014/16) was 3.0 vs. 5.4% among the normal weight ($p = 0.001$), 5.5 vs. 8.3% among the overweight ($p = 0.007$), and 10.2 vs. 19.3% among the obese ($p = 0.276$) (Figure 2).

Table 1.Comparison of the characteristics in 2008/09 and 2014/16 by gender

Characteristics	2008/09			2014/16			Overall 2008/09 vs 2014/16	F vs M 2008/09 p-value	F vs M 2014/16 p-value	Women: 2008/09 vs 2014/16 p-value	Men: 2008/09 vs 2014/16 p-value
	Overall (n=927) Mean (SD)	Women(n=709) Mean (SD)	Men(n=220) Mean (SD)	Overall (n=1969) Mean (SD)	Women (n=1488) Mean (SD)	Men(n=481) Mean (SD)					
Age, years	54.3 (14.7)	53.7 (14.4)	56.3 (15.2)	49.6 (15.2)	50.3 (14.9)	47.4 (15.7)	<0.001	0.022	<0.001	<0.001	<0.001
Waist circumference (cm)	97.1 (14.9)	98.0 (14.7)	94.1 (15.1)	92.6 (17.1)	94.7 (16.7)	86.1 (16.6)	<0.001	0.001	<0.001	<0.001	<0.001
Hip circumference (cm)	109.8 (14.8)	112.7 (14.9)	100.3 (10.0)	104.5 (16.4)	107.7 (16.2)	94.5 (12.5)	<0.001	<0.001	<0.001	<0.001	<0.001
Waist-to-hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.868	0.169	0.051	0.266	0.384
Systolic Blood Pressure (mmHg)	123.5 (19.2)	122.5 (19.5)	126.6 (18.0)	136.0 (25.9)	136.3 (25.7)	135.0 (26.5)	<0.001	0.007	0.32	<0.001	0.925
Diastolic blood pressure (mmHg)	74.9 (12.5)	74.5 (12.7)	76.3 (11.7)	85.2 (14.9)	85.8 (14.5)	83.5 (15.8)	<0.001	0.068	<0.001	<0.001	<0.001
Fasting glucose (mmol/L) *	5.6 (5.0-6.5)	5.6 (5-6.5)	5.5 (5.0-6.4)	5.0 (4.6-5.6)	5.0 (4.6-5.7)	4.8 (4.4-5.5)	<0.001	0.449	<0.001	<0.001	<0.001
2-hour glucose (mmol/L) *	6.8 (5.7-8.7)	7.0 (5.7-8.9)	6.4 (5.3-8.4)	6.1 (4.9-7.6)	6.3 (5.2-7.9)	5.1 (4.1-6.7)	<0.001	0.010	<0.001	<0.001	<0.001
HBA1c (%) *	5.9 (5.5-6.3)	5.9 (5.5-6.3)	5.9 (5.5-6.3)	5.8 (5.4-6.2)	5.8 (5.5-6.3)	5.6 (5.3-6.0)	0.005	0.847	<0.001	0.073	<0.001
Fasting insulin (mIU/L) *	6.8 (2.7-12.8)	7.5 (3.3-13.5)	4.3 (1.8-9.2)	6.8 (4.3-11.2)	7.4 (4.9-11.7)	4.9 (2.9-8.6)	0.414	<0.001	<0.001	0.057	0.023
2-hour insulin (mIU/L) *	38.1 (19.5-71.6)	42 (22.2-79.6)	25.9 (10.2-45.7)	38.8 (20.7-71.9)	45.3 (25.3-79.6)	21.8 (10.2-43.4)	0.473	<0.001	<0.001	0.096	0.595
HOMA-IR*	1.7 (0.7-3.4)	1.9 (0.8-3.7)	1.2 (0.4-2.7)	1.6 (0.9-2.8)	1.8 (1.1-3.1)	1.1 (0.6-2.1)	0.040	<0.001	<0.001	0.623	0.449
Total Cholesterol (mmol/L)	5.6 (1.2)	5.2 (1.2)	5.7 (1.2)	5.3 (1.2)	5.3 (1.1)	4.8 (1.1)	0.22	0.134	0.765	0.076	0.835
HDL-cholesterol (mmol/L)	1.3 (0.3)	1.3 (0.4)	1.3 (0.3)	1.4 (0.4)	1.2 (0.3)	1.3 (0.4)	0.183	0.837	0.955	0.168	0.595
LDL-cholesterol (mmol/L)	3.7 (1.0)	3.2 (1.0)	3.8 (1.0)	3.3 (1.0)	3.5 (1.0)	2.9 (1.0)	0.043	0.757	0.601	0.113	0.123
Triglycerides (mmol/L) *	1.3 (0.9-1.8)	1.3 (0.9-1.8)	1.3 (0.9-1.8)	1.2 (0.9-1.7)	1.2 (0.90-1.7)	1.1 (0.9-1.7)	<0.001	0.533	0.236	0.228	0.045
C-reactive protein (mg/L) *	3.6 (1.0-9.4)	4.0 (1.1-9.9)	2.9 (0.8-7.7)	4.1 (1.7-9.1)	4.5 (1.9-9.9)	2.7 (1.2-6.3)	<0.001	0.023	<0.001	0.007	0.982
Creatinine (umol/L) *	81 (71-92)	78 (69-88)	92 (82-104)	59 (52-69)	56 (50-64)	70 (63-82)	<0.001	<0.001	<0.001	<0.001	<0.001
Body mass index (kg/m^2)	29.9 (7.3)	31.0 (7.2)	26.1 (6.2)	29.2 (8.0)	30.7 (7.9)	24.6 (6.4)	0.031	<0.001	<0.001	0.349	0.003
Body Mass Index Status							0.001	<0.001	<0.001	0.067	0.003
Normal (18.5-24.9 kg/m2)	27.4 (251/917)	21.3 (149/701)	47.2 (102/216)	34.2 (669/1958)	25.5 (378/1480)	60.9 (291/478)					
Overweight (25kg/m2 to 29.9 kg/m2)	27.4 (251/917)	26.5 (186/701)	30.1 (65/216)	23.6 (462/1958)	23.6 (350/1480)	23.4 (112/478)					
Obese(>=30kg/m2)	45.3 (415/917)	52.2 (366/701)	22.7 (49/216)	42.2 (827/1958)	50.8 (752/1480)	15.7 (75/478)					
Education level							0.0002	0.056	0.007	0.653	0.856
<=7 years, % (n)	35.2 (324/920)	36.9 (259/702)	29.8 (65/218)	34.3 (670/1956)	35.9 (531/1479)	29.1 (139/477)					
> 7years, % (n)	64.8 (596/920)	63.1 (443/702)	70.2 (153/218)	65.7 (1286/1956)	64.1 (948/1479)	70.9 (338/477)					

Alcohol use							0.651	<0.001	<0.001	<0.001	<0.001
Currently drinking % (n)	27.3 (250/915)	21.2 (148/698)	47 (102/217)	26.5 (519/1957)	22.3 (330/1479)	39.5 (189/478)					
Non-drinker, % (n)	72.7 (665/915)	78.8 (550/698)	53 (115/217)	73.5 (1438/1957)	77.7 (1149/1479)	60.5 (289/478)					
Tobacco use							0.612	0.074	<0.001	0.019	0.001
Non-smoker, % (n)	57.5 (531/923)	59.1 (417/705)	52.3 (114/218)	50.2 (959/1909)	53.8 (776/1442)	39.2 (183/467)					
Smoker, % (n)	42.5 (392/923)	40.9 (288/705)	47.7 (104/218)	49.8 (950/1909)	46.2 (666/1442)	60.8 (284/467)					

*median (25^{th}-75^{th} percentiles); SD- standard deviation; F - women; M – men; vs- versus; HbA1c Haemoglobin A1c-; HOMA-IR- Homeostatic Model Assessment of insulin resistance; HDL- high density lipoprotein; LDL- low density lipoprotein

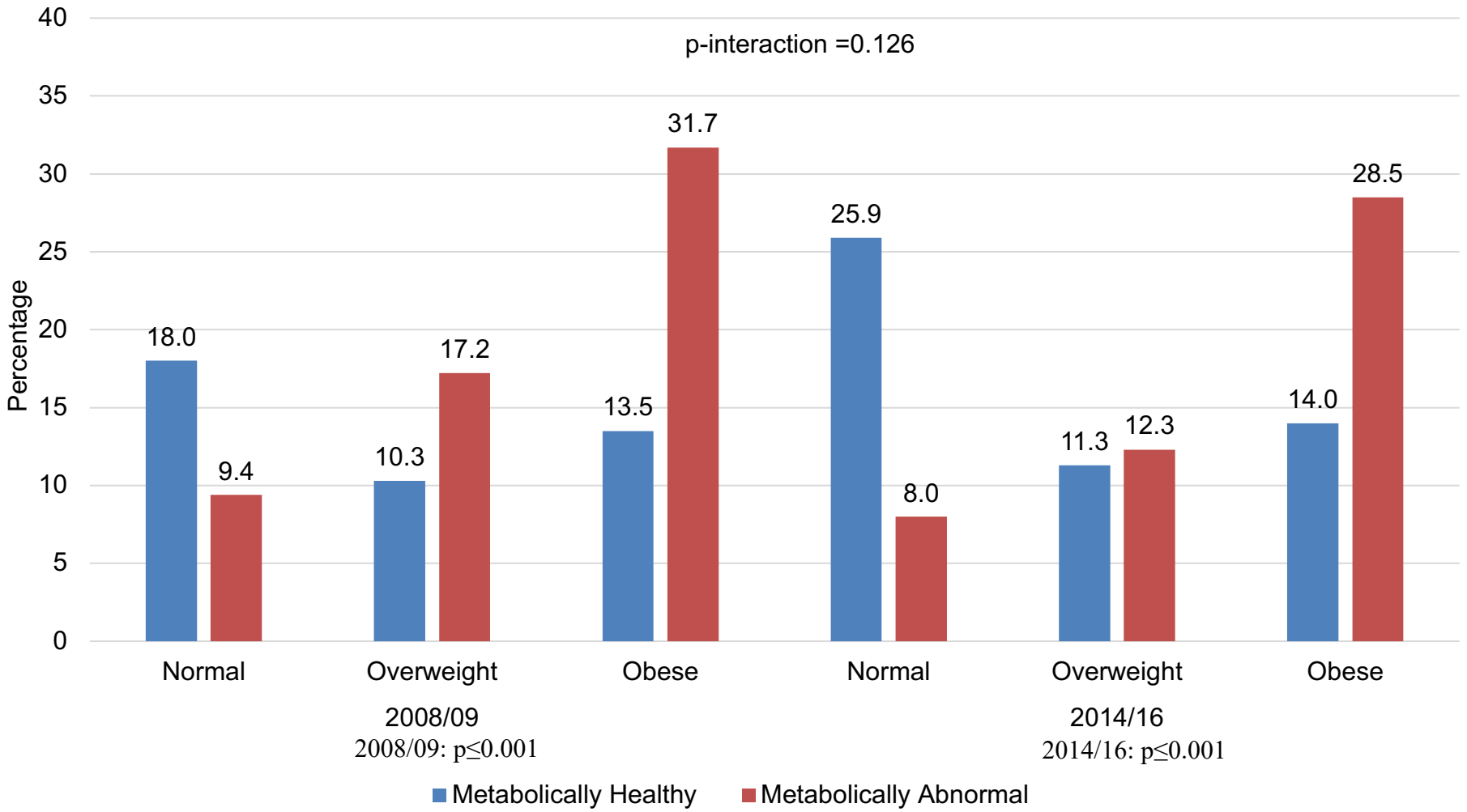


Figure 1. Distribution of obesity phenotypes per year of study. When taking 5 variables into account, NWMH had decreased from 18 to 13.5% MHO. Similar results were shown in 2014/16, NWMH decreasing from 25.9 to 14.0% in MHO, with a non-significant p-interaction

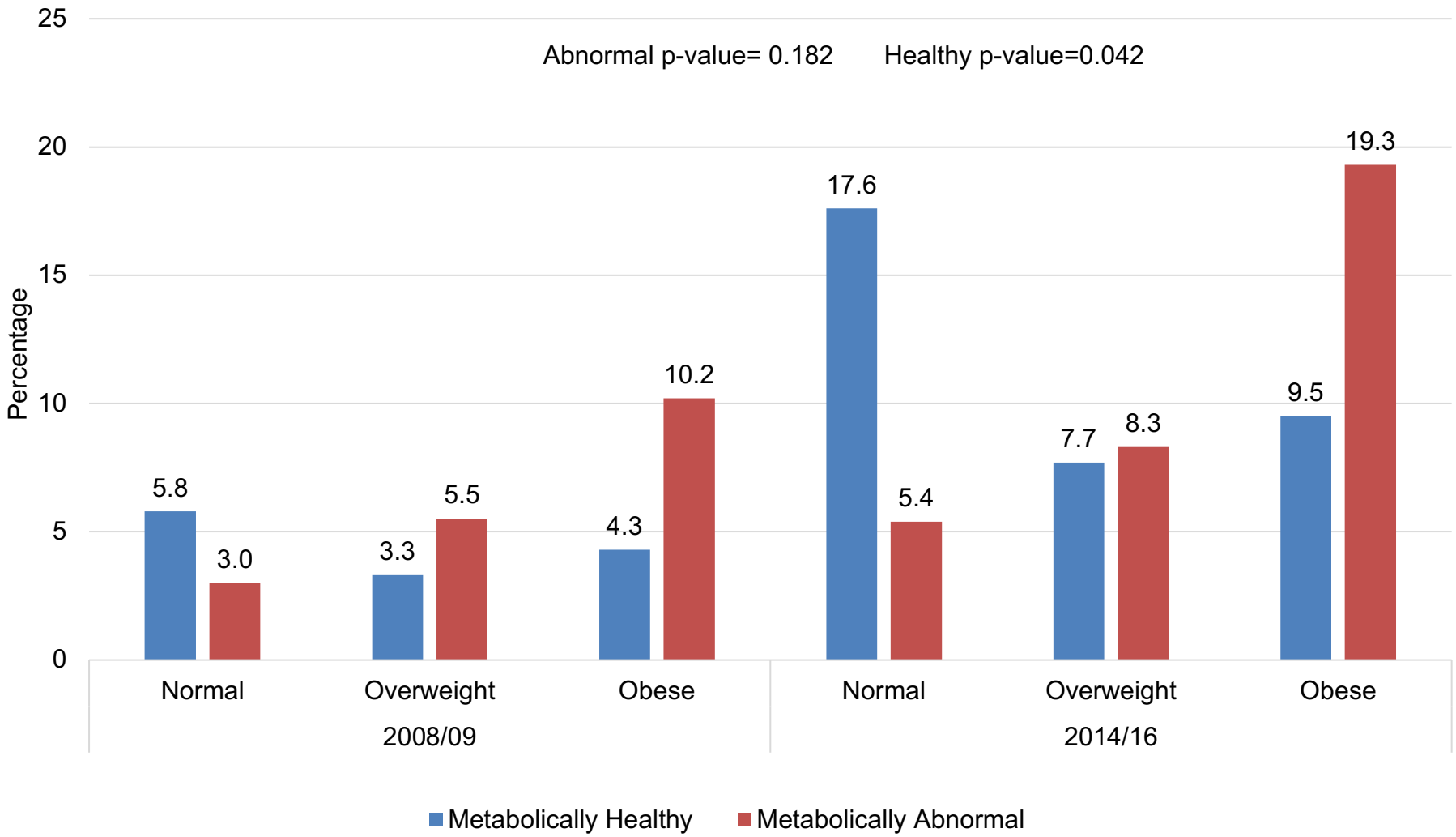


Figure 2. Prevalence metabolic phenotype within BMI categories by year of study

In women, across the two time points, there was an increase in metabolic abnormalities by BMI category (Figure 3). In men, however, the proportion of metabolic abnormalities was similar across BMI categories in 2014/16 and in overweight and obese in 2008/09. The proportion of metabolically healthy men substantially decreased across increasing BMI categories across both time-points. Interestingly, 34.1% of men in 2008/09 and 47.2% in 2014/16 had normal weight and were metabolically normal. Accordingly, there was a significant gender interaction effect in the distribution of obesity phenotypes across years (interaction $p = 0.008$) (Figure 3).

In secondary analysis accounting for high CRP as an additional metabolic abnormality, the proportion of metabolically abnormal participants linearly increased across rising BMI categories while that for metabolically healthy individuals decreased across both time-points (both $p < 0.001$ for linear trend), with no evidence of interaction by year (interaction $p = 0.225$) (Supplementary Figure 1). As expected, the proportion of metabolically healthy participants decreased overall and across all BMI categories and years of survey. The above patterns were mostly similar in women, but not in men where the proportion of metabolic abnormalities varied less across BMI categories in 2008/09 while a decreasing trend was observed in 2014/16. This apparent different pattern did not result in significant gender*year interaction in the distribution of obesity phenotypes (interaction $p = 0.869$) (Supplementary Figure 2).

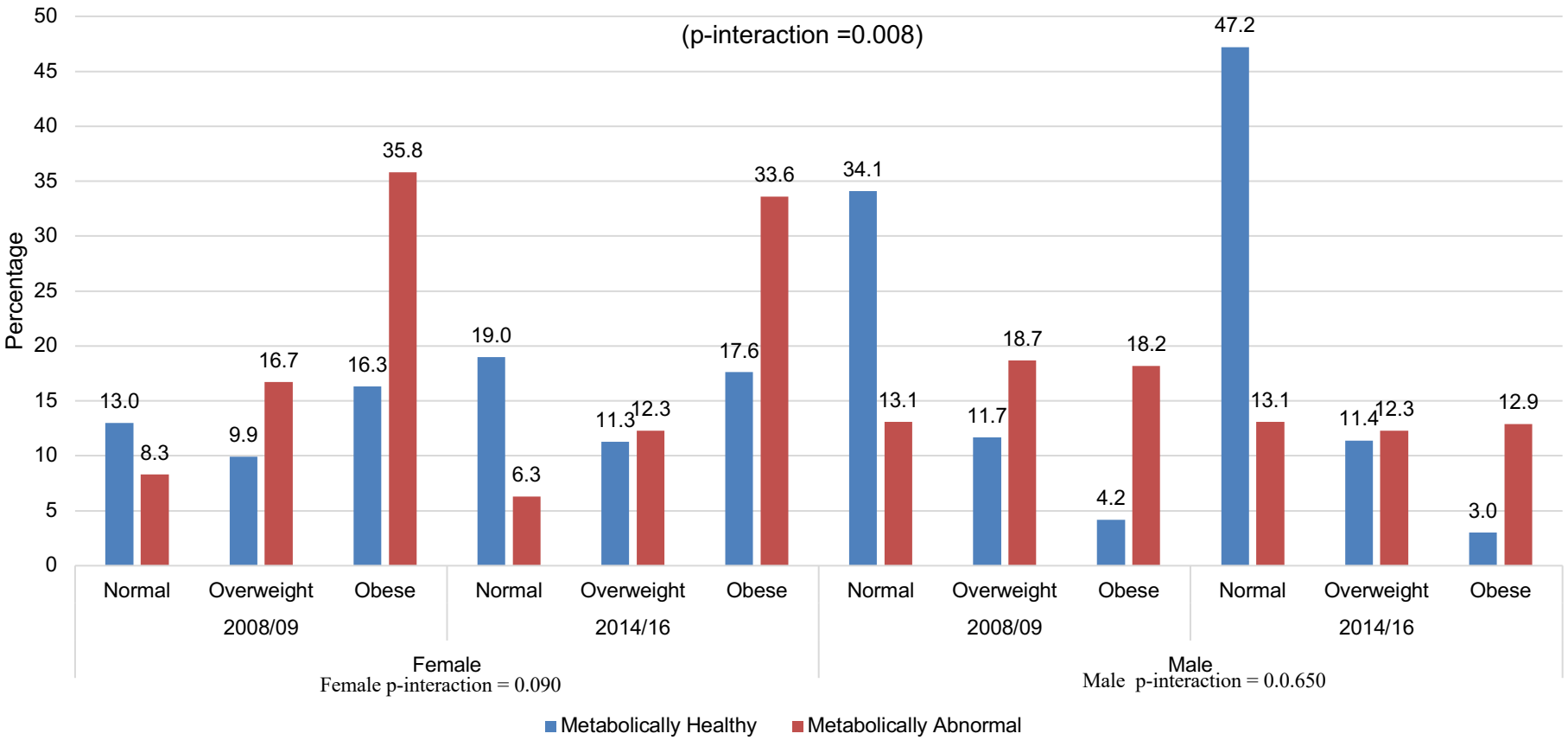
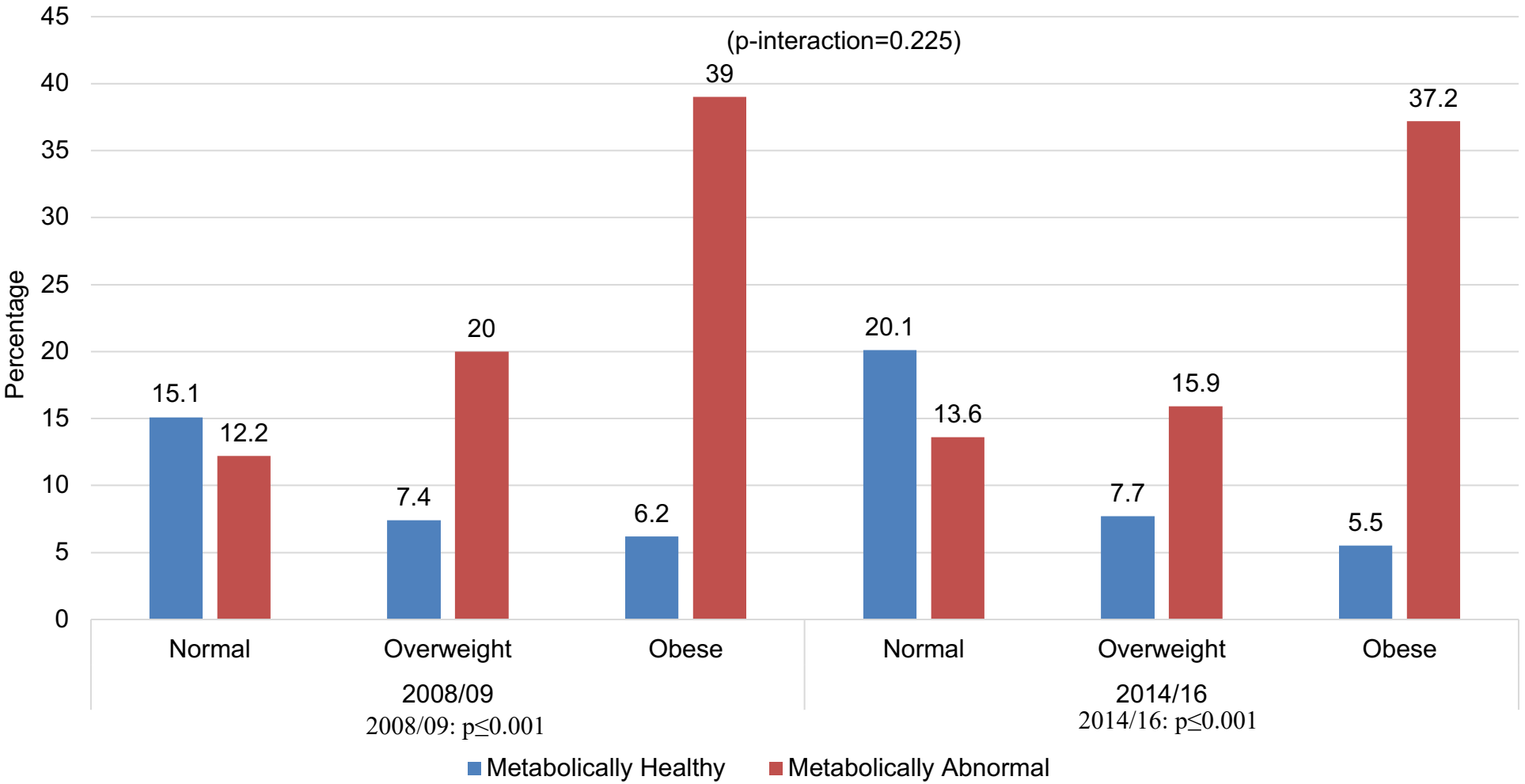
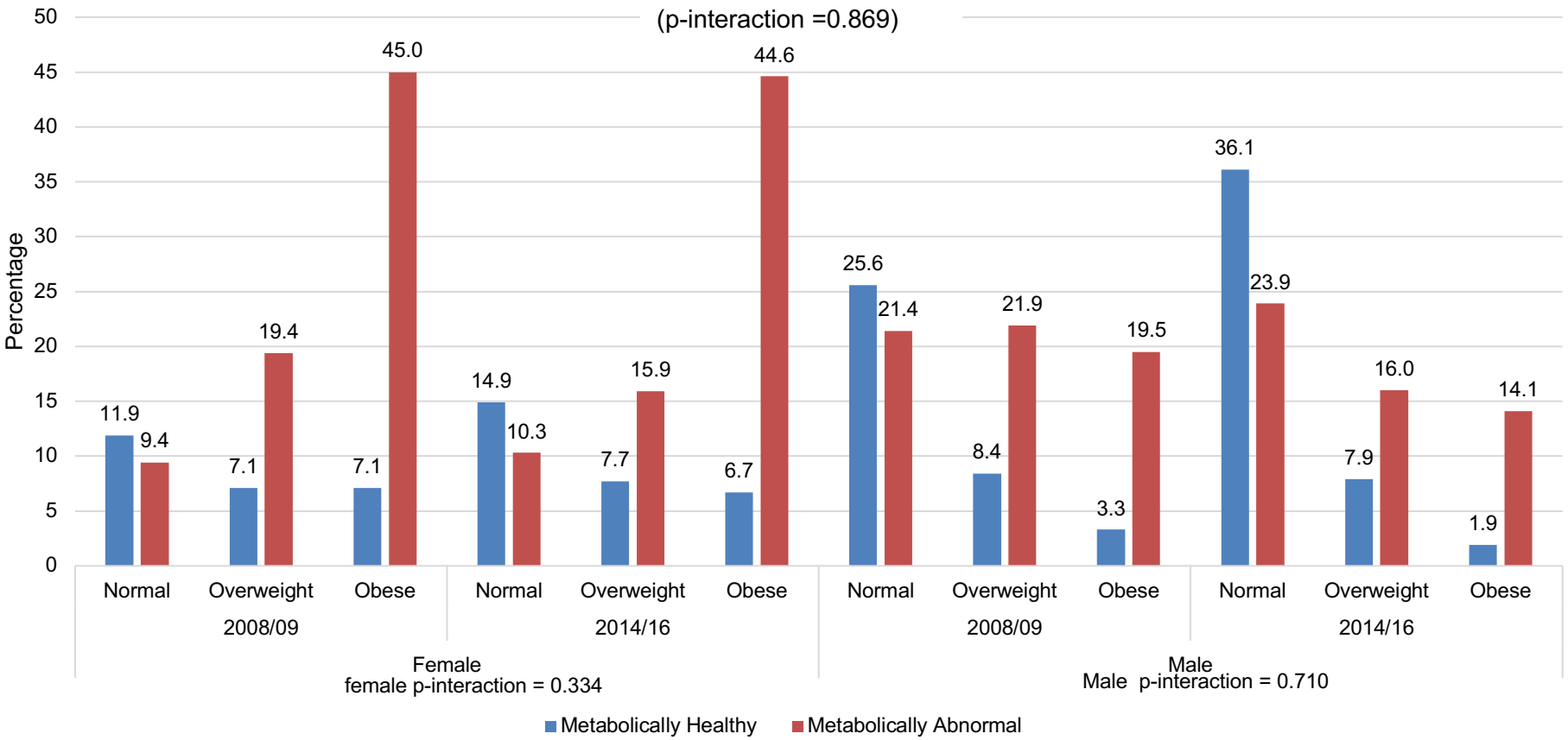


Figure 3. Distribution of obesity phenotypes per year of study and gender. In 2008/09, women had shown an increase from NWMH, 13.0–16.3% in MHO, while in 2014/16 there was a slight decrease from 19.0% in NWMH to 17.6% in MHO (women p-interaction = 0.090). Men had shown a decrease of 8-fold in NWMH to MHO in 2008/09, while 2014/16 had shown a 15-fold decrease (men p-interaction = 0.650).



Supplementary Figure 1. Distribution of obesity phenotypes per year of study using secondary data analysis, i.e. when adding a sixth variable to determine phenotype, NWMH had shown a decrease from 15.1% in 2008/09 to 6.2% in MHO. As for 2014/16, similar results are shown with NWMH to MHO decreasing from 20.1% to 5.5%.



Supplementary Figure 2. Secondary analysis determining the distribution of obesity phenotypes per year of study and gender. In women there was a similar decrease in both 2008/09 and 2014/16 between NWMH to MHO, p-interaction=0.334. Similarly, in men there was a decrease between NWMH to MHO, p-interaction=0.334. Similarly, in men there was a decreases between NWMH and MHO, with 2008/09, 25.6% to 3.3% and 2014/16, 36.1% to 1.9%, p-interaction=0.710.

The Metabolic Profile Within and Across BMI Categories

Within BMI categories, metabolically abnormal participants compared with their metabolically healthy counterparts, were older (normal weight: 56.0 vs. 44.1 years; overweight: 56.0 vs. 47.4 years and obese 55.1 vs. 50.0 years) (all $p \leq 0.035$), less educated (all $p < 0.001$) and included fewer drinkers among normal weight (31.9 vs. 42.9%; $p = 0.003$) and obese participants (15.1 vs. 20.2%; $p = 0.026$) (Table 2). However, the proportions of smokers were similar (all $p > 0.289$) as were the proportions of men among normal weight (37.7 vs. 44.7%, $p = 0.059$) and overweight (24.9 vs. 25.3% ($p = 0.907$) metabolically abnormal vs. metabolically healthy participants, respectively. Among obese participants, a higher proportion of men were metabolically abnormal than metabolically healthy (11.9 vs. 5.9%, $p = 0.001$). Unsurprisingly, metabolically abnormal participants compared with metabolically healthy participants within BMI categories displayed significantly worse metabolic profiles. However, some exceptions were WC among all BMI categories (all $p \geq 0.070$), SBP among overweight and obese participants (both $p > 0.085$), DBP among overweight ($p = 0.381$), TC and LDL-C among overweight and obese (all $p > 0.102$) and HDL-C among normal weight and overweight participants (both $p > 0.072$).

Across BMI categories, the proportion of men decreased from 44.8% in NWMH to 5.9% in MHO, and from 37.7% in NWMA to 11.9% in MAO (both $p < 0.001$ for linear trend). Age linearly increased across rising BMI categories, driven by a steeper trend among metabolically health participants ($p < 0.001$), and only a flat pattern among metabolically abnormal participants ($p = 0.407$). Across the BMI categories, current drinking, WC, DBP, hip circumference, fasting glucose, 2 h glucose, HbA1c, fasting insulin, 2 h insulin, TC, LDL-C, Triglycerides and CRP linearly increased in both metabolic healthy and abnormal participants (all $p \leq 0.018$ for linear trends). SBP significantly increased across rising BMI category among metabolically health participants only ($p < 0.001$ for linear trend); while current smoking linearly decreased in both the metabolic healthy and abnormal participants (both, $p < 0.001$ for linear trend). No linear trend was observed for education level across increasing BMI category both in metabolically healthy and abnormal participants (all $p \geq 0.105$ for linear trends) (Table 2).

In secondary analysis accounting for high CRP as an additional metabolic abnormality, despite some attenuation of some p-values, the overall pattern was broadly the same (Supplementary Table 1).

Interaction by BMI Category, Metabolic Profile, and Year of Study

Significant interactions between BMI categories and metabolic status were apparent in the distribution of gender (interaction $p = 0.001$), age ($p < 0.001$), SBP and DBP (both $p < 0.001$), fasting glucose ($p = 0.045$), HbA1c ($p = 0.012$), fasting insulin ($p = 0.024$), 2 h insulin ($p = 0.021$), HOMA-IR ($p = 0.007$), TC ($p = 0.009$), and CRP ($p = 0.002$) (Table 2). Furthermore, significant interactions between metabolic status and year of study (2008/09 vs. 2014/16) were apparent in the distribution of WC, hip circumference, SBP, DBP, 2 h glucose, HbA1c, Triglycerides and tobacco use (all interactions $p \leq 0.048$). Significant 3-way interactions BMI categories*metabolic status* year of study were found in the distribution of age, SBP, DBP, LDL-C, and CRP (all 3-way interaction $p \leq 0.008$). These were indications that some of the variations in participants' profiles across BMI categories and metabolic status were occurring in differential ways across the two years of study.

Table 2. Pairwise comparison of metabolically healthy and abnormal participants by body mass index

Characteristics	Normal weight			Overweight			Obese			P trend across BMI categories			P interaction		
	Healthy Mean (SD)	Abnormal Mean (SD)	p	Healthy Mean (SD)	Abnormal Mean (SD)	p	Healthy Mean (SD)	Abnormal Mean (SD)	p	Overall	Healthy	Abnormal	B*M	M*Y	B*M* Y
Prevalence, % (n)	23.4 (662)	8.4 (239)		11.0 (312)	13.9 (393)		13.8 (392)	29.5 (837)		<0.001			<0.001		
Gender															
Women	55.3 (366/662)	62.3 (149/239)	0.059	74.7 (233/312)	75.1 (295/393)	0.907	94.1 (369/392)	88.1 (737/837)	0.001	<0.001	<0.001	<0.001	0.001	0.449	0.335
Men	44.7 (296/662)	37.7 (90/239)		25.3 (79/312)	24.9 (98/393)		5.9 (23/392)	11.9 (100/837)							
Age, years	44.1 (16)	56.0 (15)	0.035	47.4 (15.3)	56.0 (13.7)	0.008	50.0 (14.5)	55.1 (12.6)	<0.001	<0.001	<0.001	0.407	<0.001	0.550	<0.001
Waist circumference	76.1 (8.7)	81.1 (7.9)	0.892	89.8 (8.7)	94 (7.5)	0.070	103.9 (11.5)	109.1 (11.9)	0.479	<0.001	<0.001	<0.001	0.559	0.001	0.084
Hip circumference	90.6 (8.7)	92.3 (7.1)	0.021	102.8 (7.0)	102.8 (6.1)	0.028	118.6 (12.0)	119.8 (13.1)	0.037	<0.001	<0.001	<0.001	0.271	<0.001	0.113
Waist-to-hip ratio	0.8 (0.1)	0.9 (0.1)	0.150	0.9 (0.1)	0.9 (0.1)	0.031	0.9 (0.1)	0.9 (0.1)	0.639	<0.001	<0.001	<0.001	0.875	0.959	0.853
Systolic Blood Pressure	116.0 (20.4)	136.2 (25.5)	<0.001	120.4 (20.9)	132.1 (22.5)	0.085	122.9 (20.4)	133.0 (21.5)	0.160	<0.001	<0.001	0.076	<0.001	<0.001	<0.001
Diastolic blood pressure	74.7 (13.3)	83.1 (17.1)	<0.001	77.4 (13.0)	80.8 (12.7)	0.381	79.0 (12.3)	83.6 (13.5)	0.041	<0.001	<0.001	0.005	0.001	0.001	<0.001
Fasting glucose *	4.7 (4.3-5)	5.6 (4.8-6.4)	<0.001	4.9 (4.5-5.2)	5.8 (5.1-7.9)	<0.001	5.0 (4.6-5.2)	5.9 (5.1-7.5)	<0.001	<0.001	<0.001	0.003	0.045	0.253	0.267
2-hour glucose*	5.2 (4.3-6.4)	6.4 (5.3-8.2)	<0.001	5.7 (4.8-6.7)	7.1 (5.8-9.1)	<0.001	6.2 (5.4-7.5)	7.6 (6.4-9.8)	<0.001	<0.001	<0.001	<0.001	0.178	0.037	0.099
HBA1c*	5.5 (5.2-5.7)	5.8 (5.4-6.2)	<0.001	5.6 (5.4-5.9)	6.1 (5.7-7.4)	<0.001	5.7 (5.5-6)	6.2 (5.8-7.1)	<0.001	<0.001	<0.001	<0.001	0.012	0.023	0.054
Fasting insulin*	3.5 (2.4-5.4)	5.2 (2.9-8.3)	<0.001	5.9 (4-8.6)	7.6 (5.4-11.6)	<0.001	7.6 (5.3-11.7)	11.7 (7.3-17.6)	<0.001	<0.001	<0.001	<0.001	0.024	0.531	0.16
2-hour insulin *	21.2 (11-35.4)	28.6 (14.7-47.6)	<0.001	31.0 (18.3-50.5)	49.1 (28.7-83.8)	<0.001	50.8((27.3-83)	67.1(40.6-112.5)	<0.001	<0.001	<0.001	<0.001	0.021	0.637	0.145
HOMA-IR*	0.8 (0.5-1.2)	1.3 (0.7-2.2)	<0.001	1.3 (0.9-1.9)	2.2 (1.4-3.7)	<0.001	1.7 (1.2-2.6)	3.2 (1.9-5.5)	<0.001	<0.001	<0.001	<0.001	0.007	0.962	0.121
Total Cholesterol	4.9 (1.1)	5.4 (1.2)	0.042	5.4 (1.2)	5.7 (1.3)	0.102	5.4 (1.1)	5.5 (1.2)	0.111	<0.001	<0.001	0.009	0.009	0.29	0.053
HDL-cholesterol	1.5 (0.4)	1.3 (0.4)	0.451	1.4 (0.3)	1.2 (0.3)	0.072	1.4 (0.3)	1.2 (0.3)	<0.001	<0.001	<0.001	<0.001	0.986	0.687	0.994
LDL-cholesterol	2.9 (0.9)	3.3 (1.1)	0.007	3.5 (1.0)	3.6 (1.0)	0.629	3.5 (1.0)	3.5 (1.0)	0.185	<0.001	<0.001	0.018	0.001	0.755	0.008
Triglycerides*	0.9 (0.7-1.1)	1.5 (1-2)	<0.001	1.0 (0.8-1.3)	1.8 (1.3-2.3)	<0.001	1.1 (0.8-1.3)	1.7 (1.2-2.2)	<0.001	<0.001	<0.001	0.003	0.257	0.013	0.099
C-reactive protein *	1.8 (0.7-5.1)	2.5 (0.9-5)	0.041	2.5 (1-5)	3.3 (1.5-7.7)	<0.001	5.6 (2.5-10.3)	7.2 (3.8-13.5)	<0.001	<0.001	0.002	<0.001	0.002	0.338	0.004
Creatinine*	63 (54-75)	68 (59-86)	<0.001	65.5 (55-80)	69 (56-87)	0.026	62 (53-74)	66 (55-82)	0.002	0.033	0.014	0.51	0.513	0.612	0.781
Education level			<0.001			<0.001			<0.001	0.195	0.627	0.105	0.07	0.401	0.855
<=7 years	27.2 (179/658)	47.3 (112/237)		26.1 (80/307)	40.8 (160/392)		29.2 (114/390)	39.6 (329/831)							
> 7years	72.8 (479/658)	52.7 (125/237)		73.9 (227/307)	59.2 (232/392)		70.8 (276/390)	60.4 (502/831)							
Alcohol use			0.003			0.454			0.026	<0.001	<0.001	<0.001	0.613	0.555	0.785
Non drinker	57.1 (375/657)	68.1 (162/238)		72.2 (223/309)	74.7 (292/391)		79.8 (312/391)	84.9 (702/827)							
Currently drinking	42.9 (282/657)	31.9 (76/238)		27.8 (86/309)	25.3 (99/391)		20.2 (79/391)	15.1 (125/827)							

Tobacco use			0.297			0.289			0.515	<0.001	<0.001	<0.001	0.179	0.048	0.348
Non-smoker	26.4 (171/647)	30 (71/237)		54.5 (169/310)	58.5 (223/381)		67.3 (261/388)	69.1 (571/826)							
Smoker	73.6 (476/647)	70 (166/237)		45.5 (141/310)	41.5 (158/381)		32.7 (127/388)	30.9 (255/826)							

Values are percentage, %(count), SD-standard deviation, *median (25th-75th percentile). B vs. M, interaction term of body mass index categories and metabolic status; M vs. Y, metabolic status and year of study; B vs. M vs. Y, body mass index categories, metabolic status and year of study. Units of measurements and other conventions are as per table 1

Supplementary Table 1. *Secondary data pairwise comparison of metabolically healthy and abnormal participants by body mass index (including CRP as a factor)*

Characteristics	Normal weight			Overweight			Obese			P trend across BMI categories			P interaction		
	Healthy Mean (SD)	Abnormal Mean (SD)	p-value	Healthy Mean (SD)	Abnormal Mean (SD)	p-value	Healthy Mean (SD)	Abnormal Mean (SD)	p-value	Overall	Healthy	Abnormal	B*M	M*Y	B*M* Y
Prevalence, % (n)	18.5 (524)	13.2 (374)		7.6 (217)	17.2 (489)		5.7 (163)	37.8 (1073)		<0.001					
Gender			0.881			0.911			0.921	<0.001	<0.001	<0.001	0.791	0.266	0.211
Women	57.3 (300/524)	57.8 (216/374)		74.7 (162/217)	75.1 (367/489)		90.2 (147/163)	89.9 (965/1073)							
Men	42.7 (224/524)	42.2 (158/374)		25.3 (55/217)	24.9 (122/489)		9.8 (16/163)	10.1 (108/1073)							
Age, years	43.6 (16.1)	52.8 (15.7)	0.250	45.3 (15)	55.2 (14.1)	0.134	51.6 (14.6)	53.7 (13.3)	0.068	<0.001	<0.001	0.033	<0.001	0.368	<0.001
Waist circumference	75.9 (7.9)	79.6 (9.4)	0.006	88.7 (8.7)	93.7 (7.6)	0.150	102.1 (11.5)	108.3 (12)	0.466	<0.001	<0.001	<0.001	0.064	0.006	0.005
Hip circumference	90.9 (8.2)	91.3 (8.5)	0.722	102.5 (7.4)	102.9 (6.1)	0.004	116.9 (12.1)	119.8 (12.9)	0.254	<0.001	<0.001	<0.001	0.042	0.007	0.031
Waist-to-hip ratio	0.8 (0.1)	0.9 (0.1)	0.553	0.9 (0.1)	0.9 (0.1)	0.082	0.9 (0.1)	0.9 (0.1)	0.420	<0.001	<0.001	<0.001	0.332	0.610	0.657
Systolic Blood Pressure	115.5 (19.2)	129.8 (26.6)	<0.001	118.3 (19)	130.8 (23)	0.001	119.7 (18.2)	131.2 (21.7)	0.009	<0.001	0.02	0.569	0.466	0.017	0.146
Diastolic blood pressure	74.3 (12.2)	80.6 (17.4)	<0.001	76.5 (12.7)	80.6 (12.9)	0.105	77.1 (10.5)	82.8 (13.4)	0.003	<0.001	0.011	0.003	0.332	0.006	0.029
Fasting glucose *	4.6 (4.3-5)	5.0 (4.6-6)	<0.001	4.8 (4.5-5.1)	5.6 (5-7.1)	<0.001	5.0 (4.7-5.2)	5.6 (4.9-6.9)	<0.001	<0.001	0.008	<0.001	0.005	0.019	0.013
2-hour glucose*	5.2 (4.3-6.2)	6.1 (5-8)	<0.001	5.6 (4.8-6.7)	6.6 (5.6-8.6)	<0.001	6.3 (5.4-7.5)	7.2 (6-9)	<0.001	0.001	<0.001	<0.001	0.256	0.009	0.072
HBA1c*	5.5 (5.2-5.7)	5.7 (5.4-6.2)	<0.001	5.6 (5.4-5.8)	6.0 (5.6-7)	<0.001	5.7 (5.5-5.9)	6.1 (5.7-6.7)	<0.001	<0.001	0.001	<0.001	0.001	0.368	0.035
Fasting insulin*	3.6 (2.4-5.5)	4.4 (2.7-7.5)	<0.001	5.7 (3.8-8.7)	7.2 (5.1-10.9)	<0.001	7.5 (5.3-11.1)	10.5 (6.8-16.1)	<0.001	<0.001	<0.001	<0.001	0.068	0.955	0.232
2-hour insulin *	21.2 (10.7-35.8)	25.1 (12.8-43.3)	0.006	31.6 (17.6-50.7)	43.7 (26-77.8)	<0.001	52.2 (27.8-83.8)	62.5 (36.8-106.2)	0.004	<0.001	<0.001	<0.001	0.073	0.993	0.239
HOMA-IR*	0.8 (0.5-1.2)	1.0 (0.6-1.8)	<0.001	1.2 (0.8-1.8)	2.0 (1.2-3.3)	<0.001	1.6 (1.2-2.5)	2.8 (1.6-4.8)	<0.001	<0.001	<0.001	<0.001	0.034	0.578	0.285
Total Cholesterol	4.9 (1.1)	5.1 (1.3)	<0.001	5.4 (1.1)	5.6 (1.3)	0.007	5.4 (1)	5.5 (1.2)	0.640	<0.001	<0.001	<0.001	0.474	0.873	0.604
HDL-cholesterol	1.5 (0.4)	1.3 (0.5)	0.360	1.4 (0.4)	1.2 (0.3)	0.036	1.5 (0.3)	1.2 (0.3)	0.187	<0.001	0.007	<0.001	0.661	0.514	0.92
LDL-cholesterol	3.0 (0.9)	3.2 (1.1)	0.003	3.5 (1)	3.6 (1.1)	0.080	3.5 (1)	3.5 (1)	0.095	<0.001	<0.001	<0.001	0.174	0.828	0.426
Triglycerides*	0.9 (0.7-1.1)	1.2 (0.9-1.8)	<0.001	1.0 (0.8-1.3)	1.6 (1.1-2.1)	<0.001	1.1 (0.8-1.3)	1.5 (1.1-2)	0.326	<0.001	<0.001	<0.001	0.056	0.351	0.106
C-reactive protein *	1.2 (0.7-2.5)	4.3 (1.7-9.9)	<0.001	1.5 (0.7-2.7)	4.2 (1.9-8.3)	<0.001	2.1 (1.2-4.4)	7.4 (4.1-13.6)	<0.001	<0.001	0.024	0.202	0.427	0.451	0.66
Creatinine*	64 (55-75.3)	66 (56-83.3)	0.007	65 (55-77.5)	69 (56-86)	0.019	64 (55-78)	64 (54-80)	0.667	0.033	0.253	0.107	0.711	0.728	0.969
Education level			<0.001			<0.001			0.055	0.181	0.247	0.115	0.086	0.419	0.521
<=7 years	25.1 (131/522)	43.5 (161/370)		22.1 (47/213)	39.6 (193/487)		29.6 (48/162)	37.4 (399/1066)							

> 7years	74.9 (391/522)	56.5 (209/370)		77.9 (166/213)	60.4 (294/487)		70.4 (114/162)	62.6 (667/1066)						
Alcohol use			0.026			0.010			0.888	<0.001	<0.001	<0.001	0.455	0.817	0.666
Non drinker	57.0 (297/521)	64.4 (239/371)		66.8 (143/214)	76.2 (371/487)		82.7 (134/162)	83.2 (884/1063)						
Currently drinking	43.0 (224/521)	35.6 (132/371)		33.2 (71/214)	23.8 (116/487)		17.3 (28/162)	16.8 (179/1063)						
Tobacco use			0.389			0.478			0.365	<0.001	<0.001	<0.001	0.239	0.355	0.292
Non-smoker	28.4 (147/517)	25.8 (95/368)		54.9 (118/215)	57.8 (275/476)		71.6 (116/162)	68.1 (718/1055)						
Smoker	71.6 (370/517)	74.2 (273/368)		45.1 (97/215)	42.2 (201/476)		28.4 (46/162)	31.9 (337/1055)						

Values are percentage, % (count), SD-standard deviation, *median (25^{th}-75^{th} percentile). B vs. M, interaction term of body mass index categories and metabolic status; M vs. Y, metabolic status and year of study; B vs. M vs. Y, body mass index categories, metabolic status and year of study. Units of measurements and other conventions are as per table 1.1

Discussion

In the current study, there was a differential distribution of BMI status across the two time-points, reflecting fewer overweight and more normal-weight participants in 2014/16 compared to 2008/09. However, the distribution of obesity phenotypes (that is the combination of BMI categories and underlying metabolic burden) did not differ by year of study, with about one in ten participants having normal weight and being metabolically abnormal and 13–14% being obese and metabolically healthy. Findings were also broadly consistent, regardless of whether or not subclinical inflammation (high CRP levels) was accounted for as a metabolic abnormality. Variable differences were apparent in the distribution of cardiometabolic risk profile and other key characteristics across BMI categories and metabolic status, with suggestions that some of these variations were occurring in differential ways across the 2 years of the study.

In 2016, the Government of South Africa issued a strategy for the prevention and control of obesity 2015–2016 with the target to have no increase in 2016, 3% reduction in 2017 and 10% reduction in 2020 (30). Even if effective, this policy issued when our second survey was underway, would not have accounted for differences, if any (or the lack thereof), in obesity phenotype distribution between the two time points of our study. The distribution of BMI status changed across the two time points, driven by changes in the distribution in men, but not in women. The changes in men could be attributed to their younger age in 2014/16 compared with 2008/09. This was shown in the 2016 South African Demographic and Health Survey, where young participants had a lower prevalence of obesity (31).

A number of previous studies in developed countries have investigated obesity phenotypes (27, 32). In Africa, however, such studies (26, 28) are few, with even fewer done in the Mixed-ancestry population in South Africa (33). In contrast to the findings in urban Cameroonians, where a small proportion of normal weight participants were metabolically abnormal (0.3%), a considerable percentage of NWMA participants were found in this study (8.4%), in line with a similar study in the HIV-infected population in Cape Town (28). A recent meta-analysis of 40 studies globally reported that over one-third of the obese population was metabolically healthy (34). This is similar to our findings in both surveys, but varied considerably from studies in Cameroonians and Brazilians where higher rates of MHO were reported (26, 34). These differences have

been ascribed to different ages, sample sizes and criteria used to define obesity phenotypes across studies (9, 27, 32, 35–38).

In our study, findings in women were broadly similar to those observed in the overall sample, reflecting the high proportion of women in this study. However, in the analyses stratified by gender, differences between men and women were apparent. Metabolically healthy but obese phenotype has been reported to occur more frequently in adult women compared to men (39) as was demonstrated in this study. Indeed, more than 50% of women were obese, but a significant number of them were metabolically healthy (33%), whereas more than 80% of men who were obese were metabolically abnormal. The differences in obesity phenotypes between men and women have been attributed to body shape and fat distribution (40). Women are known to have more subcutaneous adipose tissue than men, especially in the abdominal and gluteo-femoral regions (41, 42), as well as lower waist-to-hip ratios, which was also observed in this study. Lower waist-to-hip ratio is indicative of a comparatively more gynoid shaped which is associated with less metabolic complications (18, 41, 43). MHO women, tended to be younger and smoked and drank moderately compared to men of all ages (44–46). In our study, however, there were no differences in smoking and alcohol consumption between the MHO and MAO. Furthermore, MHO rates in men were similar between the two surveys despite a significant difference in age between the two studies.

The distribution of cardiometabolic risk factors differed across BMI categories and obesity phenotype, which was similar to previous reports involving different population groups (26, 28, 29, 44, 47, 48). For example, in a study by Pajunen et al. (29) Caraballo et al. (23) conducted in the Finnish population, significant interactions between phenotype and BMI were found in the distribution of fasting blood glucose, fasting insulin and HOMA-IR, in keeping with our findings.

The major strength of this study is that the two cross-sectional surveys analyzed were conducted in the same population, using similar methodological approaches. The limitations of this study are as follows: [1] the surveys were conducted in only one population group in Cape Town; thus, findings cannot be easily extrapolated to other ethnic groups, [2] comparisons in the current analyses were based on only two cross-sectional surveys which prevented a reliable assessment of time-trends, [3] the

proportion of men included in these surveys was small; consequently, the overall study findings reflect more the observations in women. In general, population-based surveys in South Africa have reported a low participation of men (49).

Conclusion

In conclusion, our study has shown negligible changes in obesity phenotype distribution between 2008/09 and 2014/16 in the South African Mixed-ancestry population. Furthermore, there was a high burden of metabolic abnormalities among normal weight participants, and a significant proportion of obese individuals who were metabolically healthy. Additional research is needed to improve risk stratification for obesity phenotypes; this may enable targeted screening and cost-effective detection of individuals at high risk for cardiometabolic diseases.

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Chapter 6- Manuscript 3

Title: The 7-year change in the prevalence of insulin resistance, inflammatory biomarkers and their determinants in an urban South African population

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Journal: Journal of Diabetes Research

DOI: https://doi.org/10.1155/2020/3781214

Abstract

Background: Insulin resistance (IR) and sub-clinical inflammation are involved in pathological pathways leading to the development of biological cardiovascular risk factors and subsequent cardiovascular events. Therefore, monitoring these processes can provide advanced information on the trajectory of cardiovascular risk profile of a population, and inform prevention and control strategies. We investigated changes in IR and sub-clinical inflammation in a population from Cape Town, South Africa between 2008/09 and 2014/16.

Methods: In a total of 2503, (n=797, 2008/09) and (n=1706, 2014/16) participants IR was calculated using five indices i.e. insulin fasting, HOMA-IR, QUICKI, McAuley and Matsuda while sub-clinical inflammation measured using us-CRP and gamma GT. Linear and logistic regression analyses and interaction tests were conducted.

Results: The mean age of participants was 53.2 (2008/09) and 48.2 (2014/16), respectively. In females, IR prevalence significantly decreased between 2008/09 and 2014/2016 by all indices, $p \leq 0.021$ whilst sub-clinical inflammation prevalence increased from 54.7% 2008/09) to 57.1% (2014/16) based usCRP, and 29.6% to 33.4% based on gamma GT. In a multivariate analysis adjusted for year of study, age and gender, prominent factors associated with increased IR or subclinical inflammation were obesity levels measured using waist circumference, glycated haemoglobin and fasting insulin levels.

Conclusions: Over the 7-year period, sub-clinical inflammation increased and this was associated with IR and the metabolic syndrome components, both of which are strong predictors of CVDs. The decrease in IR over the year period reflects in part the much younger age in the second survey.

Keywords: insulin resistance, inflammation, biomarkers, change, determinants, physiology

Introduction

Insulin resistance (IR) and sub-clinical inflammation are among the pathophysiological derangements involved in the development of cardiometabolic risk factors and related cardiometabolic diseases, the leading cause of death worldwide. Insulin is an anabolic hormone that plays a critical role in the maintenance of glucose homeostasis by promoting glucose transport into muscle and adipose tissue (AT) and inhibiting glucose output by the liver (1). Resistance to these metabolic actions of insulin (IR) is a major determinant for the development of Type 2 Diabetes Mellitus (2). In addition, a cluster of other cardiovascular disorders such as dyslipidaemia, obesity, hypertension, and endothelial dysfunction (ED) are associated with IR and are known to interact with each other to promote the development of cardiovascular diseases (CVD) (3). CVDs are associated with low-grade inflammation; this is demonstrated from increased levels of circulating markers and mediators of inflammation, which in turn are linked to IR (4). These pro-inflammatory proteins play a crucial role in the development of IR and subsequent CVDs by activating various inflammatory pathways. For instance, in obesity, macrophages secrete pro-inflammatory cytokines, tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6) that impairs insulin signalling (5). TNFα reduces the expression of glucose transporter type 4 (GLUT4) which is an insulin-regulated glucose transporter and mainly located in adipocytes, skeletal, and cardiac muscles, resulting in increased circulating Triglycerides (6). IL-6 on the other hand regulates the production of C-Reactive Protein (CRP), a systemic inflammatory biomarker that has been strongly associated with cardiovascular mortality, hypertension, coronary heart disease, stroke, and diabetes (7).

These pathophysiological derangements involved in the occurrence of CVD, develop in apparently healthy individuals in the population for some time, before CVDs and their risk factors occur. Therefore, monitoring pathophysiological biomarkers involved in the development of CVD at a population level can provide early information on the trajectory of CVD burden in the population, even before sizable changes are observed in populations level of CVD risk factors. Such pre-clinical information can assist in the planning of population-level interventions to timeously curb the rising trajectories. However, there has been a dearth of information on the prevalence and patterns of raised pathophysiological biomarkers linked to the development of CVD in the Mixed-

ancestry population of Cape Town. Therefore, the aim of this study is to investigate the temporal changes in the prevalence of IR, inflammatory biomarkers and their determinants in the Mixed-ancestry population of Bellville South, Cape Town, between 2008/09 and 2014/16.

Materials and Methods

Study population and sampling procedure

In the Mixed-ancestry population in Bellville South, Cape Town, two independent cross-sectional surveys were conducted in 2008/09 and 2014/16. Residents who were 18 years and older (2008/09) or 20 years and older (2014/16) were invited to participate in the survey by recruiters who visited each dwelling in the area. Individuals who were bed-ridden or pregnant, underweight and those who were under the age of 20 years in the 2008/2009 survey were excluded. Therefore, the number of participants was 946 in 2008/09 and 1989 in 2014/16. After excluding participants with missing data, those who did not fulfil the age criteria, had known diabetes or were underweight, the final sample size was 797 in 2008/09 and 1706 in 2014/16.

Data collection

Eligible participants were assessed at a designated research site where trained personnel took informed consent, administered the World Health Organisation (WHO) stepwise questionnaire (8), and conducted clinical and biochemical assessments. Anthropometric measurements were performed as per the WHO standardized techniques. Waist and hip circumferences were collected using a non- elastic tape measure while height was measured using a stadiometer to the nearest centimetre (8). Blood pressure was measured three times in 3-minute intervals (8). The lowest Systolic Blood Pressure (SBP) and its corresponding diastolic blood pressure (DBP) and pulse readings was used. An oral glucose tolerance test (OGTT) was administered to individuals without known diabetes after an overnight fasting to diagnose type 2 diabetes (9). Biochemical measurements were sent to an ISO 15189 accredited lab in Cape Town. The following test were performed: plasma glucose; plasma insulin, high density lipoprotein cholesterol (HDL-C); low density lipoprotein cholesterol (LDL-C); Total Cholesterol (TC); triglycerides; ultrasensitiveC-Reactive Protein (usCRP); and gamma-glutamyl transferase (gamma GT).

Assessment of insulin resistance and sub-clinical inflammation

IR was calculated using five indices: the 75^{th} percentile of fasting insulin, and the homeostatic model assessment of IR (HOMA-IR) (10) as well as the 25^{th} percentile QUICKI (11), McAuley index (12) and Matsuda index (13). The 75^{th} or 25^{th} percentiles were derived from the first survey and the same cut-off points applied to the two survey populations. Using percentiles specific to each of the sample would lead to differing cut-off points and no change in IR prevalence over time. Sub-clinical inflammation was assessed using two biomarkers with the following values defining sub-clinical inflammation: usCRP >3mg/L (14) and gamma GT ≥ 38 IU/L (15).

Calculations and Definitions

Body Mass Index (BMI) was calculated as weight [in kilograms(kg)] divided by height [in meters squared (m^2)]. For this study, BMI status was divided into three categories, as per WHO (16): normal weight (<25.0 kg/m^2); overweight (25.0 kg/m^2- 29.9 kg/m^2) and obesity (≥30.0 kg/m^2). Level of education was divided into two categories: ≤7 years of education (up to completion of primary school) and >7 years of education (secondary schooling and higher). Cotinine level of >10ng/mL was defined as current smoker. Alcohol consumption was self-reported in the administered questionnaire (8). Hypertension was defined as SBP ≥140mmHg and/or DBP ≥90mmHg or taking blood pressure lowering medication. The glucose tolerance status was determined using the recommended OGTT test. Pre-diabetes, was defined as fasting plasma glucose between 6.1 and 6.9 mmol/l and/or a 2-hour glucose value between 7.8 mmol/l and 11.1 mmol/l (17). Screened type 2 diabetes, this was defined as fasting plasma glucose ≥7.0 mmol/l and/or a 2-hour post-OGTT plasma glucose ≥11.1 mmol/l. Known type 2 diabetes was self-reported and/or on diabetes medication (17).

Statistical analysis

The software's, Statistica v.13 (TIBCO Software Inc. ,2017) and SPSS v.25 (IBM Corp, 2011) were used for the data analyses. Data was tested for normality using normality Q-Q plot. The results are reported as median (25th and 75th percentiles), mean (standard deviation), and count (percentages). For comparison, the chi-square test,

analysis of variance test (ANOVA) or Kruskal Wallis test were used as appropriate. IR was based on the 75th percentile of fasting insulin (12.5 mIU/L) and HOMA IR (3.1) or the 25th percentile of QUICKI (0.53), McAuley index (6.1) and Matsuda index (4.0). Crude prevalence of IR and inflammatory biomarkers was estimated in all participants as well as in participants only with normoglycemia and who were not taking lipid and/or blood pressure lowering medications. Linear regressions and logistic regression, adjusted for age, gender and year of study were used to determine the changes in IR indices, inflammatory biomarkers and their respective determinants between the two cross-sectional studies. A p-value <0.05 was used to characterize statistically significant results.

Ethical approval

The University of Cape Town Human Research Ethics Committee had granted ethical approval for this study (ref: 442/2016), while the Cape Peninsula University of Technology had granted ethical approval for the 2008/09 and 2014/16 studies (ref. no. CPUT/HW-REC 2008/002 and CPUT/HW- REC 2015/H01, respectively). The Ward Councillors, representing the City of Cape Town and community management, had granted permission to conduct the surveys in the designated areas. Written informed consent was obtained from all participants and the study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Results

Characteristics

The population characteristics by year is presented in Table 1. In both surveys, i.e. 2008/09 and 2014/16, majority of participants were women. The average age in 2014/16 was younger compared to 2008/09 (48.2±15.3 years vs 53.2±14.8 years, p<0.001). Waist circumference (91.4 ±17.1 cm vs 96.3±15.0 cm, p<0.001) and hip circumference (103.8±16.5 cm vs 109.8 ±14.7 cm, p<0.001) were smaller in 2014/16 vs. 2008/09. The average BMI decreased between 2008/09 and 2014/16 (p=0.013), as did both the prevalence of overweight (27.7% vs 22.9%) and obesity (44.7% vs 41.3%). However, blood pressure levels increased significantly between the two periods (Table 1) (both, p<0.001). Lipid profiles improved between the two periods: HDL-C increased from 1.2 (1.0, 1.5) mmol/L to 1.3 (1.1; 1.5) mmol/L and LDL-C

decreased from 3.6 (3.0; 4.3) to 3.1 (2.5; 3.7) mmol/L, (both p<0.001). The abnormal glucose tolerance status significantly decreased between 2008/09 and 2014/16 for pre-diabetes, 23.2% vs 17.4%, and screen-detected diabetes, 17.1% vs 7.3% (both, p<0.001). Current smokers significantly increased between 2008/09 (43.8%) and 2014/16 (52.9%) (p<0.001), while alcohol use was similar between the periods (p=0.958).

Table 1 . Characteristics of participants in 2008/09 and 2014/16

Characteristics	2008/09, n=797 (n=797) Median (25^{th};75^{th} percentiles)	2014/16, n=1706 (n=1706) Median (25^{th};75^{th} percentiles)	p-value
Gender			0.114
Women, n (%)	620 (77.8)	1278 (74.9)	
Men, n (%)	177 (22.2)	428 (25.1)	
Age, year *	53.2 ± 14.8	48.2 ± 15.3	<0.001
Level of education			
Education level <=7 years, n (%)	271 (34.2)	559 (33.0)	0.553
Education level > 7years, n (%)	522 (65.8)	1136 (67)	0.553
Alcohol use			
Current drinker, n (%)	563 (71.4)	1213 (71.5)	0.958
Non-drinker, n (%)	225 (28.6)	483 (28.5)	0.958
Cotinine (ng/ml)	10 (9; 311)	48.2 (10; 268)	<0.001
Tobacco use			
Non-smoker, n (%)	447 (56.2)	779 (47.1)	<0.001
Smoker, n (%)	348 (43.8)	874 (52.9)	<0.001
Anthropometry			
Body mass index, (kg/m^2) *	29.64±7.24	28.83±8.1	0.013
BMI status			
Normal (18.5kg/m^2 to 25kg/m^2), n (%)	218 (27.7)	603 (35.8)	<0.001
Overweight (25kg/m^2 to 29.9 kg/m^2), n (%)	218 (27.7)	385 (22.9)	0.009
Obese (>=30kg/m^2), n (%)	352 (44.7)	696 (41.3)	0.109
Waist circumference (cm)*	96.3 ± 15.0	91.4 ± 16.9	<0.001
Hip circumference (cm)*	109.8 ± 14.7	103.83 ± 16.5	<0.001
Waist-to-hip ratio*	0.9 ± 0.1	0.88 ± 0.09	0.504
Systolic Blood Pressure (mmHg)*	123 ± 19	126 ± 24	<0.001
Diastolic blood pressure (mmHg)*	75 ± 12	82 ± 14	<0.001
Fasting glucose (mmol/L)	5.6 (5.0;6.5)	5.0 (4.6;5.6)	<0.001
2hr glucose (mmol/L)	6.8 (5.7;8.7)	6.1 (4.9;7.6)	<0.001
HBA1c (mmol/mol) *	65 ±10	63±9	<0.001
HBA1c (%) *	5.9±0.9	5.8 ± 0.8	<0.001
Fasting insulin (mIU/L)	6.6 (2.7; 12.5)	6.6 (4.2; 10.4)	0.414
2hr insulin (mIU/L)	38.1 (19.5; 72.2)	38.8 (20.7; 71.9)	0.829
Normoglycemia, n (%)	474 (59.7)	1278 (75.3)	<0.001
Pre-diabetes, n (%)	184 (23.2)	296 (17.4)	<0.001
Screened-detected Diabetes, n (%)	136 (17.1)	124 (7.3)	<0.001
HDL-C (mmol/L)	1.2 (1.0; 1.5)	1.3 (1.1; 1.5)	<0.001
LDL-C (mmol/L)	3.6 (3.0; 4.3)	3.1 (2.5; 3.7)	<0.001
Triglycerides (mmol/L)	1.2 (0.9; 1.7)	1.5 (0.8; 1.7)	0.620
Ultra-sensitiveC-Reactive Protein (mg/L)	3.6 (0.9; 9.4)	3.9 (1.5; 8.6)	0.228
Gamma-glutamyl transferase (IU/L)	27 (19; 42)	28 (20; 45)	0.011
HOMA-IR	1.6 (0.6; 3.1)	1.4 (0.9; 2.4)	0.859
QUICKI	0.6 (0.5; 0.9)	0.7 (0.6; 0.8)	0.124
McAuley index	7.9 (6.1; 10.7)	7.9 (6.4; 9.4)	0.050
Matsuda index	7.9 (4.0; 17.8)	8.4 (4.8; 15.3)	0.685

*mean±SD, Screen-detected diabetes: newly diagnosed diabetics, high density lipoprotein cholesterol (HDL-C); low density lipoprotein cholesterol (LDL-C); homeostatic model assessment of Insulin Resistance (HOMA-IR).

Markers of IR and inflammation across the two time-points

Markers of subclinical inflammation increased slightly between the periods, i.e., median usCRP increased from 3.6 mg/L in 2008/2009 to 3.9mg/L in 2014/2016, p=0.228, and gamma GT from 27 IU/L to 28 IU/L, p=0.011. The indices of IR were generally similar between the two period, all p≥0.05. (Table 1).

Prevalence of insulin resistance and sub-clinical inflammation

In the overall study population including screen-detected diabetes, pre-diabetes and normoglycemia, IR prevalence significantly decreased between 2008/09 and 2014/2016, fasting insulin from 24.8% in 2008/2009 to 16.9% in 2014/2016; HOMA-IR from 24.8% to15.4%; QUICKI from 23.6% to 13.3%; McAuley from 25.5% to 21.3% and Matsuda from 25.5% to 18.8%, p≤0.021. A similar pattern was observed amongst women between the periods for all the IR indices, p<0.023. Although the prevalence of IR also decreased in men, it was not significant, p≥0.050. In participants with normoglycemia, excluding those taking lipid lowering and/or hypertension medication, the decrease in IR was not significant with McAuley index, from 35.7% in 2008/2009 to 32.8%, p=0.157 in the overall study population. A similar trend was observed in women; however, in men, significant decreases in the prevalence of IR were observed with QUICKI from 27.8% to 19.9%, p=0.034 and Matsuda index, from 26.7% to 18.2%, p=0.020 (Table 2).

Sub-clinical inflammation prevalence increased slightly between 2008/09 and 2014/16, from 54.7% to 57.1% (p=0.264) for usCRP, and 29.6% to 33.4% (p=0.055) for gamma GT. Both sub-clinical inflammatory biomarkers increased in women but this was significant only for gamma GT (26.2% to 32.1%, p=0.009). In contrast, there were no significant changes in these biomarkers in men between the periods, with both markers p≥0.368 respectively. In the group with normoglycemia without lipid lowering and/or hypertension medication, the prevalence of sub-clinical inflammation as measured by gamma GT increased significantly in women, with p=0.030 (Table 2).

Table 2. Prevalence of IR and inflammation in all participants and in those with normoglycemia and not on lipid lowering and/or hypertension medication

	Overall			Women			Men			Gender * year of study p-interaction
	2008/09 n (%)	2014/16 n (%)	p-value	2008/09 n (%)	2014/16 n (%)	p-value	2008/09 n (%)	2014/16 n (%)	p-value	
Insulin resistance: all participants										
Fasting insulin	196 (24.8)	278 (16.9)	<0.001	174 (28.4)	231 (18.7)	<0.001	22 (12.5)	47 (11.4)	0.706	0.939
HOMA-IR	196 (24.8)	253 (15.4)	<0.001	170 (27.7)	205 (16.6)	<0.001	26 (14.8)	48 (11.7)	0.296	0.375
QUICKI	186 (23.6)	218 (13.3)	<0.001	158 (25.8)	176 (14.3)	<0.001	28 (15.9)	42 (10.2)	0.050	0.550
McAuley index	201 (25.5)	348 (21.3)	0.021	167 (27.2)	275 (22.4)	0.023	34 (19.5)	73 (18.0)	0.667	0.369
Matsuda index	200 (25.5)	299 (18.8)	<0.001	174 (28.6)	255 (21.5)	0.001	26 (14.8)	44 (10.9)	0.194	0.119
Insulin resistance: normoglycemia and not on lipid lowering and/or hypertension medication										
Fasting insulin	247 (31.3)	413 (25.1)	0.001	211 (34.4)	343 (27.8)	0.004	36 (20.5)	70 (17.0)	0.317	0.765
HOMA-IR	288 (36.5)	451 (27.4)	<0.001	248 (40.5)	377 (30.6)	<0.001	40 (22.7)	74 (18.0)	0.181	0.455
QUICKI	323 (40.9)	504 (30.6)	<0.001	274 (44.7)	422 (34.2)	<0.001	49 (27.8)	82 (19.9)	0.034	0.548
McAuley index	281 (35.7)	535 (32.8)	0.157	233 (38.0)	430 (35.1)	0.216	48 (27.6)	105 (25.9)	0.678	0.236
Matsuda index	310 (39.5)	542 (34.1)	0.009	263 (43.3)	469 (39.5)	0.123	47 (26.7)	73 (18.2)	0.020	0.170
Sub-clinical inflammation: all participants										
usCRP	436 (54.7)	967 (57.1)	0.264	351 (56.6)	772 (60.8)	0.079	85 (48.02)	195 (45.9)	0.631	0.092
gamma GT	235 (29.6)	567 (33.4)	0.055	162 (26.2)	408 (32.1)	0.009	73 (42.2)	159 (37.3)	0.368	0.158
Sub-clinical inflammation: normoglycemia and not on lipid lowering and/or hypertension medication										
usCRP	160 (46.2)	480 (49.5)	0.3	124 (47.9)	356 (53.1)	0.157	36 (41.4)	124 (41.5)	0.625	0.217
gamma GT	83 (24.1)	276 (28.4)	0.12	50 (19.4)	176 (26.2)	0.03	33 (37.9)	100 (33.3)	0.372	0.166

*interaction between men and women; homeostatic model assessment of Insulin Resistance (HOMA-IR); ultrasensitiveC-Reactive Protein (usCRP); and gamma-glutamyl transferase (gamma GT).

Determinants of levels of markers of insulin resistance

From the two surveys, linear regression models for IR and sub-clinical inflammation, adjusted for year of study, gender, age and smoking, was determined using log transformed dependent variables. For IR, QUICKI, McAuley and Matsuda indices showed inverse values since their cut-off values are inverse. Using HOMA-IR index, an increased level of IR was indicated in year of study and age, while men were inversely affected, table 3. Furthermore, IR markers with the exception of the QUICKI index were positively associated with HbA1c, waist circumference, Triglycerides and gamma GT (all p≤0.004), while HDL-C, education level < 7 years, and those who reported current alcohol drinking status were negatively associated, with all (p≤0.018) (Table 3). Similarly, in a logistic regression adjusted for year of study, age and gender, the odds of IR in participants in 2014/16 were lower compared to those in 2008/09 (Table 4). Smokers and current drinkers had a lower odds ratio of IR, while usCRP and gamma GT were associated with higher odds of IR, using HOMA-IR (usCRP odds ratio (OR) 2.39, 95% CI 1.88 ;3.04 and gamma GT OR: 1.93, 95%
1.54;2.43) all p≤0.011.

Determinants of levels of markers of sub- clinical inflammation

In a secondary analysis presented in table 5, subclinical inflammation was significantly higher by usCRP in 2014/16 compared with 2008/09 [0.08% (0.04;0.13), p=0.001]. Additionally, waist circumference; hip circumference; 2-hour glucose; HbA1c; gamma GT; and education < 7 years, increased with higher usCRP levels (all p≤0.009). Similar findings were observed in the associations with gamma GT with the addition of men gender, current drinkers, systolic blood pressure, fasting glucose, fasting insulin, HDL-C, triglycerides, and usCRP, were also associated with sub-clinical inflammation, p≤0.017.

The logistic regression, adjusted for year of study, age and gender, had shown an almost 1.5-fold higher odds of inflammation in 2014/16 compared to 2008/09 for both markers of inflammation. Insulin resistance, using McAuley and Matsuda indices, had demonstrated an almost 2-fold significantly greater odds of inflammation using usCRP or gamma GT. Additionally, age was significantly associated with inflammation using usCRP, while lower level of education was associated with inflammation using gamma

GT. Sub-clinical inflammation, using gamma GT, had shown greater odds in smokers (OR 1.26, 95% 1.03; 1.53) and current drinkers (OR 2.47, 95% CI: 1.99;3.06) (Table 6).

Table 3. Year of study, gender, age and smoking adjusted linear regression models for determinants of Insulin Resistance in all participants

	Model 1:log Insulin fasting*				Model 2: log HOMA-IR*				Model 3: log Quicki index*				Model 4: log McAuley index*				Model 5: log Matsuda index*			
		95% Confidence Interval				95% Confidence Interval				95% Confidence Interval				95% Confidence Interval				95% Confidence Interval		
	B	Lower	Upper	p-value	B	Lower	Upper	p-value	B	Lower	Upper	p-value	B	Lower	Upper	p-value	B	Lower	Upper	p-value
Year of study (2014/16)	0.16	0.13	0.20	<0.001	0.06	0.03	0.10	<0.001	-0.39	-0.51	-0.26	<0.001	-0.05	-0.06	-0.04	<0.001	-0.09	-0.12	-0.06	<0.001
Gender (men)	-0.15	-0.19	-0.11	<0.001	-0.15	-0.18	-0.11	<0.001	0.18	0.04	0.32	0.012	0.04	0.03	0.05	<0.001	0.21	0.18	0.25	<0.001
Age	0.43	0.30	0.55	<0.001	0.40	0.28	0.51	<0.001	-0.39	-0.85	-0.05	0.085	-0.12	-0.16	-0.08	<0.001	-0.21	-0.33	-0.10	<0.001
Current smokers	-0.08	-0.12	-0.05	<0.001	-0.08	-0.11	-0.05	<0.001	0.09	-0.02	0.21	0.122	0.02	0.01	0.03	<0.001	0.12	0.09	0.15	<0.001
Education (< 7 years)	-0.05	-0.09	-0.02	0.002	-0.04	-0.08	-0.01	0.007	0.01	-0.11	0.13	0.829	0.01	0.01	0.02	0.002	0.04	0.01	0.07	0.012
Current drinkers	-0.06	-0.10	-0.02	0.003	-0.05	-0.08	-0.01	0.007	0.03	-0.11	0.16	0.707	0.02	0.01	0.03	0.003	0.05	0.01	0.08	0.006
Waist circumference	0.85	0.65	1.04	<0.001	0.87	0.68	1.05	<0.001	-0.82	-1.50	-0.15	0.017	-0.24	-0.29	-0.18	<0.001	-0.87	-1.05	-0.70	<0.001
Hip circumference	-0.15	-0.34	0.05	0.142	-0.15	-0.33	0.03	0.107	0.58	-0.10	1.27	0.094	0.04	-0.01	0.09	0.142	0.22	0.05	0.40	0.014
Systolic blood pressure	0.01	-0.07	0.09	0.792	0.03	-0.04	0.10	0.369	0.00	-0.26	0.27	0.993	0.00	-0.02	0.02	0.792	-0.05	-0.12	0.02	0.142
HbA1c	2.95	0.92	5.02	0.004	8.67	6.66	10.72	<0.001	-9.78	-15.87	-3.25	0.004	-0.81	-1.36	-0.26	0.004	-8.19	-9.92	-6.41	<0.001
HDL-C*	-0.28	-0.51	-0.05	0.018	-0.29	-0.50	-0.07	0.010	0.06	-0.75	0.87	0.877	0.08	0.01	0.14	0.018	0.35	0.13	0.56	0.001
LDL-C*	0.29	-0.10	0.68	0.150	0.26	-0.11	0.62	0.172	-0.46	-1.84	0.91	0.509	-0.08	-0.19	0.03	0.150	-0.27	-0.62	0.09	0.148
Triglycerides *	0.31	0.19	0.43	<0.001	0.31	0.20	0.42	<0.001	-0.20	-0.62	0.22	0.342	-0.40	-0.43	-0.36	<0.001	-0.34	-0.45	-0.23	<0.001
usCRP *	-0.02	-0.05	0.02	0.323	-0.01	-0.04	0.02	0.505	0.07	-0.03	0.18	0.177	0.00	0.00	0.01	0.323	0.00	-0.03	0.03	0.945
gamma GT*	0.10	0.04	0.15	<0.001	0.13	0.07	0.18	<0.001	-0.16	-0.36	0.03	0.098	-0.03	-0.04	-0.01	<0.001	-0.13	-0.19	-0.08	<0.001

* log transformed; homeostatic model assessment of Insulin Resistance (HOMA-IR); high density lipoprotein cholesterol (HDL-C); low density lipoprotein cholesterol (LDL-C), ultrasensitiveC-Reactive Protein (usCRP); and gamma-glutamyl transferase (gamma GT)

Table 4. Age, sex and year of study adjusted odds ratios (with 95% confidence intervals) for the determinants of Insulin Resistance in all participants

	Model 1: Insulin fasting				Model 2: HOMA-IR				Model 3: Quicki index				Model 4: McAuley index				Model 5: Matsuda index			
	Odds ratio	95% Confidence Interval		p-value	Odds ratio	95% Confidence Interval		p-value	Odds ratio	95% Confidence Interval		p-value	Odds ratio	95% Confidence Interval		p-value	Odds ratio	95% Confidence Interval		p-value
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Year of study																				
2008/09	1				1				1				1				1			
2014/16	0.57	0.46	0.71	<0.001	0.51	0.41	0.64	<0.001	0.45	0.36	0.57	<0.001	0.78	0.63	0.97	0.025	0.67	0.54	0.84	<0.001
Gender																				
Women	1				1				1				1				1			
Men	0.58	0.43	0.77	<0.001	0.67	0.50	0.89	0.006	0.72	0.54	0.97	0.031	0.83	0.64	1.06	0.137	0.53	0.40	0.71	<0.001
Age	0.99	0.98	1.00	0.002	0.99	0.99	1.00	0.106	0.99	0.98	1.00	0.031	1.00	1.00	1.01	0.538	1.00	0.99	1.01	0.548
Tobacco use																				
Non-smoker	1				1				1				1				1			
Smoker	0.66	0.52	0.83	<0.001	0.64	0.50	0.80	<0.001	0.72	0.57	0.92	0.009	0.69	0.56	0.86	0.001	0.50	0.39	0.63	<0.001
Level of education																				
<7 years	1				1				1				1				1			
>=7 years	1.26	0.99	1.61	0.063	1.14	0.89	1.45	0.310	1.13	0.88	1.46	0.349	1.09	0.87	1.37	0.461	1.21	0.95	1.54	0.115
Alcohol use																				
Non-drinker	1				1				1				1				1			
Current drinker	0.66	0.5	0.88	0.004	0.7	0.52	0.92	0.011	0.66	0.49	0.88	0.005	0.74	0.57	0.95	0.02	0.62	0.47	0.83	0.001
BMI status																				
Normal	1				1				1				1				1			
Overweight	1.18	0.88	1.56	0.518	1.07	0.80	1.44	0.778	1.19	0.88	1.60	0.538	1.08	0.82	1.42	0.501	1.15	0.86	1.54	0.563
Obese	1.11	0.86	1.43	0.518	1.1	0.85	1.41	0.778	1.08	0.83	1.41	0.538	1.15	0.91	1.46	0.501	1.12	0.87	1.44	0.563
usCRP																				
No	1				1				1				1				1			
Yes	2.28	1.81	2.88	<0.001	2.39	1.88	3.04	<0.001	2.16	1.69	2.77	<0.001	2.05	1.65	2.55	<0.001	2.38	1.89	3.01	<0.001
Gamma GT																				
No	1				1				1				1				1			
Yes	1.75	1.4	2.19	<0.001	1.93	1.54	2.43	<0.001	2.08	1.65	2.64	<0.001	2.33	1.89	2.88	<0.001	2.23	1.78	2.79	<0.001

Homeostatic model assessment of Insulin Resistance (HOMA-IR); ultra-sensitive- C-Reactive Protein (usCRP); and gamma-glutamyl transferase (gamma GT)

Table 5. Year of study, gender, age and smoking adjusted linear regression models for determinants of inflammation in all participants

	Model 1: Log usCRP				Model 2: Log gamma GT			
		95% Confidence interval				95% Confidence interval		
	B	Lower	Upper	P-value	B	Lower	Upper	P-value
Year of study (2014/16)	0.08	0.04	0.13	0.001	0.03	0.00	0.06	0.033
Gender (men)	-0.04	-0.09	0.02	0.200	0.08	0.05	0.11	<0.001
Age	0.09	-0.08	0.26	0.316	-0.28	-0.37	-0.18	<0.001
Current smokers	0.10	0.05	0.14	<0.001	0.06	0.03	0.08	<0.001
Education (< 7 years)	0.07	0.03	0.12	0.002	0.03	0.00	0.05	0.040
Current drinkers	-0.05	-0.10	0.00	0.040	0.11	0.08	0.14	<0.001
Waist circumference	0.75	0.49	1.01	<0.001	0.33	0.19	0.48	<0.001
Hip circumference	0.43	0.17	0.68	0.001	-0.29	-0.43	-0.14	<0.001
Systolic blood pressure	-0.04	-0.14	0.06	0.414	0.11	0.05	0.17	<0.001
Fasting glucose*	-0.36	-0.71	-0.01	0.043	0.24	0.04	0.43	0.017
2hr Glucose*	0.41	0.21	0.60	<0.001	0.30	0.19	0.40	<0.001
HbA1c	4.88	1.16	8.74	0.010	-1.97	-3.92	0.02	0.052
Fasting insulin*	-0.01	-0.07	0.06	0.872	0.05	0.02	0.09	0.004
2hr insulin*	-0.03	-0.09	0.04	0.442	-0.01	-0.04	0.03	0.673
HDL-C*	-0.65	-0.86	-0.44	<0.001	0.59	0.47	0.70	<0.001
LDL-C*	-0.09	-0.25	0.08	0.296	-0.10	-0.19	-0.01	0.031
Triglycerides*	-0.13	-0.25	-0.02	0.022	0.30	0.24	0.36	<0.001
C-reactive protein*	-	-	-	-	0.08	0.06	0.10	<0.001
gamma GT*	0.26	0.19	0.33	<0.001	-	-	-	-

* log transformed; High density lipoprotein cholesterol (HDL-C); low density lipoprotein cholesterol (LDL-C), ultra-sensitive- C-Reactive Protein (usCRP); and gamma-glutamyl transferase (gamma GT)

Table 6. Age, sex and year of study adjusted ORs (with 95% CIs) for the determinants of inflammation in all participants

	Model 1: usCRP				Model 2: gamma GT			
	Odds Ratio	95% Confidence Interval		p-value	Odds Ratio	95% Confidence Interval		p-value
		Lower	Upper			Lower	Upper	
Year of study								
2008/09	1				1			
2014/16	1.23	1.02	1.49	0.029	1.32	1.07	1.61	0.008
Gender								
Female	1				1			
Male	0.64	0.52	0.78	<0.001	1.30	1.05	1.61	0.016
Age	1.01	1.00	1.01	0.021	1.00	1.00	1.01	0.239
Tobacco use								
Non-smoker	1				1			
Smoker	1.03	0.86	1.24	0.722	1.26	1.03	1.53	0.024
Level of education								
<7 years	1				1			
>=7 years	0.83	0.68	1.01	0.056	0.76	0.62	0.94	0.011
Alcohol use								
Non-drinker	1				1			
Current drinker	0.82	0.67	1.01	0.062	2.47	1.99	3.06	<0.001
BMI status								
Normal	1				1			
Overweight	0.86	0.68	1.07	0.064	0.87	0.68	1.11	0.315
Obese	1.11	0.91	1.35	0.064	0.86	0.69	1.06	0.315
Insulin fasting								
No	1				1			
Yes	1.19	0.76	1.86	0.452	0.63	0.39	1.01	0.055
HOMA-IR								
No	1				1			
Yes	1.53	0.79	2.99	0.210	0.82	0.43	1.57	0.551
Quicki index								
No	1				1			
Yes	0.71	0.40	1.28	0.258	1.58	0.90	1 2.74	0.101
McAuley index								
No	1				1			
Yes	1.40	1.05	1.87	0.022	2.12	1.59	2.84	<0.001
Matsuda index								
No	1				1			
Yes	1.76	1.25	2.47	0.001	1.78	1.27	2.50	0.001

Homeostatic model assessment of Insulin Resistance (HOMA-IR); ultra-sensitive- C-Reactive Protein (usCRP); and gamma- glutamyl transferase (gamma GT)

Discussion

Our study found a significant decrease in the overall prevalence of IR over time, which was mainly driven by a significant decrease in women. Using HOMA-IR for example, IR prevalence decreased significantly from 24.8% in 2008/09, to 15.4% in 2014/16 in the overall study population and from 27.7% to 16.6% in women but was not significantly different in men (2008/09: 14.8% to 2014/16:11.7%). However, using the McAuley index, which is recommended for population-based studies, the decrease in IR prevalence was non-significant (35.7% to 32.8%, p=0.157), particularly when only normoglycemic participants excluding those on lipid lowering and/or hypertension medication were analysed separately. Sub-clinical inflammation marginally increased with both usCRP and gamma GT, indicating increases from 2008/09 to 2014/16. In a multivariable analysis adjusted for year of study, age and gender, prominent factors associated with increased IR or sub- clinical inflammation were abdominal obesity, glycated haemoglobin and fasting insulin levels. IR and inflammation are unequivocally associated with the development of type 2 diabetes and CVDs; however, it has also been established that IR even in subjects without type 2 diabetes is connected to high mortality rates, mainly through coronary heart diseases (18). Estimates from the International Diabetes Federation have shown that there is a major shift occurring worldwide with regards to type 2 diabetes and CVDs, with predictions of over 100% increases in Africa (19). In our study, the prevalence of IR ranged from 24.8% to 15.4% using HOMA-IR cut-off of 3.1 between 2008/2009 and 2014/2016. Although our study findings suggest a decrease in IR between the two time periods, these results need to be interpreted with caution. Firstly, the mean age of participants in these two cohorts were significantly different with 2014/2016 over represented by younger participants; secondly, when using the McAuley index, which is recommended for population-based studies, IR non-significantly decreased from 35.7% in 2008/2009 to 32.8% in 2014/2016; and lastly, subclinical inflammation increased between the two periods suggesting an increasing risk of CVD. With regards to comparing the prevalence of IR in our study population with the literature, our findings are somewhat similar to a report from Denmark which reported a prevalence of 17% using a HOMA-IR cut-off of 2.5 (20). However, our findings contrast with a South African study which reported a prevalence of 55.5% using a cut-off of 2.6 (21). These varying prevalence's could be related to the non-census on the cut-off criteria for the definition of IR. According to the

WHO (22), the ≥75th percentile value is recommended for the definition of IR; however, various cut-offs are reported in literature.

usCRP is a well-established inflammatory biomarker for predicting future risk of CVD events (22, 23). Thus, measurement of usCRP has been used in the identification of high-risk individuals who may benefit from therapeutic interventions (23). Another biomarker that has attracted interest is gamma GT activity which is widely accepted for the diagnosis of liver and obstructive biliary diseases as well as excessive alcohol consumption. Evidence from epidemiological studies has shown that gamma GT activity is associated with type 2 diabetes, metabolic syndrome, atherosclerosis and CVDs (24). In a meta-analysis involving 67 905 individuals, gamma GT activity was significantly associated with the metabolic syndrome in individuals in the highest versus lowest thirds of baseline gamma GT activity (25). Indeed, in our study, dyslipidaemia parameters (triglycerides, LDL-C and HDL-C), glucose homeostasis (HbA1c, fasting glucose and insulin), SBP, age and gender (men) were associated with increased gamma GT levels. Similarly, other epidemiological studies have reported these findings (26, 27). For example, a study of 1680 Han Chinese patients found that gamma GT was positively correlated with waist circumference, fasting plasma glucose, triglycerides, blood pressure levels and the metabolic syndrome (27). Several mechanisms underlying the association between gamma GT activity and the metabolic syndrome or its components have been suggested. One example is the association between gamma GT activity and IR whereby IR is viewed as a bridging mechanism linking gamma GT with CVD and coronary heart diseases (28). Indeed, in our study we have demonstrated that both usCRP and gamma GT had an almost 2.5-fold higher odds for IR.

The strength of this study is that the two surveys were conducted in the population from the same geographical area, using similar procedures. However, the study has the following limitations: *(i)* it consisted of only two cross-sectional surveys, which prevents reliable assessment of time- trends; *(ii)* the second study was not a follow-up but rather another cross-sectional study assessing new participants from the area; *(iii)* there was a low proportion of men in both studies (24%), a common problem in SA research (29); *(iv)* Cotinine levels were used to distinguish smokers from non-smokers;

thus, past smokers and those using nicotine gum could not be identified objectively, which is important as previous studies reported that past smokers and those using nicotine gum had increased levels of IR and inflammatory biomarkers (30); *(v)* Although numerous IR surrogates were used, only the McAuley index is recommended for population-based studies.

Conclusion

Our findings have shown increases in subclinical inflammation over a 7-year period and this was associated with IR and the metabolic syndrome components, both of which are strong predictors of CVDs. Given the estimated increases in the incidence of T2DM and CVD in South Africa and Africa in general, monitoring of these biomarkers involved in the pathophysiological development of CVD is important. It can provide early information on the trajectory of the CVD burden in the population, even before substantial changes are observed in population levels of CVD risk factors.

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Chapter 7: Conclusions and Perspectives

This chapter highlights the novel findings of the previous chapters in line with the aim and objectives of this thesis. Public health implications, recommendations for future research, and the strengths and limitations of the study are also discussed.

7.1 Summary of novel insights and public health implications

This thesis comprises a literature review on CVDs and their risk factors, the methodology and three publications. This study is the first to assess the temporal changes in cardiometabolic risk profiles in the Mixed-ancestry population in Cape Town, South Africa. The publications describe the temporal changes between 2008/09 and 2014/16 in (1) absolute BP levels and hypertension prevalence; (2) distribution and change in obesity or body size phenotypes; and (3) the prevalence of IR, inflammatory biomarkers, and their determinants, which are associated with the development of type 2 diabetes and CVDs.

The hypertension paper was the first to examine the temporal changes in absolute BP levels and hypertension prevalence over two time periods seven years apart in a South African Mixed-ancestry population (Chapter 4). Our study highlighted a substantial increase in the overall hypertension prevalence from 30.7% (2008/09) to 45.0% (2014/16). The rise in prevalence was attributed primarily to the increase in newly-detected hypertension from 8.3% in 2008/09 to 22.9% in 2014/16. This highlights the inadequacies in the current health system to optimally detect hypertension in this population.

Furthermore, there was a shift in the peak prevalence of hypertension over time from older ages (≥ 70 years) to younger individuals aged 40-49 years. This is particularly important because hypertension in younger working age individuals vs. retired adults can potentially have serious repercussions on household finances, sustainable development and the country's economy. Indeed, complications of uncontrolled hypertension such as stroke, heart attacks, and chronic kidney failure, among others are debilitating and frequently render the individual unable to work. This is further

linked to absenteeism from work and the loss of skilled labour, thereby resulting in the loss of productivity which directly affects the country's gross domestic product (GDP).

In the obesity phenotype paper, presented in Chapter 5, we investigated the distribution and change in obesity or body size phenotypes between 2008/09 and 2014/16 in an urban South African population. Our study revealed that adiposity decreased over the two time periods (overweight: 27.4% vs 23.6%; and obese: 45.3% vs 42.2%). However, the patterns of distribution of obesity phenotypes were similar across the two-time points. A similar proportion of normal weight participants were metabolically abnormal (defined as 2 or more metabolic abnormalities present): 9.4% in 2008/09 and 8.0% in 2014/16. Additionally, the proportion of obese participants who were metabolically healthy (0 or 1 metabolic abnormality present) was similar: 13.5% in 2008/09 and 14.0% in 2014/16. This highlights the need for improving risk stratification for obesity phenotypes, which could enable better screening and cost-effective detection of those at higher risk of developing cardiometabolic diseases, particularly amongst the younger population.

The third paper (Chapter 6) investigated the temporal changes in the prevalence of IR, inflammatory biomarkers and their determinants between 2008/09 and 2014/16 in the Mixed-ancestry population in Cape Town. Sub-clinical inflammation defined by us-CRP and gamma GT marginally increased over the seven-year period. This finding is important because us-CRP is an established inflammatory biomarker for predicting future risk of CVD events, while gamma GT is associated with type 2 diabetes, metabolic syndrome, atherosclerosis and CVDs. This study demonstrated a 2.5-fold increase in the likelihood of developing IR with elevated us-CRP and gamma GT levels. Despite the decrease in the prevalence of IR over the study period, the rising levels of these inflammatory biomarkers suggest that IR may increase in the future in this population thereby increasing the prevalence of type 2 diabetes and CVD.

7.2 Recommendations and future research

7.2.1 Surveillance

In our study, we found an increasing prevalence of hypertension, over a 7-year period, particularly those with undetected hypertension, and a shift in peak hypertension prevalence to younger ages. This highlights the importance of regular surveillance to observe the changing patterns of hypertension, BP levels and other cardiometabolic diseases. Such surveillance studies enable a better understanding of population health and shine a spotlight on the gaps in the current healthcare system. This allows for appropriate policies and strategies to be developed and for resources to be optimally directed to target these health challenges.

Local or regional surveillance studies have some advantages over national surveillances such as the SADHS, which is regularly conducted in South Africa [1–3]. The former, because of smaller sample sizes compared to national surveys, allow for in-depth investigation into various cardiometabolic diseases. These include the ability for detailed cardiometabolic disease assessments that require biochemical analyses, such as OGTT. The high cost of such testing and the requirement of specialised healthcare workers (phlebotomists) render these investigations prohibitively expensive in national studies.

In the current context, future surveillance studies in the local population are required to observe the changes in cardiometabolic disease trends in relation to changes in health intervention strategies and policies implemented by local or national governments.

7.2.2 Screening for hypertension

7.2.2.1 NCD policy and screening

The high and increasing prevalence of undetected hypertension observed in this Mixed-ancestry population over two-time points 7 years apart, underscores the need for regular BP screening. Actively screening for raised BP in those without known hypertension, is currently not among the primary focus of NCD policies in South Africa [4,5] and likely contributed to this study findings. Current NCD policies are focused on disease treatment rather than prevention.

Clear guidelines are available for the screening of hypertension of all adult patients seeking care at primary health care (PHC) facilities [6], but this has likely not been successfully implemented [7]. A recent study has demonstrated that there are long waiting times for BP to be checked, BP machines are constantly breaking due to heavy use, and those with high BP levels are sometimes ignored [7]. Although this study highlighted the challenges in implementing hypertension screening in PHC clinics, there are currently no government initiatives to address these problems. There is a need to develop an audit and monitoring system to ensure that BP screening policies and guidelines are correctly implemented and, importantly, to address the challenges described above.

7.2.2.2 Harness the potential HIV Testing Services (HTS) and COVID testing and vaccination

Additionally, novel inexpensive initiatives are required to improve the screening and detection of hypertension. Considering that effective testing programmes are available for infectious disease such as HIV and TB [8–10], these processes could be harnessed to improve screening for hypertension and other NCDs. Testing of HIV occurs at the PHC facilities, but has an allocated section within the facilities [10]. The effectiveness of this strategy is reflected in that over 13 million people in South Africa have been screened for HIV via the HIV Counselling and Testing campaign [9]. A similar approach may be implemented for BP screening; this potentially presents a good opportunity to leverage for simultaneous BP screening when testing for HIV infection. Nevertheless, this will likely require streamlining of screening processes, additional staff, the training of staff, allocation of resources, and regular monitoring and evaluation of an integrated screening programme.

The HIV campaign increased testing for HIV by using social mobilisation activities to raise awareness of the availability of testing at local facilities [9], and a similar campaign may be included for hypertension. These social mobilisation strategies, which are run by community health care workers (CHWs), include educating people on the benefits of testing by either going door to door allowing people to engage with CHWs more easily, or by targeting large community groups at places of worship, youth organisations etc. Such campaigns can easily incorporate increasing awareness and

education for hypertension. Considering the success of the HIV Counselling and Testing campaign, screening for hypertension could also be included as part of this campaign, given that these tests are non-invasive and only require an inexpensive BP apparatus.

The current COVID-19 testing and vaccination centres present another novel opportunity for hypertension education and screening. At these sites, trained CHWs may use this opportunity to engage the public and perform hypertension education and screening. However, these activities will need careful planning and implementation so as not to interfere with COVID-19 related activities.

These initiatives described above are low-cost requiring minimal investment but have the potential for substantial impact on healthcare. They require training of lower-level healthcare workers i.e., CHWs, functioning inexpensive BP monitors, streamlined and efficient processes, and regular monitoring and evaluation to ensure their effectiveness.

7.2.2.3 Pop-up screenings

Further initiatives may include advantageous use of community gatherings such as religious gatherings at churches, and queues at governmental departments where there are long waiting times, such as the Department of Home Affairs or the South African Social Security Agency. Here, there could be pop-up BP screening and education stations run by trained CHWs.

7.2.3 Assessment of adiposity for CVD risk

This study highlighted the weakness in using BMI as the key determinant to identify individuals at high risk for cardiometabolic diseases. Our study demonstrated high a proportion of normal weight individuals with cardiometabolic dysfunction while a substantial number of obese individuals was considered metabolically healthy. A better alternative to BMI is likely to be WC. This measures central/abdominal obesity which has a stronger link to cardiometabolic diseases and likely better able to identify individuals with these conditions [11,12].

Nevertheless, these are all proxy measures for adiposity, and should not be the main determinant used i.e., normal weight should not be as an exclusion criterion when screening for cardiometabolic diseases. Other non-invasive and inexpensive measures such as age, family history and BP readings should be used in conjunction with adiposity measures to identify individuals at high risk for cardiometabolic diseases such as diabetes and dyslipidaemia. An African specific scoring system has been developed to identify individuals as high risk for cardiometabolic diseases, specifically diabetes [13,14]. This will likely better identify those individuals who should be screened for diabetes leading to greater efficiency and cost-effectiveness in identifying individuals at high risk for diabetes.

7.2.4 Assessment of sub-clinical inflammation

Sub-clinical inflammation biomarkers in our study increased over time in participants without known diabetes. This demonstrates that healthy individuals are acquiring increases in inflammatory markers which could be an indicator of future increased development of IR and dysglycaemia as described by Herder et al. [15]. Furthermore, sub-clinical inflammation has been reported to increase the risk for adverse cardiovascular outcomes such as IHD and stroke [16,17]. Further research is required to evaluate the utility of testing for these inflammatory biomarkers as part of routine care and examine their ability to prognosticate outcomes [15]. This may identify individuals at higher risk of adverse cardiovascular outcomes who may benefit from intensive therapeutic interventions.

7.2.5 Future studies

Following the implementation of policies and strategies to improve health service delivery, additional surveys need to be conducted to assess their effectiveness and measure improvements such as the detection of hypertension. Studies to validate the effectiveness of the scoring system which was developed for Africans with high risk of cardiometabolic diseases could be conducted [13,14]. It should be noted that currently in Cape Town, the South African Diabetes Prevention Programme (SA-DPP) study [18] has used the scoring system developed by Mayige [13] to identify individuals with undiagnosed diabetes in the Black and Mixed-ancestry communities.

7.3 Strengths and limitations of the study

The study comprised two large cohorts of >900 participants, each of which were directly comparable because of the application of the same questionnaire in the same population. Additionally, similar blood assessments, such as OGTTs, lipid profiles, sub-clinical inflammation, etc, were conducted in both surveys allowing for easier comparison over the two periods.

The study limitations include the lack of generalizability to other populations in South Africa. The reason for this is that lifestyle and behavioural factors differ substantially in urban and rural centres, and across ethnic groups, including Mixed-ancestry populations living in other South African provinces. Additionally, the use of cross-sectional studies with different participants did not allow for the determination of incidence of (1) hypertension, (2) IR and sub-clinical inflammation, and (3) changes in obesity phenotype in this community. Furthermore, only about one-quarter of participants were males, which is common in South African epidemiological studies [19]. The likelihood of high female participation compared to males could be due to males having an aversion to having blood drawn or that they are absent from home due to work commitments. Also, genetics, ethnic differences, physical activity and dietary information were not collected in this study. This would likely have provided greater insights into the factors contributing to the changes in hypertension, obesity, IR and sub-clinical inflammation in this population. Furthermore, inflammatory cytokines were not evaluated in this study; these may have provided insight into the role of sub-clinical inflammation and its association with hypertension [20,21]. For example, this would have allowed for the exploration of vascular inflammation as a contributor in the development of hypertension [20].

7.4 References

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Appendix

Appendix 1: Student ethics approval -UCT

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 June 2016

HREC REF: 442/2016

Prof AP Kengine
Department of Medicine
NCDRV
SA MRC ROB 19070
Tygerberg

Dear Prof Kengine

PROJECT TITLE: TEMPORAL CHANGES IN THE CARDIOMETABOLIC DISEASE RISK PROFILE OF THE BELLVILLE SOUTH MIXED ANCESTRY COMMUNITY BETWEEN 2008/09 AND 2014/16 (PhD-candidate- Ms S Davids)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th June 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Saarah Davids will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 442/2016

Appendix 2: The Bellville South (2008/09) ethics approval - CPUT

Cape Peninsula University of Technology

14 January 2008
Ref: CPUT/HW-REC 2008/002

P.O. Box 1906 • Bellville 7535 South Africa •Tel: +27 21 442 6162 • Fax +27 21 447 2953
Symphony Road Bellville 7535

OFFICE OF THE CHAIRPERSON:
HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE (HW-REC)

At a meeting of the Health and Applied Sciences-REC on the 6 December 2007 ethics approval was granted to David J Solta, for research activities related to the M Tech [redacted] at the Cape Peninsula University of Technology, pending amendments which are now fulfilled.

TITLE:
The prevalence of impaired glucose tolerance and diabetes amongst the middle aged population residing in the Bellville South area of Cape Town.

Comment:
Research activities are restricted to those detailed in the ethics application submitted subsequent to revisions requested on 6 December 2007. Ethics approval must be applied for anew should further studies, utilizing the blood samples from participants in this study, be embarked on.

This ethics approval is granted to 31 December 2008. An extension must be applied for should the study continue beyond this date.

Dr PENELOPE ENGEL-HILLS
CHAIRPERSON: HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE

e-mail: engelhillsp@cput.ac.za

Appendix 3: The VMH study (2014/16) ethics approval - CPUT

Cape Peninsula
University of Technology

HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE (HW-REC)
Registration Number NHREC: REC- 230408-014

P.O. Box 1906 • Bellville 7535 South Africa
Symphony Road Bellville 7535
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15 April 2014
CPUT/HW-REC 2014/H01

Faculty of Health and Wellness Sciences – Biomedical Sciences Department

Dear Prof Matsha

YOUR APPLICATION TO THE HW-REC FOR ETHICAL CLEARANCE

Approval was granted by the Health and Wellness Sciences-REC on 14 April 2014 to Prof Tandi Matsha for ethical clearance. This approval is for research activities related to staff research in the Department of Biomedical Sciences at this Institution.

TITLE: Progressive research on risk factors of type 2 diabetes and cardiovascular diseases in South Africa.

Co-investigators:

1. Prof Rajiv Timothy Erasmums, Pathology Department - Stellenbosch University.
2. Prof Andre Pascal Kengne, Chronic Diseases of Lifestyle Department – MRC.
3. Mr Mogamat Shafick Hassan, Nursing and Radiography Department – CPUT.

Project Manager:
1. Dr Gloudina Hon – CPUT.

Comment:
Approval will not extend beyond 15 April 2015. An extension should be applied for 6 weeks before this expiry date should data collection and use/analysis of data, information and/or samples for this study continue beyond this date.

The investigator(s) should understand the conditions under which they are authorized to carry out this study and they should be compliant to these conditions. **It is required that the investigator(s) complete an annual progress report that should be submitted to the HW-REC in December of that particular year, for the HW-REC to be kept informed of the progress and of any problems you may encounter.**

Kind Regards

CHAIRPERSON – ETHICS RESEARCH COMMITTEE
FACULTY OF HEALTH AND WELLNESS SCIENCES

Appendix 4: The VMH study (2014/16) ethics approval The VMH study (2014/16) ethics approval - US

UNIVERSITEIT•STELLENBOSCH•UNIVERSITY
jou kennisvennoot • your knowledge partner

Approval Notice
Response to Modifications- (New Application)

09-Apr-2014
Matsha, T

Ethics Reference #: N14/01/003
Title: Progressive research on risk factors of type 2 diabetes and cardiovascular diseases in South Africa.

Dear Prof T Matsha,

The **Response to Modifications -** ***(New Application)*** received on **20-Mar-2014**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **09-Apr-2014** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: **09-Apr-2014 -09-Apr-2015**

Please remember to use your **protocol number (N14/01/003)** on any documents or correspondence with the HREC concerning your research protocol.

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

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/hds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 0219389207.

Included Documents:
Protocol & Budget
Application
Participant Information&Consent Form
Proposal_Matsha.pdf