PREVENTING CARDIOVASCULAR DISEASE IN RURAL SOUTH AFRICA

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Declaration

I, Mandy Maredza, declare that this thesis is my original work. Contributions from other people have been duly acknowledged. It is being submitted for the degree of Doctor of Philosophy in Public Health in the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other University.

Name: Mandy Maredza

Signature: 

Date: 18 October 2018

Dedication

This work is dedicated to my family. To my husband Douglas Mubayiwa, for your friendship, patience, and undying support throughout the PhD period, and for your endurance during prolonged lonely moments. Thank you for experiencing the turbulent emotions with me and encouraging me to never give up. To my daughter Makanaka who was born during this period; you fuelled my determination to complete the work so I could spend quality time with you. To my late parents, Alexio and Rosemary Maredza, I am grateful to you both for teaching me the importance of hard work and perseverance. To my brothers and sisters: Priscilla, Caroline, Tendai, Marshel, Colleen and Tatenda for continuing to believe in me, praying for me, and giving me the solitary space I needed to get the work done. To the rest of my extended family, too numerous to name, for your love and support, I dedicate it to you all.

Most of all to my God almighty and Lord Jesus Christ for your grace and unmerited favour, and for giving me the strength to go on.

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Abstract

Background: The epidemiological, nutritional and demographic transitions occurring in developing countries, have resulted in an unprecedented rise in non-communicable diseases, in particular, cardiovascular disease (CVD). Consequently, CVD are contributing significantly to disease burden in populations where infectious diseases and maternal and perinatal conditions still persist. Rural areas which are least equipped to deal with this burden are no exception; recent evidence points towards a similar trend of increased CVD, particularly stroke. Understanding the disease burden and cost-effective strategies for prevention is therefore of critical importance. Such information should assist policymakers to justify policy decisions on interventions to prevent cardiovascular disease.

Aims: To better understand the epidemiological profile and pattern of stroke and its risk factors in rural South Africa so as to select interventions that are effectively targeted, are cost-effective, and have the potential to reduce the cardiovascular disease burden in key populations.

Methods: The study utilised two methodological approaches to address the research aims. First, existing validated methods and epidemiological tools were used. The Global Burden of Disease Study approach was the framework for analysing years lost due to premature mortality (YLL), years lived with disability (YLD) and disability adjusted life years (DALYs). The mathematical tool - Dismod II - was used to estimate the disease incidence. The World Health Organization's comparative risk assessment framework was used to estimate burden attributable to metabolic risk factors; namely high blood pressure, raised blood glucose and excess body mass index. All data for the analyses were derived from the Agincourt health and socio-demographic surveillance system, which covers a population of over 100,000 individuals in rural North-east, South Africa, adjacent to Southern Mozambique. Extrapolation to 'mostly rural' South Africa was based on the conservative assumption that all municipalities that are considered 'mostly rural' share an epidemiological profile similar to that of Agincourt sub-district; thus only population figures (by age and sex) adjusted the incidence and DALYs. Second, an economic model to assess the cost-effectiveness of CVD prevention interventions was

developed, customised for the Agincourt sub-district population. This is a Markov model which simulates disease progression in a cohort of people, starting from a healthy (disease-free) state until death or 100 years of age by accounting for changing risk factor profiles in each age-sex cohort. The application of the model is illustrated by estimating the cost-effectiveness of alternative pharmaceutical interventions for CVD prevention. Interventions are targeted to groups with varying degrees of absolute CVD risk over the next 10 years of '<10%' (low risk), '≥10% & <20%' (medium risk) and '≥20%' (high risk). A fourth target group was individuals with untreated stage 2 hypertension.

Results: Baseline burden of CVD was substantial: crude stroke incidence rate was 244 per 100,000 person years in Agincourt sub-district. An estimated 33, 500 strokes occurred in 2011 in "predominantly" rural municipalities of South Africa, a population of some 13,000,000 people. Crude stroke mortality was 114 per 100,000 person-years in 2007–11 in Agincourt sub-district whilst 1,070 DALYs (CI 750 - 1680) were lost due to stroke. Preventable risk factors were responsible for a significant proportion of the stroke burden: Among males, 40% of the stroke burden was attributable to high blood pressure. Similarly, 38% of the stroke burden in females was attributable to high blood pressure. There was marked variation in stroke burden attributable to excess body mass index (BMI) by gender. Approximately 11.4% of the stroke burden in males was attributable to excess BMI compared to 22.5% in females. Despite some uncertainty, it appears that diabetes plays a relatively small contributory role to the overall CVD burden. Furthermore, it has been assumed that cholesterol does not play an important role in this setting based on previously published data.

By combining actual health care utilization estimates from the Agincourt sub-district with incidence and prevalence data, we estimated that direct costs of stroke treatment comprised 1-3% of the sub-district expenditure in 2013. Average cost-effectiveness ratios (ACERs) for all pharmacotherapies, across all target groups, fell in the range of US$160-500 per DALY averted. Incremental cost-effectiveness ratios (ICERs) for the optimal interventions (i.e. after removal of costlier yet less effective 'dominated' interventions) were US$156 (combination of β-blocker and diuretic) and US$373 (polypill – a single tablet containing a statin and three antihypertensive agents) per DALY averted for the high-risk group. ICERs indicate the additional cost needed to avert an additional DALY as successively less cost-effective strategies are

adopted. The same interventions were cost-effective for the medium-risk group and patients with stage 2 hypertension. The optimal treatment pathway for low risk individuals (10-year risk of <10%) included low-dose diuretic with an ICER of US$228; combination of β-blocker and diuretic (ICER: US$454 per DALY averted); polypill (ICER: US$683 per DALY averted) and ACE-I/diuretic combination which yielded an ICER of US$2,752 per DALY averted. ICERs were sensitive to discount rates, doubling the costs of drugs and halving the drug treatment effects. The budget impact analysis indicated that giving the optimal interventions of β-blocker /Diuretic and polypill to at least 90% of individuals with high CVD risk in the entire rural South Africa would cost the government, per year, approximately US$4.06 million, US$6.28 million respectively.

Conclusions: The burden of stroke in Agincourt HDSS as estimated in this study is considerable and is currently propelled by, amongst other risk factors, the high prevalence of hypertension and obesity. If we assume similar prevalence and distribution of risk factors for the other 69 rural municipal areas, then the effect on rural South Africa is equally substantial. By applying the custom-built economic model, we show that several pharmaceutical options are potentially cost-effective and affordable in reducing CVD. Furthermore, the cost-effectiveness modelling showed that a total risk factor approach is more cost-effective than a single risk factor approach. The model, which is an output of this thesis can be applied across other health and socio-demographic surveillance sites to build an augmented dataset that will assist in better profiling of CVD prevention across other sub-Saharan African sites.

Keywords: Cardiovascular disease, stroke, rural, Agincourt health and socio-demographic surveillance system, South Africa, cost-effective, incidence, mortality, DALYs

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List of Abbreviations

ACE-I	ACE-Inhibitor
ACER	Average cost-effectiveness ratio
AHRI	Africa Health Research Institute
AIDS	Acquired immune deficiency syndrome
ARVs	Anti-retrovirals
BP	Blood pressure
CER	Cost-effectiveness ratio
CHE	Catastrophic health expenditure
CVD	Cardiovascular disease
DALY	Disability adjusted life-year
DBP	Diastolic blood pressure
ECEA	Extended cost-effectiveness analysis
GBD	Global burden of disease
GDP	Gross Domestic product
HAART	Highly active antiretroviral therapy
HDSS	Health and socio-demographic surveillance system
HICs	High income countries
ICER	Incremental cost-effectiveness ratio
IHD	Ischaemic heart disease
LiST	Lives Saved Tool
LMICs	Low and middle-income countries
NCD	Non-communicable diseases
RCT	Randomised control trial
SBP	Systolic blood pressure
SA	South Africa
SSA	Sub-Saharan Africa
WHO CHOICE	World Health Organisation Choosing Interventions that are Cost-effective
YLD	Years lived with disability
YLL	Years of life lost due to premature mortality

Prologue

Looking back at my PhD journey I realize that the fateful day I received the phone call that my father had suffered a stroke marked a turning point for me; that point when I understood the true value of work that I had just embarked on.
I had registered for my PhD barely 5 months earlier. For those few months, my journey was a “normal” one: I was convinced that there were gaps in literature that my study could fill; I would acquire much-needed skills through the process and someday I would be awarded the much coveted qualification. What I believe I lacked in those months was the conviction that my work was not just a missing part of the literature but a much needed if not urgent piece of work. With hindsight, I believe now that it took a painful experience of seeing my father suffer though a stroke to realize the importance of the work I was doing.

I would be lying if I said that learning my dad had suffered a stroke immediately gave me the drive to carry out my study. Like any other human being I went through the motions. I was angry at God for letting me embark on a study that focused on stroke prevention, only for my father to fall prey to this before I was even in a position to help him. I had to deal with the emotional and financial consequences of dealing with a stroke in the family. For at least a year it was extremely painful for me to focus on the work because everything about the project had become a painful reminder of my then-present reality. I could go as far as saying I was living my studies in my personal life.

My dad - may his soul rest in peace - passed away on the 28th of December 2014 after a recurrent stroke. Everything inside of me told me I had failed because my work could not save his life. However, as I witnessed one neighbour after another fall victim to stroke I resolved that my painful experience needs to be a reason to help find solutions to preventing this impending epidemic. It is my hope that this thesis is a small contribution towards that endeavour.

I thought often, during the writing of my thesis, of my father whose life was prematurely cut short because of stroke. Though this work will never be able to save him, I hope that it can save another person’s loved one. Thus it is to my dad and the unknown and unnamed families of stroke victims that I also dedicate this work.

Mandy Maredza, 2016

"*The gravest health threats facing low- and middle-income countries are not the plagues, parasites, and blights that dominate the news cycle and international relief efforts. They are the everyday diseases the international community understands and could address, but fails to take action against."*
(Council on Foreign Relations, 2014)

Chapter 1 Introduction

There is increasing recognition that non-communicable diseases (NCDs), particularly cardiovascular diseases (CVD), are a critical global health challenge. Cardiovascular diseases are already the leading cause of death globally [1, 2]. In 2015, there were approximately 55.8 million deaths worldwide; of which 17.9 million (or 32%) were attributable to CVD [2]. In low and middle-income countries (LMICs) that are still fighting HIV/AIDS, CVD now occur at rates twice that of traditional communicable diseases [3]. The health challenge appears to be compounded by the concentration of CVD at younger ages in developing countries. In 2013, the mean age at death attributable to CVD in Sub-Saharan Africa (SSA) was the youngest in the world at 64.9 years, reflecting in part the higher all-cause mortality and shorter-life spans in the region [4]. The proportion of CVD deaths amongst the economically active age group (35-64 years) is also much higher in South Africa (41%) compared to many other middle income and high income countries such as India (35%), Brazil (28%), United States (12%) and Portugal (9%) [5].

Existing risk factors suggest that CVD will become a major health challenge for developing countries, in both urban and rural areas. Despite the dearth of good quality data and marked variation between and within studies, the increasing hypertension prevalence appears to be the most important risk factor contributing towards the increased CVD burden. It is estimated that hypertension affects 10-60% of people in developing countries but this varies significantly across countries [6]. In South Africa, more than 50% of the adult population (>35 years old) have hypertension [6, 7] and these rates approximate those reported in high income settings

where CVD have reached endemic proportions [2]. Even in rural areas, hypertension is a challenge with estimates suggesting that 50% of the adult population have hypertension [8]. The growing incidence of obesity in many sub-Saharan African countries is likely to exacerbate the CVD challenge. Associations between excess body weight and blood pressure have been observed in diverse populations in both adults and children [9, 10]. Whilst the exact pathophysiologic links between body weight and blood pressure remain an area of research, results indicate that in most populations, blood pressure increases linearly with increasing relative body weight [11]. Recent pooled estimates from studies across 4 geographical regions (Africa, East Asia, South America and South Asia) indicate that with each standard deviation increase in BMI or waist circumference, the probability of hypertension in men and women is 1.65 times and 1.34 times higher respectively [12]. Nonetheless, there are limitations to this study that warrant cautious interpretation of findings. Notably, Africa as a region, was represented by a single study of 1,200 participants from Cape Town, South Africa. Notwithstanding the limitations of the latter study, the combined evidence in literature suggests that the rising incidence of obesity in SSA may further challenge CVD prevention efforts. In South Africa, for example, combined overweight and obesity rates (BMI > 25 kg m^{-2}) increased from 51% in 2008 to 60% in 2012 [13]. Though the obesity transition is less pronounced in rural areas, prevalence rates are as high as 30% in women compared to 5% in men [14].

Other risk factors apart from overweight and hypertension are also significant in developing countries. Over 14 million people with diabetes mellitus were in sub-Saharan Africa in 2015 [15]; this number is projected to more than double by the year 2040. There is paucity of data on physical activity. However, the available estimates indicate that the proportion of people classified as physically active (at least 150 minutes of moderate activity per week) varies widely across countries; from 46.8% (Mali) to 96.0% (Mozambique) [16]. Smoking rates are relatively low but not insignificant and range between 10% - 35% amongst males in Africa [17]. Several factors may contribute to this high prevalence of risk factors. At a macro, structural level, they include urbanisation and globalisation which have homogenised cultures towards 'leisurely' unhealthy lifestyles [18]. This is contributing to a demographic and epidemiological transition with a corresponding increase in rates of chronic diseases that affect older people [19].

Despite data limitations, it is apparent that CVD imposes important social and economic costs. The death of an adult family member can be devastating to the household. When there is an adult death—most often from CVD—a child of less than 2 years has a 12-fold higher probability of death in India [20]. Similar findings have been reported for a rural South African community [21]. At the household level, CVD and other non-communicable diseases contribute to poverty due to catastrophic health spending and high out-of-pocket expenditure. For instance, an extended cost-effectiveness analysis of the impact of a salt reduction policy in South Africa, estimated that this policy would prevent 1,680 cases of CVD annually [22]. That would consequently avert 2,400 cases of catastrophic health expenditures or 2,000 cases of poverty yearly [22]. Similar findings are reported for India where an estimated 1.4 million to 2 million people experienced catastrophic spending in 2004; and 600,000 to 800,000 people were impoverished by the costs of caring for cardiovascular disease and cancer [23, 24]. Furthermore, more than half of the total costs of stroke care in populations studied in Africa can be attributed to income losses of the patient and caregiver [25]. Combined, these results indicate that cardiovascular disease is also a development issue in low and middle-income countries.

At a macro-economic level, CVD place a heavy burden on the economies of low- and middle-income countries. This is because in those countries, CVD occur at much younger, economically active age groups. People with CVD often require time off work to recover from illness and this reduces work-related productivity for employers, and economic output for the wider economy [26]. Whilst reliable estimates of actual economic losses are lacking, projections for the period 2005-2015 indicate that, productivity losses in China and India due to heart disease, strokes and diabetes were 558 billion and 237 billion international dollars respectively [27].

There are implications of these findings that are relevant to decision-makers in the health and financial sector. Whilst the social implications of CVD and underlying risk factors cut across several sectors, the responses and costs are mostly borne by the health sector. Because governments in developing countries are already fiscally constrained in how much more they can provide to the health system, the long term solution for preventing CVD requires embracing prevention as the first step. However, it is important to understand which strategies should be implemented as prior experience in many settings suggest that changing behaviours through

modifying lifestyle risk factors could be costly, and may be ineffective as behaviour change (at individual or population-level) may be difficult to achieve [28]. Consideration should be given towards interventions that are cost-effective and present “win-win” solutions for multiple sectors. For example, legislative interventions to reduce tobacco, salt [22, 29] and sugar-sweetened beverages [30] have a double benefit. The evidence suggests that they reduce unhealthy behaviours amongst the population, a major risk factor for CVD, whilst simultaneously generating extra revenues for Government [31]. Though one objection to a tax on sugar-sweetened beverages is that it would be regressive[1], widespread experiences from the tobacco legislation policies has indicated that the poor who tend to suffer from a disproportionate burden of tobacco-related disease are equally sensitive to price changes [32, 33]. Contrasting evidence suggests that such policies could in fact be pro-equity and reduce further impoverishment amongst the poor [22].

Governments need to act now to weigh evidence and decide on the appropriate CVD prevention response. Deciding on the options that are cost-effective for their particular settings and circumstances remains a challenge. Identifying appropriate policies for CVD prevention relies partly on economic evaluations which are in turn dependent on accurate epidemiological data and estimates of resource use. The underlying objective of economic evaluations is to assist policy makers choose the best buys whilst making the most of scarce health budgets. Health economic evidence has generally been lacking in Africa, but is becoming more available as generalized economic evaluation tools are developed by international organizations [34]. The latter tools come with the caveat that context-dependent effects are rarely captured in the analysis and a ‘one-size fits all’ model of costs and effects of interventions is generally assumed for a region or country. In reality, no single model has sufficient breadth to simulate disease progression in population groups across different countries due to varying epidemiological profiles coupled with contrasting social determinants. National and subnational analyses are thus essential to inform policies. As such, the critical decisions for the local decision-maker continue to be:

[1] A regressive tax is a tax that is applied uniformly to all payers regardless of income and tends to take a larger percentage of income from low-income earners compared to high-income earners.

Amongst the array of interventions proposed, which interventions should we prioritise; in which population groups or subgroups; to maximise population health benefits at a cost we can afford?

This thesis aims to address this knowledge gap by assessing the cost-effectiveness of alternative interventions for CVD prevention within marginalized or rural communities in South Africa. Stroke is used as the marker condition for CVD, as stroke rather than ischemic heart disease is the dominant manifestation of CVD in black[2] South African communities and Sub-Saharan Africa more generally [35-43].

The research is premised upon the overarching hypothesis that: '*the epidemiological profile and burden of CVD and associated risk factors is markedly different in rural areas of South Africa compared to the rest of the country. Based on this evidence, prioritized interventions will differ'*.

To permit such an extensive analysis, a mathematical model that is based upon high quality data from a rural South African population is constructed. The model combines the best available local data on disease parameters (whenever possible) and local costs. The research proposes that such locally derived, easily accessible, cost-effectiveness models permit a better and more time-sensitive understanding of the context-specific costs and impacts of new and existing interventions compared to analysis based primarily on general economic models.

The research is timely. South Africa is currently undergoing wide-ranging health system reforms to strengthen primary health care and promote integrated chronic care with the overall aim of reducing the disease burden. This transitional period is a window of opportunity to present scientific evidence on cost-effective approaches to

[2] The terms black, white and coloured indicate a statutory stratification of the South African population based on the former Population Registration Act (Act 30 of 1950). This study refers to population groups in South Africa using this classification to maintain consistency with referenced studies and with national documents. However, their use does not imply legitimacy of any racial connotations that may be associated with these terms.

CVD prevention in heterogeneous communities. Furthermore, it is an opportunity to put forward a range of analytical tools that can be adapted to undertake much broader analyses related to the spectrum of non-communicable diseases.

1.1 Thesis overview and structure

1.1.1 Integrating narrative

The integrating narrative includes five chapters. **Chapter one** is the introductory chapter which places this work into context. Further it provides a framework for the thesis, and presents the overall aims and objectives of the work. **Chapter two** comprises the background and literature review. This chapter presents the burden of CVD in SSA and South Africa in terms of the epidemiological parameters of mortality, incidence, prevalence and disability adjusted life years (DALYs). DALYs are a summary measure of population health which combine estimates of premature mortality and non-fatal health loss into a single metric. Originating from the initial Global Burden of Disease (GBD) study conducted in 1993, the DALY is becoming an increasingly popular metric for measuring, over time, the progress and challenges in improving disease burden [44]. To provide a more integrated summary, the literature is presented from the perspective of key findings on observed trends in disease burden. The review proceeds by summarising evidence on the socio-economic consequences of cardiovascular disease. A comprehensive overview of interventions that have been implemented in SSA is provided to assess the evidence-base and identify potential gaps. Evidence on economic evaluations to establish 'best-buys' for CVD prevention is also assessed including analytical approaches used to derive cost-effectiveness estimates. The review concludes by outlining country responses to CVD prevention and identifying gaps in literature that this study seeks to fill.

Chapter three synthesises the methods that were applied in the studies that constitute this thesis (study design, study population, data collection and analysis). Further information on methodology is presented in each of the appended papers 1 to 4. This chapter also describes how and why existing methods for estimating burden of disease, and attributable burden were identified, adapted and applied (papers 1-3); and how new methods and tools were developed to assess the overall cost-effectiveness of interventions (paper 4).

Chapter four synthesises the main findings of the four studies (detailed results are presented in the individual papers). The key cross-cutting themes that emerge from the work are discussed in **Chapter five,** while highlighting the significance of the findings in light of current literature, and their implications for priority setting in South Africa. This chapter also discusses the contributions of this thesis to knowledge, outlines research limitations, makes recommendations for policy and practice for South Africa and identifies key future research questions while highlighting issues of relevance to similar settings in sub-Saharan Africa. This chapter ends with an overall conclusion.

1.1.2 Original Papers

Four inter-related studies were undertaken as part of this PhD, and each was accompanied by an original research paper. The titles of the four papers are provided below and the papers are added as Appendices, A, B, C, and D.

1. Maredza M, Bertram MY, Tollman SM: **Disease burden of stroke in rural South Africa: an estimate of incidence, mortality and disability adjusted life years**. *BMC Neurology* 2015, **15**(1):1.

Student's contribution to the paper
Conceptualizing the study; data management and analysis; drafted the manuscript, revised all subsequent drafts.

2. Maredza M, Bertram MY, Gomez-Olive XF, Tollman SM: **Burden of stroke attributable to selected lifestyle risk factors in rural South Africa**. *BMC Public Health* 2016, **16**(1):143.

Student's contribution to the paper
Conceptualizing the study; data management and analysis; drafted the manuscript, revised all subsequent drafts.

3. Maredza M, Chola L: **Economic burden of stroke in a rural South African setting**. *eNeurologicalSci* 2016, **3**:26-32.

Student's contribution to the paper

Conceptualizing the study; data management and analysis; drafted the manuscript, revised all subsequent drafts.

4. Maredza M, Bertram M, Tollman S: **Cost-effectiveness of medical primary prevention strategies to reduce stroke in rural South Africa: a mathematical modelling study.** Submitted. *BMC Cost-effectiveness and Resource Allocation.*

Student's contribution to the paper

Model development; model-based data analysis; drafting the manuscript.

1.2 Aims and Objectives

1.2.1 Thesis Aims

The overall aim of this thesis is to estimate the current morbidity and mortality burden of cardiovascular disease, particularly stroke, in rural South Africa, and estimate the cost-effectiveness of alternative prevention approaches to reduce this CVD burden.

This thesis is based on the overarching hypotheses that:

1. *Knowledge of the epidemiological profile and pattern of cardiovascular disease and its risk factors in rural South Africa is a pre-requisite for selecting interventions that are effectively targeted and have the potential to reduce the disease burden, stroke in particular, in key populations*.
2. *Data from prospective studies and modelling exercises that project the future costs and burden of disease in specific populations are essential for evaluating interventions that can inform targeted and cost-effective health policies.*

1.2.2 Specific Objectives

In the Agincourt sub-district[3] of rural northeast South Africa:

1. To estimate the burden of stroke – including incidence, (premature) mortality and morbidity – over the 5-year period 2007-2011 in order to highlight the public health challenges and to quantify the economic cost of caring for people with stroke (paper 1 and 3)
2. To estimate the burden of stroke attributable to selected lifestyle risk factors and in so doing determine the proportion of the burden that could potentially be prevented by targeting prevention efforts at prominent risk factors (paper 2)

[3] The Agincourt study site falls in the health sub-district of Bushbuckridge and will be called the "Agincourt sub-district" in this thesis.

3. To evaluate the cost-effectiveness of interventions to prevent stroke events using a mathematical model custom-designed for this purpose (paper 4 – submitted).

1.3 Thesis themes

Findings are discussed according to three main themes:

- The ongoing epidemiological, demographic and social transition in rural South Africa
- Implications of a rapidly rising CVD burden
- Policy and practice: Locally generated evidence and tools to support priority-setting adapted to the local South African context

1.4 Links between papers

The mathematical model (paper 4) is the ultimate product of the thesis. The model is used as a basis for projecting both the future burden and costs of stroke in the presence and absence of intervention; and to inform how much of the burden estimated in (paper 1) can potentially be prevented through alternative strategies. Paper 1 is a foundation paper used to generate baseline estimates that provide input to further analyses. The estimates of epidemiological burden of stroke in rural SA derived in this paper act as input parameters in the mathematical model. Furthermore, the estimates of incidence derived from this paper were central to establishing the current economic burden of stroke in the Agincourt sub-district (paper 3). This provided context and acted as a useful discussion paper for this thesis. In paper 2, hypertension and excess weight were identified as major risk factors for stroke in rural South Africa and this aided selection of interventions that were assessed in the stroke intervention model. The relationships between the papers are expressed in Figure 1.

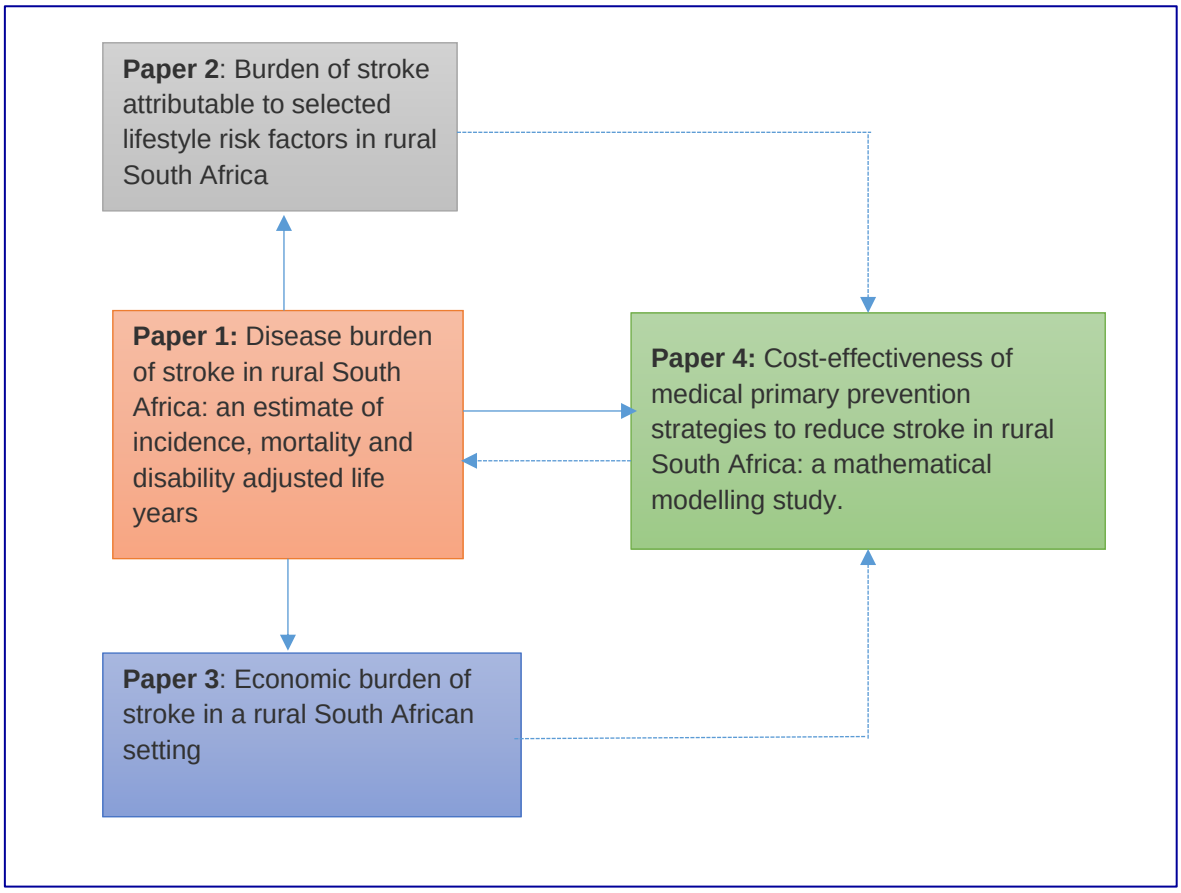


Figure 1: Papers in the thesis and their connection

1.4.1 Conceptual Framework

Figure 2 presents a conceptual framework developed for this thesis. It illustrates the influence of various determinants and risk factors on disease occurrence, the interconnectedness between these risk factors, and how they influence choice of interventions to prevent cardiovascular disease. The framework recognises that in order to effectively prevent CVD, one needs to understand that risks to health do not occur in isolation. The chain of events leading to a person developing cardiovascular disease (e.g. stroke) may be rooted in a complex chain of environmental events that began in childhood, which were subsequently shaped by broader socio-economic determinants [45]. For example, "poor nutrition during organ development, could, later in life, lead to increased risk of hypertension, obesity and insulin resistance" [46]. This risk may be exacerbated by certain societal and cultural practices (e.g. eating salty foods) which influence outcomes such as stroke via physiological processes including raised blood pressure. An appropriate range of policies can thus be

generated if a range of risks (starting from infancy) are assessed that have high impact on population health.

Understanding the socio-economic environment of the population that will potentially benefit from the intervention can assist in developing culturally appropriate interventions. For instance, an educational intervention in a low-literacy setting may need to be broadcast via radio instead of distributing printed reading material. A further consideration for successful CVD prevention is that selected interventions should be effective. Ideally the impact of each policy measure should be assessed in terms of a “common metric” that incorporates quality of life and survival. The principal metric shown in the framework and used in this thesis is the DALY (disability adjusted life year) – one DALY being equal to the loss of one *healthy* life year. The framework further recognises that individuals, society and governments operate in an environment of finite resources where costs of interventions should be assessed alongside their health benefits. Consequently, the best course of action for preventing cardiovascular disease - as illustrated in the framework - is one that achieves the best value (health benefits) for the resources spent.

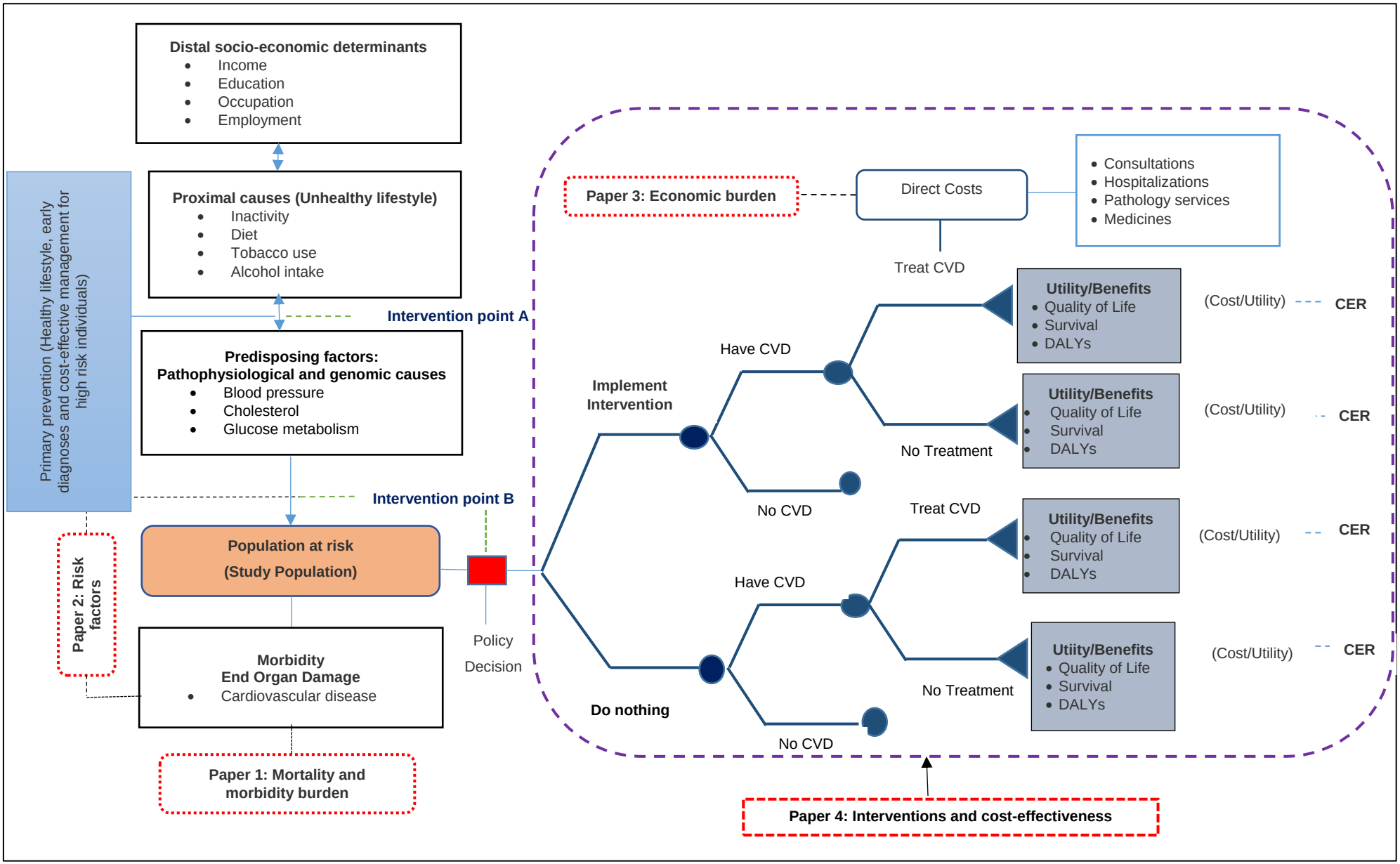

Distal socio-economic determinants
Income
Education
Occupation
Employment
Proximal causes (Unhealthy lifestyle)
Inactivity
Diet
Tobacco use
Alcohol intake
Primary prevention (Healthy lifestyle, early diagnoses and cost-effective management for high risk individuals)
Intervention point A
Predisposing factors: Pathophysiological and genomic causes
Blood pressure
Cholesterol
Glucose metabolism
Intervention point B
Paper 2: Risk factors
Population at risk (Study Population)
Policy Decision
Morbidity End Organ Damage
Cardiovascular disease
Paper 1: Mortality and morbidity burden
Paper 3: Economic burden
Direct Costs
Consultations
Hospitalizations
Pathology services
Medicines
Treat CVD
Implement Intervention
Have CVD
Utility/Benefits
Quality of Life
Survival
DALYs
(Cost/Utility)
CER
No Treatment
No CVD
Do nothing
Have CVD
Treat CVD
Utility/Benefits
Quality of Life
Survival
DALYs
(Cost/Utility)
CER
No Treatment
Utiity/Benefits
Quality of Life
Survival
DALYs
(Cost/Utility)
CER
No CVD
Paper 4: Interventions and cost-effectiveness

Figure 2: Conceptual framework of factors influencing cardiovascular disease burden, stroke in particular; and outline of a model for cardiovascular disease prevention.

The left side of the figure shows the inter-relationships between risk factors and consequences on CVD outcome, stroke in particular, as assessed in paper 1; it is an adaptation of the prevention intervention framework proposed by Steyn and Bradshaw (2001)[47]. The right side of the framework is a conceptual representation of a cardiovascular disease population-based model that assesses impact of different interventions on economic costs and health improvements using different measures to assess health benefits. The policy decision box is highlighted to indicate whether proposed interventions will be implemented and these interventions can be evaluated against the option of doing nothing or against status quo (current standard of care).

CVD = cardiovascular disease; CER = cost-effectiveness ratio

Chapter 2 Background and Literature Review

2.1 Cardiovascular Disease: Epidemiological transition and risk factors

It is a widely accepted phenomenon that the major causes of death and disability in developing countries are shifting from a predominance of infectious diseases and nutritional deficiencies, to degenerative chronic diseases such as cardiovascular disease (CVD) and diabetes. Borne out of seminal works by Omran, this shift has been termed the 'epidemiological' transition [48, 49]. To date, it provides a useful framework for understanding the changes in patterns of disease that are associated with demographic and socio-economic developments. According to this theory (and subsequent adaptations), the epidemiologic transition consists of five basic stages: (i) Stage 1 - the age of pestilence and famine; (ii) Stage 2 - the age of receding pandemics; (iii) Stage 3 - the age of degenerative and man-made diseases; (iv) Stage 4 - the age of delayed degenerative diseases and; stage 5 - age of health regression and social upheaval. To summarise, rheumatic heart disease, infections and nutritional-deficiency related disorders characterise the disease profile of countries in the earliest stage of development. As nutrition improves and life expectancy increases, vascular risk factors emerge with hypertension as the predominant risk factor initially. During the third stage, urbanisation and improved socio-economic status drive unhealthy lifestyles such as cigarette smoking, high-fat diets and sedentary lifestyles. In this stage, non-communicable diseases (namely ischaemic heart disease and stroke) as well as diabetes predominate and they tend to occur at younger ages. For developing countries that are still fighting a continuing burden of infectious diseases, the increasing incidence of CVD tends to add to this burden, resulting in what others have termed triple or quadruple burden of disease. In the fourth stage, increased efforts to prevent, diagnose and treat ischemic heart disease delays onset of NCDs to much older ages and life expectancy continues to increase and this is the stage that most developed countries are at. However, in the fifth stage (proposed by Yusuf and colleagues) [49], social upheaval or war breaks down existing social and health structures and results in

increased deaths due to CVD and infectious diseases and subsequently a decrease in life expectancy.

Whilst Omran's epidemiological transition theory offers a useful framework for understanding disease trends more generally, the consistent report that stroke is an important cause of morbidity, disability, and death in adults of black African origin, whether living in Africa, the Caribbean, US, or the UK does not seem to wholly support a linear transition theory for vascular diseases in populations of Sub-Saharan African origin. Following a study on trends in stroke mortality among African-Americans living in the US, Gillum proposed that the epidemiological evolution of patterns of CVD in people of Sub-Saharan African origin is better explained in six stages spanning pre-colonial populations living in Africa to poor inner-city, and affluent urban African-American populations [50] (Table 1). According to Gillum's framework, "the evolution is characterised by advancing acculturation, urbanization, and affluence with a progressive increase in salt intake, smoking habit, and saturated fat intake"[51]. Cappuccio (2004) [51] uses Gillum's six postulated stages of the health transition to graphically depict the influence of salt intake, fat consumption and cigarette smoking on incidence of cardiovascular disease (and associated transitions between hypertensive and atherosclerotic disease) (Figure 3). To summarise, increased urbanisation and affluence (associated with moderate fat intake, and smoking and high salt intake) result in the appearance of hypertension and (associated stroke) in stages 2-4. Meanwhile, atherosclerosis (and associated ischaemic heart disease) is predominant in the later stages (4 and 5); those stages are characterised by high smoking, high fat and high salt intake. The final stage is similar to Omran's fourth stage where better prevention and management results in a decline in morbidity and mortality from vascular disease.

However, whether one considers Omran or Gillum's theory as the better framework for understanding vascular transition, the consistent message from both theories is that certain traditional risk factors seem to drive the cardiovascular disease burden in developing economies with some risk factors e.g. hypertension playing a far more significant role than others. Epidemiologic studies such as the INTERSTROKE study [52] have been critical in confirming the latter. Through its case-control design, that study

demonstrated that five risk factors accounted for more than 80% of global risk of stroke. These risk factors were: hypertension, current smoking, abdominal obesity, diet and physical activity (more details appear on Section 2.2.1).

Thus, by considering the combined evidence from empirical and theoretical literature, the thesis focusses solely on stroke as stroke remains the dominant manifestation of CVD in sub-Saharan Africa and the second cause of mortality in South Africa after HIV/AIDS. However, I acknowledge that other cardiovascular diseases, particularly rheumatic heart disease (RHD) are still a challenge in developing countries [53]; it seemed logical to exclude them in this thesis due to the difference in underlying pathology and different risk factor profile to stroke.

Table 1: Stages in the epidemiologic evolution of patterns of cardiovascular disease among persons of Sub-Saharan African origin* (from Gillum 1996)

Stage	Acculturation	Urbanisation	Affluence	Saturated fat intake	Salt intake	Smoking	Cardiovascular Disease	
							Hypertensive	Atherosclerotic
1	0	0	0	+	+	0	0	0
2	+	++	+	++	++	+	++	0
3	++	++	++	++	+++	++	++++	+
4	+++	+	++	+++	++++	+++	++++	++
5	+++	++++	+++	++++	++++	++++	++++	++++
6	++++	++++	++++	+++	+++	+++	++	+++

*The degree to which each factor or disease is present in each stage is shown, with 0 denoting virtually absent and ++++ denoting present at the highest level

Key

Example populations by stage:

Stage 1: pre-colonial sub-Saharan Africa;
Stage 2: modern urban Africans;
Stage 3: modern black populations living in the West Indies
Stage 4: rural populations living in the Southern United States
Stage 5: inner-city black Americans
Stage 6: affluent suburban or urban black Americans

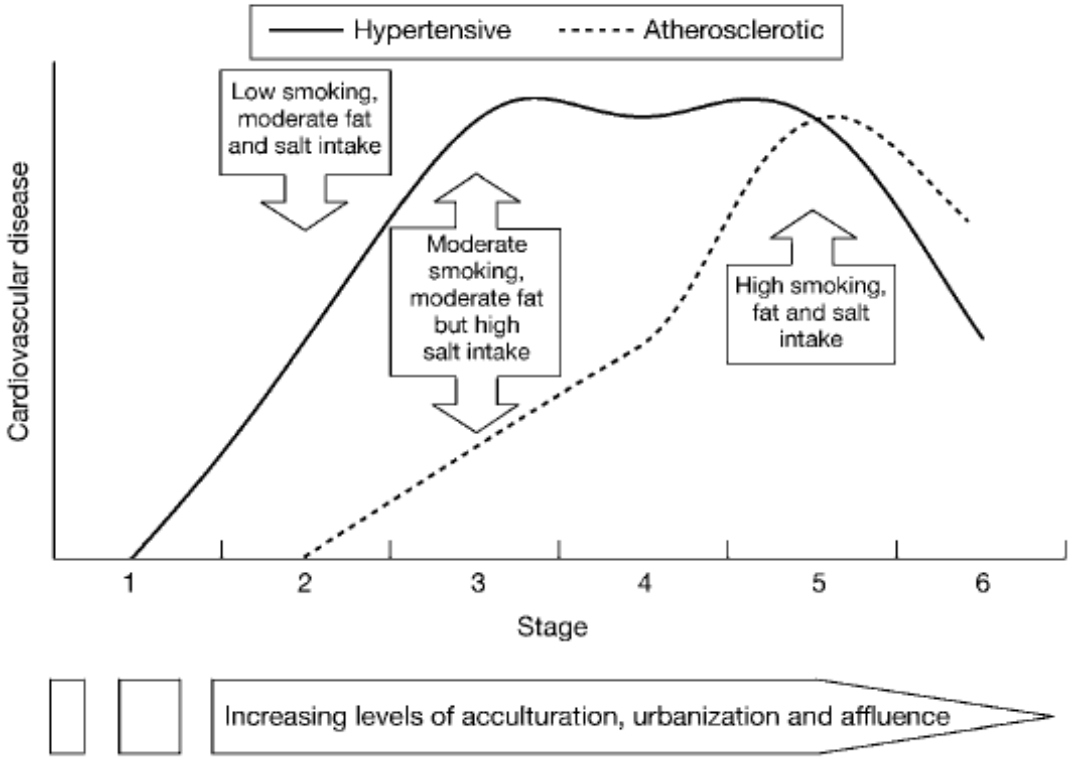


Figure 3: Gillum's stages in the epidemiological evolution of patterns of cardiovascular disease among people of sub-Saharan African origin (from Cappuccio 2004)

2.2 Literature Review

A comprehensive literature review was undertaken at the start of research and updated at different stages of this thesis. The literature review was done to provide a background to the research by presenting a review of: trends and drivers of the CVD burden; proposed interventions; and current evidence supporting proposed intervention choices in South Africa. Furthermore, the literature review aimed to identify information gaps in evidence-based priority setting for CVD, and provide an overall rationale for this thesis. The literature review focusses primarily on published research on South Africa and sub-Saharan Africa, as studies conducted in high-income countries may yield different outcomes due to major contextual differences. However, due to the limited evidence

base on successful community-based interventions in the region, the review highlights selected key intervention studies that were successful in other low and middle income countries.

To provide an overview of the current literature, a systematic search of current epidemiological (descriptive and analytic), public health (primary and secondary prevention strategies), and health economic literature on CVD (cost-effectiveness and analytical tools), as well as documentation on regulatory and policy issues was conducted. For the descriptive and analytical epidemiology of CVD and cost-effectiveness of interventions, various online databases were searched including: the Cochrane database of systematic reviews, Google Scholar, PubMed-Medline, NHS Health Economic Evaluation database (HEED) and Scopus using keywords related to CVD and cost-effectiveness (appendix E). For proposed primary and secondary prevention strategies, South African government and institutional websites of authoritative scientific societies and international organisations were searched and the relevant reports and position papers on the topic were collected.

2.2.1 Cardiovascular disease: Burden, Risk Factors, Preventive Options, and Priority Setting tools

Accurate data on trends in CVD are reliant on the availability of good quality epidemiological studies (i.e. population-based) and complete vital registration systems. It needs to be emphasized that there are persistent limitations with the available data in SSA. Although many countries in SSA have improved vital registration systems, the quality of the data varies substantially across countries [54]. Some estimates indicate that uncertainty in the overall causes of death profile ranges between 15-20% [54]. This uncertainty is apparently higher for conditions such as ischaemic heart disease (IHD) which form part of the focus of this review. There are limited population-based studies to estimate incidence and prevalence. Population-based studies are important in that the denominator or “population at risk” can be accurately captured. Furthermore, the population-based studies that are available are usually based on short-term follow up

periods and long term impacts such as mortality are principally derived from statistical projections or mathematical simulations. Whilst projection models are useful, it is often not easy to compare estimates from different models due to the varying modelling approaches, assumptions and estimates used. However, over the past three decades, the Global Burden of Disease Studies have, through modelling techniques, attempted to fill this data gap by utilising data from diverse sources to derive and estimate consistent and comparable epidemiological parameters. These studies provide near-comparable data across countries and given extreme data gaps are the only sources of information for countries such as Somalia and Equatorial Guinea. A few countries, including South Africa also conduct national burden of disease studies, and data for the second national burden of disease study has recently become available [55]. Data on economic costs is severely limited. Many estimates on direct and indirect economic consequences of CVD are either dated [56] or based on very small population sizes [57-60]; the latter results in imprecise estimates.

With those caveats in mind, the following section summarises statistics on burden of CVD and risk factors in Sub-Saharan Africa and South Africa in terms of the key themes that emerge.

2.2.2 Mortality in SSA: Increasing absolute numbers of deaths and mortality rates

Through analysing available mortality data for the period 1990-2013, the GBD team published estimates that showed that deaths due to CVD almost doubled in SSA - from 526,000 to 930,000 [4]. This figure comprised approximately 40% of all NCD deaths and 11.5% of all deaths. The relatively lower contribution of CVD to total mortality in the region is partly due to the predominance of HIV/AIDS which is still the leading causing of premature mortality, particularly in Southern Africa. In comparison, CVD deaths comprised 34.4% of total deaths globally [3]. There are inter-country variations in the contribution of CVD to total mortality with rates varying from 6% in Chad (a low-income setting) to 40% in Seychelles (a high income country). South Africa is in the middle of

these ranges with contribution of CVD to total mortality estimated at 15% in the country. Age-standardised mortality rates vary within the region from 56 per 100,000 (in Botswana) to 362 per 100,000 (Seychelles) in 2013 [3]. South Africa was amongst the five countries with the highest CVD mortality rates in the region. Contrary to the pattern observed for developed and developing countries (as a whole), age-standardized rates for CVD increased in SSA over the period 1990-2013. The largest increases were observed in Southern Sub-Saharan Africa, where CVD mortality increased from 147 to 159 per 100,000 [3]. This sub-region is worst hit by HIV/AIDS epidemic. Emerging literature suggests that HIV infection increases the risk of cardiovascular events via several mechanisms including accelerated atherogenesis and endothelial dysfunction [61, 62]. Furthermore, some studies have shown an association between antiretroviral (ARV) use, notably protease inhibitors, and increased risk of CVD [62-64]. Whilst there is still some uncertainty surrounding the relative risk of CVD due to HIV/AIDS it is possible that some of the observed increase in CVD is due to the HIV infection itself or ARV use [65]. Notably, the level of increased risk is considered minimal compared with traditional risk factors such as smoking, hypertension, diabetes, and dyslipidaemia [63].

A demographic transition seems to be a critical factor driving the mortality burden. An exploratory analysis based on the same GBD 2013 dataset, found that at least 55% and 25% of this mortality could be explained by population ageing[4] and increased population growth respectively [66]. Already, mortality data on NCDs indicate that 16% of the increase in mortality that was observed between 1997-2010 may be attributable to population growth in South Africa and a further 10% to a changing population age structure [55]. As this demographic transition continues, the burden of NCDs can be expected to rise.

[4] Population ageing, or demographic ageing, refers, in simple terms, to the process by which the older population (60 years or older) becomes a proportionally larger component of the total population. Population ageing increases the dependency ratio of a country i.e. the proportion under 15 years or above 60 years of age relative to the working age population (15-60 years old).

There are persistent age-sex differences in the mortality burden but the pattern differs across cardiovascular diseases. Mortality from cerebrovascular disease appears to be disproportionately concentrated among women and individuals 60 years and over and this pattern has persisted since the 1990s. On the other hand, IHD is much higher amongst males with average age-standardised mortality rates of 30 per 100,000 in men vs. 27 per 100,000 in females in 2013 in sub-Saharan Africa [3]. The same pattern is observed in South Africa though the contribution of cerebrovascular disease to total mortality in the country is much higher. Nojilana and colleagues reported that cerebrovascular disease became the second leading cause of total deaths following HIV/AIDS (accounting for 5.1% of total male deaths and 8.6% of total female deaths) in 2010 [55]. Mortality rates for stroke were around 114 per 100,000 and slightly increased amongst both males and females between 1997-2010. In contrast, IHD mortality rates declined slightly and male rates were twice as high as rates for females in 2010. Despite improvements in data quality over the years, it is worth mentioning that death certification is still a critical challenge in the country. The proportion of ill-defined and misattributed causes is relatively high, particularly for cardiovascular disease and diabetes [55]. Ethnic variations in mortality from CVD are noteworthy. In South Africa, stroke is more predominant amongst the Black Africans (mortality rate of 140 per 100,000 in 2010) and exceeds rates for Coloureds, Whites and Asians. On the other hand, Asians have distinctively higher mortality from IHD which has been attributed to the high incidence of diabetes mellitus, a major risk factor for IHD [67]. Data for the years 2010 showed that mortality in Asians from IHD of 215/100,000 was twice as high as rates for Whites and Coloureds and more than six times higher than rates in African populations. Whilst not firmly established (because of conflicting findings) there are indications that as atherosclerosis becomes more common – consequent on dietary and lifestyle changes - IHD mortality will increase in black African populations [68, 69].

Proportion of deaths that are premature is much higher than in high income countries. The mean age of death attributable to CVD in SSA was the youngest in the world at 64.9 years (95% CI 64.4 – 65.4) compared to the global average of 67.6 - 81.2 years [70]. In 2013, the absolute number of premature deaths – defined as deaths between 30 and 70 years was 231,248 (95% CI 216,576–247,674) amongst males and 200,443 (95% CI

177,291–240,632) amongst females [71]. Higher rates of premature mortality were observed in Central and Eastern Sub-Saharan Africa compared to Western and Southern sub-Saharan Africa; again reflecting the heterogeneity within the region. There are limited country-specific studies that show the age-sex distribution of CVD mortality. However, where they are available in South Africa they show that cardiovascular disease, stroke in particular is not just the second most common cause of death but of premature mortality as well [72]. Projections of the impact of rising risk factors on premature mortality suggest that unless, effective preventive measures are put in place through managing the major risk factors (tobacco smoking, raised BP, obesity, diabetes mellitus and physical inactivity), they will be a 50% increase in the proportion of premature deaths from CVD by 2025 [71] (Table 2).

Table 2: Absolute numbers of premature cardiovascular deaths in 2013 and estimates in 2025 for adults 30 to 70 years of age in Sub-Saharan Africa

Gender	Premature Deaths, 2013 (95% CI)	Premature Deaths in 2025 if Current Risk Factor Trends Continue (95% CI)	Change in Mean No. of Deaths, 2013–2025, %	Premature Deaths in 2025 if Risk Factor Targets Are Achieved (95% CI)	Change in Mean No. of Deaths, 2013–2025, %	No. of deaths averted if targets reached
Males	231,248 (216,576–247,674)	350,375 (327,371–374,645)	52	289,286 (269,767–311,035)	25	61,089 (57,604 - 63,610)
Females	200,443 (177,291–240,632)	296,141 (257,813–347,694)	48	237,249 (207,346–282,389)	18	58,892 (50,467 – 65,305)

2.2.3 Incidence of stroke

Trends in incidence rates from the GBD modelling studies indicate that there was a general increase in incidence of stroke within SSA during 1990 and 2010. Age-adjusted

incidence rates for stroke grew by as much as 12% (South Africa and the Gambia) to 31% (DRC) (Figure 4). Whilst tempting to conclude that things are getting better for South Africa, it is perhaps more accurate to assert that other SSA countries are "catching-up" to South Africa as the country recorded the highest baseline incidence rates in 1990 [73, 74]. In addition, a separate modelling study for South Africa that was based on the 2008 population indicated that the number of new cases of stroke in that year was around 75,000 [75]. This figure is 1.5 times higher than estimates from the GBD 2010 of 49,113. The varying figures are a reflection of the inherent uncertainty that exists with any modelling work. Nonetheless, because the authors in the South African based study reported using more local data sources compared to the GBD 2010 study, the figures obtained in their study could well be closer to the actual incidence estimates in South Africa.

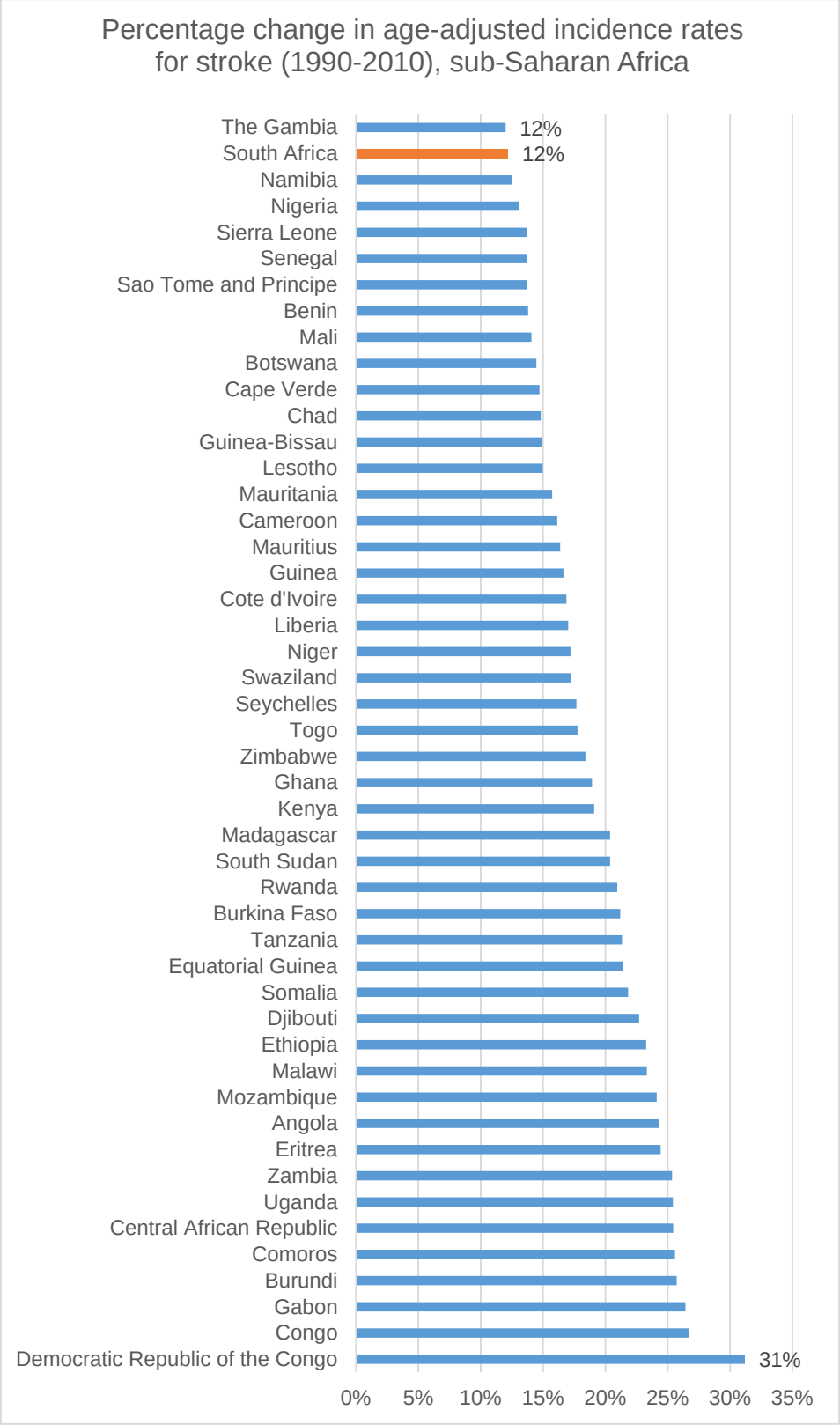


Figure 4: Percentage change in age-adjusted incidence of stroke in sub-Saharan Africa (1990-2010).

*The estimates for Figure 4 are drawn from the GBD 2010 study [74]

Population-level studies on incidence are limited but indicate a 'potential' increase in CVD. There are significant barriers to estimating incidence of CVD including the lack of population-based studies globally. This review identified three population-based incidence studies on cerebrovascular disease for the whole of SSA, conducted in Nigeria and Tanzania [76-78]. Case ascertainment varied across studies which made it difficult to compare incidence rates across settings.

One of the landmark community-based studies of stroke incidence in an African setting was based on the (1973-75) stroke registry in Ibadan, Nigeria, which covered a population of 803,000 people [79]. To ensure 'near- complete' identification of new stroke cases, data was collected from all participating facilities including hospitals, general practitioners, private nursing homes, medical officers' and coroners' offices. Based on this study, age-adjusted stroke incidence was 26 per 100,000 i.e. 318 strokes occurred over the 2-year period. Incidence was twice as high in males compared to females (25 vs. 13 per 100,000 respectively). Though this figure was lower than rates reported in developed countries at the time, it was likely an underestimate as case detection excluded those patients that sought care at traditional healers, herbalists or prophets. That figure is potentially high in African settings where "stroke-like symptoms are considered to be both a physical and social condition, and as a result plural healing using clinical and social diagnostics is sought to address both these dimensions" [80].

Other published studies of stroke incidence in SSA, were conducted three decades later in Nigeria (in 2007) [76] and Tanzania (2003-06) [78]. In Nigeria, stroke incidence was determined within the mixed-income urban community of Lagos State (Surulere Local Government Area), South-Western Nigeria, where approximately 750,000 people reside. Patients with stroke were identified by use of a system of community-based study assistants and liaison with focal persons at each of the participating health facilities. No attempt was made to identify stroke victims in the community who would not have sought any treatment at participating health facilities. Based on this study, 189 first-ever strokes were documented (112 men and 77 women), giving a crude incidence rate of 25.2 per 100,000 per year. The gender-specific rates were 28.3/100,000 and

21.3/100,000 for males and females respectively. The age-adjusted incidence rate was 54.08 per 100,000 per year (adjusted to the WHO New World Population). Whilst the crude rates reported from the 1973-75 stroke registry [79] are similar to the ones from this study, crude rates are affected by population size and age-structure of a study population. In countries or communities, where strokes occur at much younger ages, crude rates can underestimate the economic and social impact of stroke.

Tanzania provided estimates of stroke incidence within two health and demographic surveillance sites covering well-defined populations: Hai, located in a rural area (population of 159,814 people) and Dar-es-Salaam, which is urban (56,517 people) [78]. Stroke cases were identified through two means: community-based investigators identified patients with stroke within the community and at health facilities; and verbal autopsy was used to identify all deaths in the community caused by stroke during the study period. Crude annual stroke incidence over the study period was 94·5 per 100,000 (95% CI 76·0–115·0) in Hai and 107·9 per 100,000 (95% CI 88·1–129·8) in Dar-es-Salaam [78]. Age-standardised rates were 108·6 per 100,000 (95% CI 89·0–130·9) in Hai and 315·9 per 100 000 (95%CI 281·6–352·3) in Dar-es-Salaam. The sex-specific pattern resembles that reported for Nigeria in the 1960s; stroke incidence rates were higher for males than females aged 55–64 years, 65–74 years, and 75–84 years in Hai rural district. In the Dar-es-Salaam surveillance site, stroke incidence rates were higher for males than for females aged 65–74 years and 75–84 years. The age-adjusted rates reported in this study for Dar-es-Salaam are twice as high as the rates reported in the urban community of Surulere, South-Western Nigeria. Whilst this could point to increase in risk factors for stroke, hence burden in Tanzania, the differences in incidence rates could be attributed to more complete case ascertainment in Tanzania. There are claims that much of the reported differences in mortality and stroke incidence rates between populations may be attributed to methodological challenges [81].

2.2.4 Prevalence of stroke on the increase in SSA

In comparison to incidence based-studies, there are a few more studies on stroke prevalence in sub-Saharan Africa [82] (Table 3). Availability of health and demographic

surveillance sites seem to have aided collection of such data. It can be argued that, to date, these sites provide the best estimates of stroke prevalence because of their well-defined populations and hence accurate denominators. In 1994, the Hai HDSS, reported that crude prevalence of disabling stroke was 73 per 100,000 [83]. Age-standardised rates were 154 per 100,000 in men (114 per 100,000 in women) [84]. Stroke cases were identified by means of validated questionnaires followed by neurological examination of suspected cases. In 2001, a similar study was conducted in Agincourt sub-district, rural North-Eastern South Africa. This study provides the best estimates of stroke prevalence within a community in South Africa. It reported that crude stroke prevalence was 290 per 100,000 whilst age adjusted rates (adjusted to Segi World population) were 281 per 100,000 and 315 per 100,000 in males and females respectively [84]. The much higher prevalence rates in Agincourt sub-district compared to Tanzania could indicate that rural SA is indeed further along a health transition due to a higher level of lifestyle risk factor exposure. However, other factors such as higher case fatality or lower incidence of stroke amongst Tanzanians or the fact that only disabling strokes were reported in Tanzania could account for these differences. Potentially supporting the latter, a recent study conducted within the same location in Tanzania, found that prevalence of stroke was 2,300 per 100,000 [85]. However, the study sample was individuals 70 years and older in whom incidence of stroke is already high.

Overall, between 1980 and 2015, seven published studies [79, 83-88] reported crude prevalence rates of stroke ranging from 15/100,000 population in Ethiopia in 1986 [86] to 2,300 per 100,000 in the Hai DSS, rural Tanzania [85]. The sizes of populations studied differed across settings: In Nigeria, Igbo-Ora state, 18,954 people were screened [79] in comparison to 2,232 participants in Hai DSS, Tanzania [85]. The small denominator(s) lead to wide confidence intervals or imprecise estimates. Moreover, target populations differed and ranged from sample populations that targeted high-risk groups (above 70 years) to those that included all adult individuals within the study setting.

Table 3: Population based studies reporting on prevalence of stroke survivors in sub-Saharan Africa

Authors (Study Year)	Country/setting	Study population	Major findings	
			Crude Prevalence	Age-adjusted prevalence
Osuntokun et al (1982) [79]	Nigeria	All people >7 years old in Igbo-Ora, Nigeria (population approx. 20 000)	11 strokes in 18954 people screened. Crude prevalence of 58 per 100 000	Not Reported
Tekle-Haimanot et al (1986-8) [86]	Ethiopia	All people in Butajira DSS (60,820 people screened)	9 strokes in those screened Crude prevalence: 15 per 100 000	Not Reported
Walker et al (1994) [83]	Tanzania (rural)	All people >15 years old in Hai rural district of Tanzania (population 148 135)	108 participants with disabling stroke identified Crude prevalence of disabling stroke: 73 per 100 000	Age standardised rates: 154 per 100 000 in men 114 per 100 000 in women (standardised to to the Segi World population)
Connor et al (SASPI project team) (2001) [84]	South Africa (rural)	All people >15 years old in Agincourt HDSS, rural north-eastern SA. (population 68,525)	103 participants with stroke identified Crude stroke prevalence: 243 per 100, 000 (95% CI: 198 - 295) Crude stroke prevalence adjusted for proportion not examined: 300 per 100 000 (95% CI: 250-357)	Stroke prevalence age standardised to the Segi World Population: 290 per 100 000 (95% CI: 238-343)
Danesi et al (2006) [87]	2006	Lagos, Nigeria (urban)	Crude Prevalence: 114/100, 000 (males: 151; females: 69)	Age adjusted rates per 100,000 (adjusted to the USA population 2000) were: 9,33,71,98,204 and 74 for age groups '35-44', '45-54','55-64','65-74' '75-84' and >85 years respectively
Cossi et al (2009) [88]	Benin (Cotonou)	15,155 individuals aged ≥15 years	70 confirmed cases of stroke Crude prevalence 460 per 100,000	Age-adjusted prevalence: (870/100,000 and 770/100,000 adjusted to the WHO and SEGI World Population respectively)
Dewhurst	Tanzania (rural)	2,232		Age-adjusted

Authors (Study Year)	Country/setting	Study population	Major findings	
et al (2010) [85]		participants aged ≥70 years		prevalence of stroke: 2,300 per 100,000

2.2.5 Combined measure of mortality and morbidity: the disability adjusted life-year (DALY)

Because the consequences of CVD are not just premature mortality but also long-term disability, composite measures of mortality and morbidity such as the DALY are important for tracking disease burden. The DALY is the sum of years of life lost due to premature mortality (YLL) and years lived with disability (YLD). This measure was developed by the WHO and has mainly been used in the GBD studies [54, 89, 90]. According to the 2013 GBD study, the proportional contribution of DALYs due to CVD has increased from 1990 (3.1% (95% CI 2.9–3.4), to 2013 (4.38% (95% CI 4.1–4.8) in SSA. This is a diverging trend from that observed in developed countries of reducing DALYs during that time period. Apart from the demographic transitions cited earlier, less optimal CVD prevention and management could account for this trend in SSA. In contrast, statistics for South Africa indicate a decline in contribution of CVD to total DALYs during 1990-2013 when compared to the rest of SSA. By decomposing the DALY measure, it appears that the decline in premature mortality from CVD is the driving force behind the downward trend in DALYs since years lived with disability almost doubled during that time. To summarise implications of these findings for South Africa from my perspective: more people are surviving premature deaths due to CVD but they do so with significant disability.

2.2.6 Economic Consequences of CVD in sub-Saharan Africa

There are few recent estimates of the economic impacts of CVD in the literature. Bloom and colleagues estimated that the total cost attributable to CVD in the World Health Organization (WHO) African regions D and E was US$11.6 billion in 2010 of which 40%

were indirect costs due to productivity losses [91]. Whilst similar studies are scarce in many of the SSA countries, a study conducted in South Africa estimated the overall cost of stroke and heart diseases at US$1,250 million, which approximated 4-5% of the GDP of the country at the time the study was conducted in 1991 [56, 92]. There are a few studies on economic costs of stroke in SSA (Table 4). However, the studies are based on small sample sizes, and they vary in terms of the cost components included, study population (community vs. inpatient) and period of follow-up.

Apart from the direct costs to government, CVD poses a great financial risk on households particularly in countries without universal health coverage. In a recent analysis, Watkins and colleagues investigated the broader health system and socio-economic impacts of a salt reduction legislation in South Africa [22]. They concluded that, the policy, through reduction in CVD could prevent 2,400 cases of catastrophic health expenditures (CHEs) or 2000 cases of poverty yearly. In that study, catastrophic health expenditure (CHE) was defined as CVD expenditure exceeding 10% of total yearly household income whilst CVD expenditure was considered impoverishing if it reduced individual income below the poverty line of US$78 (in 2012) [22]. Of particular note were distributional impacts of the policy across the socio-economic gradient. The authors observed that the policy impacts were significantly higher for individuals in quintile 2 who were already closer to the poverty line prior to implementation of policy. Though no cases of poverty were prevented in quintile 1 (all households were already under the poverty line), it would have been useful if the authors had further estimated the extent to which CVD-related expenditure pushed households already in poverty deeper into poverty i.e. intensity of CHE. A separate study in Ethiopia established that approximately 27% (95% CI 23.1 to 30.6) of the households experienced CHE through seeking preventive and treatment services for CVD [93]. Noteworthy, the bottom income quintile was 60 times more likely to suffer catastrophic health expenditure compared to the top quintile [93]. In contrast, in the South African study, the top quintile were more likely to suffer CHE (i.e. spend more than 10% of annual household income) due to the more expensive treatment services they sought [22]. There are a few other studies which corroborate that, in the absence of universal health financing, CVD imposes a major financial risk on households, particularly in developing countries [94-96].

Table 4: Cost of Stroke Studies in Sub-Saharan Africa

Setting (reference)	No. of stroke patients	Length of follow up	Costs included	Costs per patient	Comment
Congo[97]	90	6 months	Direct costs (diagnosis, inpatient care,medication)	158 ± 10 euros	Only 1st day of hospitalization included (article in French)
Togo [59]	412	12 months	Direct costs (diagnosis, inpatient care, medication)	430 ± 190 euros for ischaemic stroke; 940 ± 40 euros haemorrhagic stroke[5]	Article in French
Senegal [98]	383	12 months	Direct costs (diagnosis, inpatient care, medication)	USD160	Article in French
Nigeria [57]	240	Cross-sectional /folder review	Direct costs (diagnosis, inpatient care, medication)	USD600 in public facility; USD5000 in private facility	
Tanzania [25]	16	6 months	Direct costs (diagnosis, inpatient care, medication) transport indirect costs (productivity losses)	USD 107 in rural Hai; USD 420 in urban Dar es Salaam (excluding productivity losses)USD137 in rural Hai vs. USD380 in urban Dar es Salaam (productivity losses)	Included productivity losses. Unit costs shown for some cost parameters
South Africa [60]	261	12 months (retrospective folder review)	Inpatient costs	USD2240	Only inpatient costs included
Burkina Faso [58]	122	7 months	Direct costs; transport cost to designated hospitals	USD145–USD940	

[5] The marked difference in inpatient care costs is a direct consequence of the longer length of hospital stay by individuals who suffer a haemorrhagic stroke compared to those of ischaemic stroke.

Setting (reference)	No. of stroke patients	Length of follow up	Costs included	Costs per patient	Comment
			physiotherapy and out-of-pocket payments to other points of care.		

2.2.7 Underlying Risk factors for CVD in sub-Saharan Africa

"The worldwide increase of NCDs is a slow-motion disaster…but the unhealthy lifestyles that fuel the disease are spreading with a stunning speed and sweep."

Margaret Chan, Director-General of the World Health Organization

Many risk factors drive the CVD burden. Whilst some of the risk factors are non-modifiable (e.g. age), others can be wholly or partially modified and include behavioral risks (tobacco smoking, diet, physical activity), metabolic factors (elevated blood pressure and blood glucose levels) and socio-cultural factors (poverty and urbanisation). Several studies have been conducted across the world to understand the contribution of known risk factors to the CVD burden by either: (i) relating changes in known causal risk factors to changes in CVD incidence (e.g. WHO MONICA (Multinational Monitoring of trends and determinants in Cardiovascular disease) project or, (ii) estimating the attributable fractions of known risk factors (e.g. the INTERHEART study).The MONICA project was established to monitor trends in cardiovascular diseases in 38 populations across 21 countries, and to relate these to risk factor changes in the population over a ten year period [99]. Some of the main findings of this project include that prevalence of smoking and elevated blood pressure explains a substantial proportion of the variation of stroke attack rates between populations" [100]. The INTERHEART study was a global case-control study of risk factors for acute myocardial infarction across 52 countries [101]. The main findings from this study were that diabetes, elevated blood pressure, smoking

and abdominal obesity are strong predictors of acute myocardial infarction risk [101]. Taken together, these studies have strengthened the evidence base of causality of CVD risk factors.

Raised blood pressure is arguably the biggest risk factor for CVD in SSA and is affecting both urban and rural dwellers. This is compounded by the fact that management of high blood pressure is poor. Approximately 40% of Africans with hypertension are undiagnosed, less than 30% of those who are diagnosed with hypertension are on treatment, and less than 20% of those on treatment have optimal blood pressure control [102, 103]. Estimates of hypertension prevalence in SSA vary between and within studies and depend on the age-groups of sampled populations and the methods used to determine hypertension (self-report of medication use vs. clinical assessment[6]) [104, 105]. In South Africa alone it is estimated that hypertension affects 56% of women (29% of men) above 65 years whilst the prevalence in adults 18 years and above is estimated at 10.4% [106]. Other estimates of hypertension are of adults over 50 years which report prevalence rates of up to 79% in South Africa; the high rates confirm what has been firmly established that high blood pressure tends to be highest and poorly controlled amongst the older age groups [7]. Cross-country comparisons of hypertension prevalence in SSA also indicate that there are stark differences in hypertension[7] prevalence between sub-Saharan African countries [107]. For example, a population based cross-sectional study conducted at 6 study sites across 4 African countries: Burkina Faso (Nanoro), Ghana (Navrongo), Kenya (Nairobi), and South Africa (Agincourt, Dikgale, Soweto), found that mean prevalence of hypertension ranged from 15.1% in Nanoro to 54.1% in Soweto [107]. Of note in that study was that, hypertension prevalence was greater than 40% across the 3 study sites in South Africa: 47.3%

[6] Hypertension is clinically assessed using JNC 7 guidelines in most published studies. According to these guidelines hypertension is defined as systolic blood pressure ≥140mm Hg or diastolic blood pressure ≥90mm Hg.

[7] Hypertension was defined as systolic blood pressure 140mm Hg or diastolic blood pressure 90mm Hg or taking antihypertensive medication.

(Agincourt), 41.6% (Dikgale) and 54.1% (Soweto). There was no marked urban-rural difference in hypertension prevalence amongst females residing in Agincourt HDSS and Soweto: 53.4% (urban Soweto) and 52.1% (rural Agincourt).

However, even at lower age ranges the prevalence of hypertension in rural areas is equally high. The proportion of adults aged 15 years and above with hypertension was estimated to be 50% in 2010 in Agincourt HDSS [8, 108]. Similar results have been reported at the Dikgale HDSS in Limpopo province [109]. In West Africa, hypertension is estimated to affect 30-40% of people above the age of 65 in rural areas and this figure rises to 50% amongst urban dwellers. There are also ethnic variations in prevalence of hypertension. In South Africa, the black African and coloured populations have a higher prevalence of hypertension [106]. Comparative risk assessment studies which estimate the proportion of a disease that is attributable to a particular risk factor indicate that in South Africa, in 2000, hypertension was responsible for 50% of stroke deaths and 42% of IHD deaths [110]. With the advent of new data from randomised controlled trials [111] which show that achieving lower blood pressure levels (SBP of less than 130 mmHg) [8] significantly reduces stroke and myocardial infarction rates, it is likely that re-analysis of that data may indicate that the contribution of hypertension as a risk factor was much higher than previously estimated.

Type 2 diabetes mellitus, once considered a rare disease in SSA, is on the increase and contributing towards the CVD burden. The World Diabetes Federation estimated that 14.2 million people with diabetes mellitus (3.4% of the global estimate of 415 million) were in sub-Saharan Africa in 2015 and this figure would rise to 34.2 million by 2040. It is estimated that Nigeria has over 3 million people with diabetes whilst South Africa has 1.9 million. Within the region, prevalence of diabetes varies from 2% in Malawi to 4% in

[8] New blood pressure guidelines have been developed to reflect the new evidence. The new guidelines use a lower cut-off for BP compared with JNC 7. Adults with an average SBP of 130 to 139 mm Hg or DBP of 80 to 89 mm Hg are categorized as having stage 1 hypertension; these were previously classified as prehypertension in JNC 7.

South Africa [112] but these are likely to be underestimates as approximately 80% of people with diabetes in sub-Saharan Africa are undiagnosed [113].

The empirical data on physical activity remains scant. This may be attributable to the fact that objective measurement of physical activity is costly and complicated. Nonetheless, recently, the WHO published comparable estimates of prevalence of physical activity across 57,038 individuals from 22 African countries (11 national and 11 subnational samples) that participated in the STEPwise approach to chronic disease risk factor surveillance during 2003-2009 [16]. This study revealed that "overall, 83.8% of men and 75.7% of women met WHO physical activity recommendations (at least 150 minutes of moderate activity per week or equivalent)". However, the prevalence rates across countries varied widely from 46.8% (Mali) to 96.0% (Mozambique). Other studies have been conducted in Nigeria, in a metropolitan city and found that prevalence of physical inactivity was approximately 30% [114]. There is evidence in South Africa that the amount of sedentary time is high amongst adolescents in rural communities where physical activity is generally expected to be high [115].

Overweight and obesity is on the rise in SSA, while the competing epidemic of undernutrition still exists. A cross-sectional study of 3,511 children and adolescents aged 1-20 years in Agincourt sub-district, rural North-eastern South Africa found that prevalence of obesity was 20-25% in late adolescence. Yet levels of malnutrition, underweight and stunting are still high within this community [116]. Prevalence rates vary widely across the region. In Benin, prevalence of obesity is estimated at 10% whilst rates in South Africa (amongst women) exceed 35% and in Seychelles (43%). However, the different measures used to classify obesity may partially account for these discrepancies. Abdominal obesity was used to derive estimates for Benin whilst the other cited studies typically used the body-mass index. Though there is some agreement that central obesity and waist-to-hip circumference are better measures of obesity than BMI, the latter is easier to measure and obtain and thus remains more widely used.

Summary: Cardiovascular risk factors
• Given limited evidence and few prospective studies in SSA, it is possible some key mediating risk factors are yet to be uncovered. Nonetheless; • Hypertension seems to be the most important risk factor for CVD in SSA; control could result in significant reductions in CVD burden but clinical management remains poor • The attributable burden of other risk factors (overweight and obesity, physical inactivity, diabetes etc.) is becoming more important as urbanisation and globalisation propel cultures towards unhealthy lifestyles • As access to HAART increases in developing countries, including South Africa it is crucial to continue to invest efforts to understand metabolic complications associated with HIV and HAART which may increase cardiovascular risk and disease.

2.2.8 Preventive interventions

The literature on risk factors for CVD has grown and along with it our understanding of the major risk factors to target, yet studies of implementation of effective preventive and therapeutic strategies remain scanty in sub-Saharan Africa. Whilst stronger evidence exists on the risk factor reduction initiatives that have been successful in high income countries, these interventions may be less successful in LMICs due to the very difficult social and economic circumstances that prevail. This section provides a review of evidence-based interventional measures to address known risk factors for CVD in sub-Saharan Africa with the aim of establishing whether identified interventions are applicable across the region; and to determine whether recommendations for scale-up can be made based on these studies. I have excluded modelling based-studies in this section as the main goal is to assess impact within a real-life setting.

2.2.9 Highlights from available data

Limited intervention studies of variable quality have been conducted in SSA that report on changes in risk factors for cardiovascular disease. The interventions studied include: health education initiatives to promote dietary modifications or physical activity [117-119], product reformulations [120-122], and cash-back incentives [123]. Product reformulations and counselling on dietary modifications targeted mainly salt reduction and its relationship with blood pressure [117-121]. Various study designs have been used including cluster randomised trials (e.g. villages as clusters) [118], individually randomised control trials [120], observational studies, before-after studies [123], quasi-experimental designs and cross-sectional surveys [122]. Overall, five countries, including South Africa, Ghana, Tanzania, Nigeria, and Mauritius were covered in these studies.

Dietary counselling and advice to promote dietary modifications. Three studies examined the impact of education and counselling on dietary modifications. In all studies, changes in urinary sodium excretion and blood pressure were assessed. Adeyemo and colleagues investigated the impact of reducing discretionary salt intake among 86 normotensive individuals in 2 rural communities, South-West Nigeria [117]. Participants were counselled to: reduce the salt added during cooking by half, and eliminate the use of stock cubes and monosodium glutamate seasoning for a 2-week period. After 2 weeks on the reduced sodium diet, 55 (67%) individuals (65% of men, 70% of women) had achieved at least a 50mmol reduction in 24-hour urinary excretion of sodium, and 84% (83% of men, 85% of women) had achieved at least a 25mmol reduction. Reductions in systolic and diastolic blood pressures were observed in both men and women with women achieving a higher mean reduction in SBP of 7mmHg (compared to 4.2mmHg in men). In a similar study in Ghana, aimed at reducing discretionary salt intake at a population level, community health workers delivered hourly long health advice sessions on salt reduction to villages (clusters) every day for a week, then once a week thereafter, in addition to standard health messaging. In that study, mean urinary sodium excretion and SBP did not differ significantly between intervention and control groups. However, DBP reduced by a mean of 4.0mmHg. In the latter study, the investigators report that there was possible contamination of the intervention (control villages became aware of the intervention) therefore the quality of the study and intervention could have been compromised [118]. In the third study by Forrester and

colleagues conducted in rural Nigeria, participants were enrolled into a cross-over design involving 3 weeks of low/high salt diet, two-week wash-out and 3 weeks of high/low salt diet. The low salt-diet was equivalent to a 70mmol reduction in daily salt intake. A statistically significant difference in the mean change in systolic blood pressure was observed between the high and low-salt phase at the end of the intervention period [119]. The study investigators concluded that the efficacy of sodium reduction initiatives in LMICs equals those noted in high income countries. However, the short duration of the study makes it difficult to draw firm conclusions regarding the long term sustainability of a daily 70mmol reduction in sodium. Furthermore, the high salt diet was achieved by giving a sodium supplement and not through observing a normal diet and the investigators reported that many participants struggled to comply with the high-salt diet.

Product reformulations to reduce salt and mono-unsaturated fats. Three studies examined product reformulations; two targeted at salt reduction and one at content of saturated and mono-unsaturated fats in cooking oil. The latest study was a RCT conducted in South Africa among a small sample of 80 Black African residents in Cape Town with mild to moderate hypertension [120]. The intervention included reduced sodium content in commonly consumed foods in the intervention group whilst the control group consumed the same foods but with standard commercial compositions. A significant reduction in SBP of 6.2mmHg was observed between the intervention and control group but no changes were observed in diastolic blood pressure. A similar finding was reported by Mtabaji and colleagues in Tanzania based on a RCT of normotensive individuals. However, in the latter study, participants in the control arm were given sodium supplements rather than being kept on a normal diet and this has implications for intervention effectiveness outside the trial setting [121]. In Mauritius, the impact of a government policy that changed the composition of the commonly used cooking oil from being mostly palm oil (high in saturated fatty acids) to being wholly soya bean oil (high in unsaturated fatty acids) was investigated through 2 surveys conducted in 1987 and 1992 [122]. At the end of this 5-year follow-up period, intake of saturated fatty acids decreased by 3.5% of energy intake in men and by 3.6% in women, and the intake of polyunsaturated fatty acids increased by 5.5% and 5.6% of energy intake, respectively. There was a statistically significant reduction in mean total cholesterol concentrations

over this time period among both men and women. It is important to note that though the changes in total cholesterol concentrations were attributed to changes in composition of the cooking oil, a separate study conducted in Mauritius indicates that this was one part of a much broader nationwide intervention implemented between 1987 and 1992 [124]. The other components of the programme included extensive use of the mass media and widespread community, school, and workplace health education activities. In the latter study, that assessed the impact of all elements of the non-communicable disease programme, the authors reported "significant decreases in the prevalence of hypertension (15.0% to 12.1% in men) and (12.4% to 10.9% in women); cigarette smoking (58.2% to 47.2% men and 6.9% to 3.7% women respectively); and heavy alcohol consumption". Moderate leisure physical activity also increased amongst both men and women but was much higher in men (increase of 5% vs. 1.4%). Thus, in the short-term it appears that a more comprehensive programme targeting a wide variety of risk factors appears to be more effective at reducing burden of key risk factors within a population. A survey on non-communicable diseases in Mauritius conducted in 2015, reported prevalence rates of hypertension that are more than double that reported in 1992 [125]. This suggests that the effects of the intervention or the intervention itself were not sustained over the long-term.

Cash-back incentives as a strategy to promote healthy food purchases. There is currently one observational study that investigated the impact of cash-back incentives as a means to promote healthy lifestyle including healthy food purchases in South Africa. Members of the Discovery Medical Scheme who belonged to the Vitality programme[9], received an automatic 10% discount on healthy food purchases which increased to a 25% rebate upon online completion of a risk assessment questionnaire [123]. More than 6,000 items are eligible for discount. By linking household supermarket purchases of

[9] Vitality programme aims to incentivise members to improve their quality of life and reduce their long-term medical costs. Vitality rewards members for looking after their health by giving them access to a range of benefits, including discounted access to wellness facilities. However, there is an extra monthly cost (in addition to normal medical aid cost) of joining Vitality.

more than 170,000 households during the period 2009-2012, the study investigators showed that cash-back rebates increased healthy food purchases by 6%; ratio of fruit and vegetable to total food expenditure by 7.5% and decreased the ratio of less desirable to total food expenditure by 5.6%. No other secondary outcome measures were assessed in this study. A key issue to note with this study is the highly selected population involved. Members of the Discovery Medical Scheme are largely middle-class enrolled in the private health care system; the impact of the intervention in lower socio-economic groups may thus be different. In terms of the potential direction of impact, a systematic review indicated that 'price' interventions to promote healthy eating tend to preferentially improve healthy eating outcomes in lower socioeconomic groups compared to higher-income groups [126].

Workplace based interventions. Only one study was found through this literature search that explored the impact of a workplace fitness programme and its associations with biological markers of blood pressure, BMI and cholesterol [127]. This study was conducted amongst 143 male colliery executives in South Africa and compared a conventional fitness programme to an enhanced fitness programme (included health promotion). At the end of the 32-week period, systolic and diastolic blood pressures had reduced more in the intervention arm and fitness was also higher in this group. However, cholesterol remained unchanged in the intervention group. Nonetheless, it is unclear how the authors evaluated the pathway from risk factor (physical fitness) to effect (change in total cholesterol) and how they accounted for other confounding factors (e.g. potential dietary changes).

Integrated community-based health education programmes. According to Goenka and colleagues, *"*a vital component of a successful prevention programme is community empowerment initiatives aimed at influencing social norms, health beliefs, and behaviours of the community". Because society influences to a great extent personal lifestyle choices, such interventions may broadly, and positively, impact healthy behaviour change across society. Two studies were identified that investigated the impact of integrated community-based health promotion packages. One complex intervention was conducted in Mauritius [124] and described above. The second was

conducted in South Africa, in the Western Cape Province and comprised 7,188 participants, from 3 white South African communities [128]. The intervention comprised 2 components: (i) a structured health education programme aimed at promoting regular blood pressure checks, reducing dietary salt intake and increasing physical activity through mass-media campaigns (also termed low-intensity intervention); (ii) the structured health education programme plus interpersonal interventions targeted at high-risk groups (termed high-intensity Intervention). With the exception of total cholesterol, all the main risk factors decreased after the four-year follow-up period in the intervention groups compared to the control groups with the highest decline experienced in the high-intensity group. There was a 3.7% decline in risk of IHD in the intervention groups compared to a 1.5% decline in the control group. It is difficult to generalise the findings of this study to the rest of the South African community as it was based on solely white participants, and it is not clear if the impact would be similar across the other population groups. However, the intervention delivery approach may be generalised, fits in with proposed strategies for preventing NCDs in South Africa and elements of the interventions could be scaled up across the country. According to the National Strategic Plan for NCDs, "community health workers, [part of ward-based outreach teams] will visit households directly, inform community members of the importance of healthy lifestyles and what constitutes healthy living. People identified as high risk will be referred for a full assessment at their local clinic or health centre." [129]

Absolute risk assessment in primary care facilities to reduce mean blood pressure. One interventional study, led by the World Health Organization, investigated the impact of using an absolute risk assessment tool developed by the WHO to assess risk of CVD, provide counselling and initiate treatment in those at moderate risk of developing CVD [130]. Two countries were studied, China and Nigeria with results for the Nigerian arm provided here. Following the 12-month follow-up period, systolic and diastolic blood pressure decreased in both intervention and control groups but the decline was higher in intervention patients than in controls. Behavioural risk factors (smoking and fruit and vegetable consumption) also showed a significant improvement. All participants who were smoking at the beginning in the intervention group, reported quitting, whilst 74.4%

did so in the control group. It is unclear whether the intervention effectiveness has been sustained to date due to lack of follow-up data.

There is limited evidence linking risk factor interventions to CVD events (e.g. stroke incidence). As such, it is difficult to draw conclusions as to the effectiveness of such interventions on cardiovascular disease prevention. There is some evidence that multiple risk factor interventions may lower blood pressure but the studies from which the evidence is derived are of variable quality. There are a number of other risk-reduction initiatives that are being implemented across SSA. However, their impact has not been assessed, or evaluations are of poor quality and this has limited the pool of good quality evidence in SSA. Coupled together, these findings suggest that longer-term prospective designs are needed to evaluate intervention effects on events particularly those presenting to health services.

Focussing on the evidence-base beyond SSA, to include other LMICs, the conclusions above still hold; there are limited studies indicating the effectiveness of interventions on CVD events [131]. However, there are a few studies with sufficient statistical power due to their large sample sizes that report on impact on CVD risk factors that are worth mentioning. These include the Community Interventions for Health (CIH) programme designed to reduce the risk of NCD by targeting the three main risk factors of tobacco use, physical inactivity and unhealthy diet in China, India and Mexico during the period 2008-2011 [132]. In this programme, each of the countries decided on and adapted culturally-appropriate interventions for local application in designated communities of populations of between 150,000-200,000 individuals. Examples of the interventions included: subsidies on healthy choices at workplace canteens; displaying nutritional information of dishes served in local canteens; providing salt-measuring spoons and oil pots which indicated maximum daily intake to adults in the local community; enforcing smoking restrictions in public places, providing street gyms and fixed exercise equipment in local parks and distributing health related messages through the local media. The main findings of the study were that physical activity, intake of fruit and vegetables and obesity increased in control groups but remained unchanged in intervention groups; the proportion of individuals adding salt to food decreased in the

intervention group [132]. Whilst it is encouraging that the secular trend towards unhealthy behaviours that was observed in the control group was not evident in the intervention group, a more desirable outcome that would reverse the CVD epidemic would have been an absolute reduction in risk factors within the intervention communities. Thus, it is difficult based on these findings to draw firm conclusions on the impact of this programme on risk factor reduction and consequently cardiovascular disease incidence.

2.2.10 Economic evaluation of interventions to prevent CVD and reduce risk factors in SSA

The previous section identified interventions that have been implemented predominantly in SSA; some of which have shown promising effectiveness. This section reviews the evidence-base on interventions that represent “good value for money” within these settings. Understanding the cost-effectiveness of interventions within low-resourced settings is important as some of the extensive strategies pursued in high income countries might be unaffordable and unsustainable in sub-Saharan Africa, at least without major adaptations to local circumstances.

2.2.11 Economic Evaluation

Rising health care costs globally and in South Africa have increased pressure among health care policy makers to justify decisions not only on effectiveness but also costs. Economic evaluation involves the comparative assessment of alternative courses of action in terms of both their costs and consequences [133]. It is a crucial analytical tool to ensure resources are used as effectively as possible. Economic evaluation goes beyond the question ‘does it work?’ that other impact evaluations address, to answer the question ‘is it worth it?’[134]

There are four main types of economic evaluation: cost minimisation analysis (CMA), cost utility analysis (CUA), cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA). Monetary units are used as the measure of costs for all types of analysis , however the benefits are measured in different units for each technique [133]. Cost-

minimisation analysis is used when the outcomes of two procedures being compared are identical. The objective when using CMA is to find the lowest cost programme and the unit of measurement is cost per intervention [135]. The challenge is that very rarely do any two programmes give the exact outcome; thus limiting the usefulness of this technique. CEA is used when the programmes may have differential success in outcome, as well as differential costs, but the outcome must be common to both programmes and is measured in natural units (e.g. life years gained; immunization cases prevented). The disadvantage of a CEA is that it cannot be used to compare programmes with different clinical effects. In such cases a CUA which uses aggregate outcome measures (that incorporate a utility outcome into the natural unit) such as the quality adjusted life year (QALY) or Disability Adjusted Life Year (DALY) is useful. However, derivation of both QALYs and DALYs is sometimes met with criticism. For example, discounting and non-uniform age-weighting in DALY calculations result in less weight given to years lived at young and older ages. In practice though, the terms CUA and CEA tend to be used interchangeably. A CBA measures outcomes in monetary units and has a solid foundation in welfare economics. Valuing health in monetary terms presents with its challenges. For example, under the human capital approach, health improvement is valued on the basis of the individual's future 'worth' to society in terms of future earnings. A second method – the willingness to pay (WTP) approach – values an intervention on the basis of how much people are willing to pay for it. There are problems with the WTP approach particularly in a society that is not used to paying for its own health care.

Costs included in an economic evaluation are both financial (total money spent) and economic (opportunity cost) [136]. Derivation of costs can be done via a bottom-up (micro-costing) approach where each ingredient for an intervention is separately costed or via a top-down (macro-costing) approach where the average cost of a program per capita is used as an approximate cost [137]. The range of costs included is dependent on the study perspective taken. For example, a provider perspective only includes costs that the health care provider will meet whilst a societal perspective will include other costs such as income losses due to lost productivity. The types of costs included thus depend on the objective of the assessment.

Deciding whether an intervention is cost-effective or not requires some sort of "decision rule," a guiding principle (preferably pre-specified) that defines the circumstances where a new intervention is accepted as cost-effective. However, developing such rules requires one to know the maximum amount that the payer would be willing to spend for an additional benefit. Consequently, very few health systems have yet explicitly implemented any cost-effectiveness thresholds and the question of what decision thresholds to use remains an area of debate [138, 139] [140]. There are generic rules that are adopted particularly in developing countries. For example, in 2001, the Commission on Macroeconomics and Health suggested that interventions costing less than three times GDP per capita for each DALY averted represented good value for money [141]. These thresholds were calculated with a demand-based approach and represent the amount that an individual is willing to pay for an additional year of healthy life. However, there are criticisms surrounding this "decision rule [142]. One of these is that these thresholds tend to make almost all health care programmes cost-effective. There are many other theoretical thresholds suggested in literature by institutions and individuals such as the US$150/DALY gained threshold. In the absence of one acceptable threshold, it is suggested that a range of thresholds be presented when determining cost-effectiveness. However, this approach could be confusing to individuals less experienced with cost-effectiveness analysis.

There are other ways of applying cost-effectiveness analysis to decision making other than the threshold concept. For example, "league tables" could be used which list cost-effectiveness results in descending order of cost-effectiveness. The most cost-effective programs (at the top of the table) can thus be implemented first; programs are funded up until the budget is exhausted. The number of programs funded are thus dependent on amount of resources available. Though attractive in theory, the league table requires comprehensive information on the costs and effects of the complete menu of programs, which is not usually available.

Suffice to say that whilst cost-effectiveness is critical in decision making, results from its analysis should not be prescriptive. They should be considered alongside other factors such as equity implications of the intervention, feasibility of implementation and budget

impact. There are recent advances to the 'traditional' CEA, namely the extended cost-effectiveness analysis (ECEA) approach [143] that could counteract most of the limitations of economic evaluations highlighted. For example, whilst the traditional CEA focuses solely on estimating the health impact per dollar spent of interventions [22], ECEA goes beyond CEA by explicitly considering the multiple dimensions and outcomes that ensue from health policies such as: 1) the health gains; (2) the financial risk protection benefits; (3) the total costs to the policy makers; and (4) the socio-economic distribution of health gains. Because of its multi-faceted nature ECEA is an attractive analytical option that should, if feasible, be considered when conducting cost-effectiveness analysis. Nonetheless, it is important to acknowledge that data limitations which are already prevalent in CEA are likely to be more severe in ECEA. Extended cost-effectiveness analysis requires disaggregated inputs per specific population subgroups and out-of-pockets costs borne by individuals and their families [143] and much of this data is not readily available in developing countries.

2.2.12 Characteristics of economic evaluation studies

Based on the literature search focussed on SSA, fifteen articles on interventions to prevent cardiovascular disease were found (Table 5). Forty-seven percent of these were published in the last 5 years indicating an increased interest in the area in recent times. However, with the exception of regional or multi-country analysis, studies that focused on single countries only covered four countries: South Africa, Ethiopia, Nigeria and Tanzania. We included studies focussed on WHO regions as it was easier to select the relevant findings for SSA. South Africa had the highest number of published economic evaluations which increased rapidly over the past 6 years and coincides with the set-up of the PRICELESS SA initiative from where several publications have emanated. This initiative aims to assist evidence based decision-making through use of economic evaluation techniques and one of its focus areas has been non-communicable disease. Primary prevention was the most frequent type of intervention assessed (n=13). Most of the primary prevention measures assessed prior to 2012 were personal interventions targeted at high risk groups, whilst interventions studied in the last 5 years have mainly been population-based indicating a shift in emphasis from person based to more

population-based strategies. All, but one study were based on modelling techniques, and the modelling approaches varied across countries from macro to microsimulation approaches. With the exception of a regional analysis which used modelling software that could be accessed upon request (http://www.who.int/choice/cost-effectiveness/tools/popmod/en/), the models used to conduct the analysis were not freely available. As such, it was challenging to assess whether the results could be easily replicated.

2.2.13 The evidence by intervention type

All of the studies reviewed presented positive results supporting one or all of the interventions assessed. It was not always clear what threshold of cost-effectiveness was considered for full economic evaluations. However, in some instances the thresholds proposed by the Commission on Macroeconomics and Health were used and these classify interventions as cost-effective if the cost per DALY averted is less than 3X GDP per capita; or very cost-effective if less than GDP per capita [141]. The challenge of using these thresholds has been dealt with more extensively in the previous section. To re-iterate one of the more important limitations: these thresholds tend to make almost all interventions assessed appear cost-effective.

Pharmacological primary prevention using an absolute risk approach

Six studies evaluated the cost-effectiveness of providing preventive medication on the basis of absolute cardiovascular disease risk [93, 144-148]. All, but one study indicated that this approach was either cost-effective or highly cost-effective in preventing CVD. Tanzania was the exception where the intervention was mostly cost-effective if targeted at individuals with greater than 40% CVD risk [145]. The results for Tanzania are a reflection of the much lower risk of CVD in the country at the time the study was conducted, relative to the risk in the other countries such as South Africa where risk had already escalated. The evidence base for the pharmacological interventions was based on evidence from meta-analysis of RCTs conducted in high income as well as LMICs,

supplemented by cost data from the countries under study. However, there have been concerns that the risk stratification tools such as the Framingham tool that are used to calculate risk scores have limitations when applied in LMICs countries as they were developed based on populations in high income countries [149]. A recent study conducted in South Africa shows that this is not necessarily the case as the study found a high level of correlation between a simple, non-laboratory-based CVD risk score (latest Framingham) and commonly-used laboratory-based risk scores [150].

Interventions targeting individual risk factors

Out of the 14 studies included in this review [22, 29, 30, 144-148, 151-156], 8 evaluated the impact of reducing individual risk factors for CVD by targeting high risk individuals [22, 29, 30, 151, 153-155, 157]. Five studies evaluated the use of pharmaceutical agents to lower blood pressure and cholesterol [145, 146, 148, 151, 153]. Blood pressure lowering agents were mostly cost-effective but the cost-effectiveness depended on the class of drugs assessed [151]. Diuretics were generally more cost-effective whilst brand name ACE-inhibitors were generally less cost-effective. When compared to the absolute risk approach, individual risk reduction with blood pressure lowering agents was less cost-effective indicating that an approach that is based on consideration of multiple risk factors is the optimal approach for CVD prevention. Statins, administered alone, showed less favourable cost-effectiveness results [152]. However, in combination with other drugs, for example as part of a polypill they had much higher cost-effectiveness. The remaining 3 studies assessed the cost-effectiveness of shifting the task of hypertension management within the community to community health workers [154]; using a diabetes capitation model to manage diabetes [155] and; implementing a 20% tax on sugar sweetened beverages to reduce diabetes incidence [157]. All 3 studies, conducted in South Africa, reported that the interventions assessed were cost-effective.

Tobacco control interventions

There was one study that assessed the impact of several tobacco control interventions in WHO regions including taxation, bans on tobacco advertisements and labelling regulations [144]. The results indicated that for the WHO Afro-E region, tobacco taxation

was by far the most cost-effective intervention, followed by a combination intervention of tobacco taxation and advertising bans.

Legislative measures to control salt and sugar intake

Five studies evaluated the impact of introducing legislation that controlled the non-discretionary or discretionary sugar and salt intake in commonly consumed foods [22, 29, 30, 144, 157]. All studies found that mandatory legislation was a highly cost-effective strategy for CVD prevention and dominated mass media campaigns and other educational interventions to reduce salt consumption. However, in most of the studies, strong assumptions on effects were made based on available data from high income countries. However, these assumptions need further empirical testing.

2.2.14 Country responses to CVD prevention: Illustrative examples

Although many countries in SSA seem to recognise the importance of addressing CVD, the number of countries that have taken steps towards implementing CVD prevention strategies that can have a population-level impact are few and for those that have, the plans are uncoordinated with no clear understanding of the level of investment needed for each intervention strategy. South Africa has drafted two strategic plans that relate to non-communicable diseases (including CVD) - the Strategic Plan for the Prevention and Control of NCDs 2013 – 2017 [129], and National Strategy for the Prevention and Control of Obesity 2015 – 2020 [158]. These strategic plans outline ambitious targets to: reduce by at least 25% the relative premature mortality (under 60 years of age) from NCDs by 2020; reduce obesity prevalence by 10 per cent by 2020; reduce mean population intake of salt to <5 grams per day by 2020; and reduce the prevalence of people with raised blood pressure by 20% by 2020 (through lifestyle and medication). Following public release of these documents and increasing evidence that population-based interventions are a highly cost-effective approach to controlling disease, two population-based policies targeting reduction of salt and sugar content of commonly consumed foods and beverages have been proposed, one of which is already gazetted. Section 15(1) of the foodstuffs, cosmetics, and disinfectants Act, 1972 (act 54 of 1972),

stipulates regulations relating to the reduction of sodium in certain foodstuffs. The foodstuffs specifically mentioned include “bread, butter spread, fat spread, processed meats, raw processed meat sausages and ready to eat savoury snacks. According to these regulations the first total sodium reductions should be effected by 30 June 2016; for bread that means total sodium content of bread should be 400mg (per 100g of bread) by that date”. A further reduction of 20mg should be achieved by June 2019. On 8 July 2016, the National Treasury of South Africa published for public comment a policy paper and proposals on the taxation of sugar-sweetened beverages (SSBs) (excludes 100% fruit juices, unsweetened milk). The proposed tax for SSBs which apply nutrition labelling will be 2.29 cents per gram of sugar; whilst those that do not apply nutrition labelling will pay a higher tax based on the assumption that they include at least 15.152 grams of added sugar per 100 ml [159]. The latter could further incentivise proper labelling which itself is considered an effective intervention for raising consumer awareness on dietary components of food [160]. In addition to these interventions, there are pilot studies on integrated chronic disease care in South Africa which aim to leverage off the success of HIV/AIDS management at government supported primary care clinics for NCDs [161]. Preliminary findings on the success of the integrated chronic disease management programme in Agincourt sub-district indicate that this model does not yet benefit patients receiving treatment for hypertension as a result of occasional stock-outs of anti-hypertension drugs and malfunctioning BP machines [162]. These findings have broad implications for scale-up across the country where integrated chronic care is currently perceived to be a solution to the challenge of effective risk factor management.

In Mauritius, in response to rapidly escalating risk factors, a nationwide strategy to address NCDs was implemented between 1987 -1992 to address NCD risk factors [124]. The complex intervention included changing the composition of commonly used cooking oil from palm oil to entirely soya bean oil which is high in unsaturated fats. The other components of the programme included extensive use of the mass media; and widespread community, school, and workplace health education activities. Currently there are plans to implement a further multi-pronged nationwide campaign, involving “the use of mobile clinics or medical teams to address primary prevention at community level (including schools and workplaces), and a community-based network of health

centres to address prevention needs at the secondary level, and a structured prevention programme at the tertiary level (involving specialized units in all regional hospitals)" [163]. Furthermore, following a recent survey, which revealed that salt intake of 7.9 g was much higher than the WHO recommended limits, the Ministry of Health and Quality of Life undertook a dialogue with bakery owners to reduce salt content in bread [164]. However, details on the extent of reduction or any incentives to promote compliance are not available.

In Ghana, several policy and programme initiatives have been pursued since 1995 but with limited success due to challenges, mainly of funding for NCD control [165]. Interventions that have been proposed by the Department of Health include a package of priority health services including treatment of hypertension and diabetes; introduction of a smoking ban in public health facilities; training multidisciplinary teams in regions and districts to improve the care of diabetes, and health promotion campaigns organised and led by non-governmental organizations. There are general plans to institutionalise programmes for promoting healthy settings i.e. "healthy homes, schools, workplaces and communities. Healthy schools will be promoted through fostering collaboration among the Ministry of Health, Ghana Education Sector and private schools to facilitate the adoption of healthy lifestyles among students through the curriculum, physical education, environmental sanitation and the promotion of healthy eating" [165].

Whilst a few examples have been chosen to illustrate country responses for CVD control in SSA, many other countries have drafted national response strategy documents. However, these are not always accompanied by practical action to implement relevant polices which raises key issues on policy translation. Most health systems in SSA are still oriented towards infectious diseases, acute and curative care and re-orienting the health system (as well as resources) towards NCD (including CVD) management remains a major challenge. Such interventions will require a focussed approach to chronic care. Furthermore, there are practical concerns that whilst interventions for reducing infectious diseases are much clearer, it is more difficult to grasp which strategies or combination of CVD prevention strategies should be implemented, and in what order, to give governments the best value for every dollar spent.

2.2.15 Summary, important gaps, justification for current study

The empirical data on CVD prevention in SSA has increased over the past few years. Yet key data on which to base firm, specific recommendations is still missing. In the literature review, I noted that whilst the evidence on burden of key CVD risk factors has increased in SSA, there is still limited evidence on the impact of preventive interventions in these settings.

Improving the data and evidence base to inform better decisions on policies and programmes is a strategic priority. Currently, key data on the epidemiology of CVD, costs of treating current NCDs, and impacts of preventive interventions are either missing or unreliable. This undermines optimal decision-making. Better data would allow decision-makers to make resource allocation decisions that make the most out of scarce resources. Because available health information systems at a country level do not always collect all the indicators necessary to inform decision-making, it is important to aggregate information from other sources, namely, health and demographic surveillance systems which collect routine data in well-defined populations. Whilst the latter occurs regularly and comprehensively for collection of mortality data, this could be expanded to understanding cost-effectiveness of interventions in these settings.

Prioritising prevention of premature deaths would appear to be a strategic goal. The section on burden of CVD demonstrates that South Africa and SSA more generally experience high levels of premature CVD deaths. Rather than focussing on overall mortality across all age-sex groups, it would be worthwhile to understand how best we can reduce the level of premature mortality and associated economic losses as well as household distress that come with it. There is ample data to direct us to high-risk groups where targeted interventions are needed. In particular, adolescent girls would be a priority group as early-onset obesity is high in this population group.

Primary prevention as a priori. The extensive literature on CVD risk factors shows that hypertension, obesity, diabetes and to some extent physical inactivity are widespread in SSA, and have increased dramatically in rural areas. Notwithstanding the limited evidence on cost-effectiveness of population-wide prevention initiatives in SSA, data derived from South Africa indicates that such strategies have potentially high pay-offs for governments. Also noteworthy is that higher returns are achieved when vulnerable population groups are reached [22].

Several critical questions about the economics of CVD suggest themselves based on the findings of this literature review. These include: What is the full economic cost of CVD to national and local governments of treating or not treating CVD? How do the costs vary by country, province, rural or urban area? What are the costs and consequences of alternative CVD interventions, including the costs of doing nothing or continuing with the status-quo? Based on modelling and projections, what are the projected lifetime costs or savings of preventing CVD and what are the immediate budgetary implications of choosing any of the alternative options? What are the costs of sustaining improved health behaviours?

The body of work covered in this thesis aims to address such questions in an integrated way for a well-defined rural population living in a typical sub-district of South Africa. I approach the questions by first establishing the current burden of CVD in rural South Africa in terms of both mortality (premature) and morbidity. The current economic costs of prevalent stroke are then established before modelling the future costs and impacts of implementing alternative preventive interventions.

Table 5: Summary of economic evaluation studies in sub-Saharan Africa, 1990 to 2016.

Authors, year and title	Setting, study type	Aim	Intervention Description	Study outcome	Main economic findings	Comments
Tolla et al.,2016 [93]Prevention and treatment of cardiovascular disease in Ethiopia: a cost-effectiveness analysis	Ethiopia, Modelling study	To assess cost-effectiveness of prevention and treatment of ischemic heart disease (IHD) and stroke in an Ethiopian setting	Fifteen single interventions and sixteen intervention packages	DALYs averted	Combination drug treatment for individuals having >35 % absolute risk of a CVD event in the next 10 years is the most cost-effective intervention	Representative of the setting of interest; assumptions clearly stated
Manyema et al., 2016 [30], Modelling the potential impact of a sugar-sweetened beverage tax on stroke mortality, costs and health-adjusted life years in South Africa	South Africa, Modelling study	To determine impact of a 20% sugar tax on stroke-related burden and economic costs in South Africa	Legislative reduction of sugar content in sugar-sweetened beverages	Stroke deaths averted Stroke related HALYs averted Costs averted	Cumulatively, over 20 years 72 000 deaths, 550 000 stroke-related health-adjusted life years and over ZAR5 billion, (USD400 million) in health care costs are averted (USD296-576 million)	Representative of the setting of interest; assumptions clearly stated
Manyema et al., 2015 [157], Decreasing the Burden of Type 2 Diabetes in South Africa: The Impact of Taxing Sugar-Sweetened Beverages	South Africa, Modelling Study (Life-table based approach)	Impact of a 20% sugar tax on burden of diabetes in South Africa	Legislative reduction of sugar content in sugar-sweetened beverages	DALYs averted; Costs Averted. Type 2 diabetes mellitus deaths averted	Cumulatively over 20 years, approximately 21 000 (95% UI: 14 000–29 000) adult T2DM-related deaths, 374 000 DALYs attributed to T2DM (95% UI: 299 000–463 000) and over ZAR10 billion T2DM healthcare costs (95% UI: ZAR6.8–14.0 billion) equivalent to USD860 million (95% UI: USD570 million–USD1.2 billion) may be averted.	Modelling of outcomes is given in detail and more transparent but estimation of cost parameters is not discussed in detail and it is difficult to understand what was fully captured
Watkins et al., 2015 [22], Cardiovascular disease and impoverishment	South Africa, modelling study	An extended cost-effectiveness analysis study to determine the impact of the proposed salt	Informational campaign to reduce discretionary salt use Mandatory regulation	CVD deaths averted Catastrophic health expenditure averted	Policy potentially averts 403 deaths and 1680 cases of CVD a yr Approx. US$2.5 million is saved per yr by govt	New method that accounts for effects of financial protection of interventions not

Authors, year and title	Setting, study type	Aim	Intervention Description	Study outcome	Main economic findings	Comments
averted due to a salt reduction policy in South Africa: an extended cost-effectiveness analysis		reduction policy in South Africa	of maximum salt content in commercially produced foods	Health systems costs averted Total govt. costs averted	Programme costs per capita = US$0.01	just the cost per health gain. Generally applicable to many developing country settings where policies have equity impacts
Gaziano et al., 2014 [154], Hypertension education and adherence in South Africa: a cost-effectiveness analysis of community health workers	South Africa, Markov modelling study	To determine whether training community health workers (CHWs) about hypertension in order to improve adherence to medications is a cost-effective intervention	CHWs visit patients with uncontrolled hypertension two times a year	DALYS averted	Annual cost of CHW intervention is $8 per patient. Approximately 2% reduction in CVD events over a life-time is expected If non-fatal CVD events are incorporated, lifetime costs are $6.56 per patient. The CHW intervention leads to an incremental cost-effectiveness ratio of $320/DALY averted. At an annual cost of $6.50 or if the blood pressure reduction is 5 mmHg or greater per patient the intervention is cost-saving.	Task-shifting to lower cadres of staff an important intervention that is applicable to many resource limited settings in SSA
Volmink et al., 2014 [155], Applying a private sector capitation model to the management of type 2 diabetes in the South African public sector: a cost-effectiveness analysis	South Africa, modelling study	Determine cost-effectiveness of adapting a private sector diabetes management programme (DMP) to the South African public sector.	Each patient enrolled in the DMP is offered a service package that adheres to 'Minimum Care Guidelines.' Medical aid schemes pay a monthly premium, in advance, for this care at a rate that is negotiated on an annual basis. Service providers are liable for any costs associated with diabetes-related emergencies (such as	Life years gained	Incremental cost-effectiveness ratio (ICER) of ZAR 8 356 (USD 1018) per life year gained (LYG) for the DMP against the usual practice model. National roll-out could result in cumulative gain of 96 997 years of life (95% CI 71 073 years – 113 994 years).	The authors were willing to share their modelling tools as such it was easy to understand the modelling approach taken

Authors, year and title	Setting, study type	Aim	Intervention Description	Study outcome	Main economic findings	Comments
			diabetic ketoacidosis)			
Bertram et al., 2012 [29], Reducing the sodium content of high-salt foods: Effect on cardiovascular disease in South Africa	South Africa, Comparative Risk Assessment Study	To determine number of fatal CVD events (stroke, ischaemic heart disease and hypertensive heart disease) and non-fatal strokes that would be prevented each year following a reduction in the sodium content of bread, soup mix, seasoning and margarine	Reductions in sodium content of selected foods that would decrease the average salt intake by 0.85 g/person/day	CVD deaths averted Cost averted	An estimated 7 400 fewer CVD deaths and 4 300 less non-fatal strokes per year would occur compared with 2008 figures. Cost savings of up to R300 million would also occur	Strength of study is use of local data to estimate salt intake etc. However, the cost estimates were based on inflation adjustments of a study conducted in 1991.
Ortegon et al., 2012 [144], Cost effectiveness of strategies to combat cardiovascular disease, diabetes, and tobacco use in sub-Saharan Africa and South East Asia: mathematical modelling study	WHO regions, modelling study	To determine the relative costs and health effects of interventions to combat cardiovascular disease, diabetes, and tobacco related disease	Variety of individual based and population-based strategies assessed including: tobacco taxation (40%, 60%); banning advertising of tobacco products, CVD-1: mandatory Salt reduction in processed foods via voluntary agreement; CVD-2: Salt reduction in processed foods via legislation; CVD-3: Health education through mass media Primary prevention, targeting individuals with antihypertensive medication, antithrombotic therapy etc. Treatment based on absolute risk of a cardiovascular event* in next 10 years Acute treatment:	Cost per disability adjusted life year (DALY) averted, expressed in international dollars ($Int) for the year 2005	Combination drug therapy for people with a >25% chance of experiencing a cardiovascular event over the next decade, either alone or together with specific multidrug regimens for the secondary prevention of post-acute ischaemic heart disease and stroke (<$Int150 and <$Int230 per DALY averted in AfrE and SearD respectively); and retinopathy screening and glycaemic control for patients with diabetes (<$Int2100 and <$Int950 per DALY averted in AfrE and SearD respectively	Strength of the study is its comparative analysis of individual and population-based interventions

Authors, year and title	Setting, study type	Aim	Intervention Description	Study outcome	Main economic findings	Comments
Ker et al., 2008 [148], Decision-making using absolute cardiovascular risk reduction and incremental cost-effectiveness ratios: a case study	South Africa, Modelling study	Single person simulation study. Hypothetical patient aged 56 years, male with following specified biological markers: , BP 160/100mmHg, total cholesterol 6 mmol/l, low-density lipoprotein (LDL) cholesterol 4.2 mmol/l, and high-density lipoprotein (HDL) cholesterol 0.7 mmol/l	Patient given alternative drugs and risk profile based on Framingham risk score recalculated each time a) Hypertension treatment with perindopril-indapamide combination (4 mg/2.5 mg);b) Lipid treatment Atorvastatin 10 mg; c) Lipid treatment Atorvastatin 40mg d) Hypertension treatment and lipid treatment Atorvastatin 10mg Comparator was no drug treatment	% of CVD risk reduction	*Cost per % risk reduction:* a. R21.35 - antihypertensive treatment strategy b. R22.93 – statin treatment c. R12.77 – high dose statin d. R23.84 – combination treatment	Based on a simulated case study of one male patient. Only representative to the population of males with same clinical characteristics
Lim et al., 2007[146], Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs	Multinational including South Africa, Modelling study	Assessed impact of pharmaceutical interventions on CVD incidence when targeted at high risk groups aged 40-79 years	Individuals w/ existing CVD would receive aspirin, an angiotensin-converting-enzyme inhibitor, a β blocker, and a statin. Individuals w/o existing CVD but who are at high risk would receive aspirin, an angiotensin-converting-enzyme inhibitor, a thiazide, and a statin	CVD incidence	The intervention could avert almost 18 million deaths in 23 low-income and middle-income countries over the next 10 years. The financial resources needed to scale-up this intervention are an average investment per year of around $5 billion, or $1.08 per head. In South Africa, intervention would cost approx.. US$2 per capita but total cost as proportion of current health expenditure would be lower than 0.5%	More generalizable for LMICs. Standardised methodology used to assess CE in multiple countries and sensitivity analysis conducted

Authors, year and title	Setting, study type	Aim	Intervention Description	Study outcome	Main economic findings	Comments
Robberstad et al., 2007 [145], Cost-effectiveness of medical interventions to prevent cardiovascular disease in a sub-Saharan African country – the case of Tanzania	Tanzania, modelling study	Pharmaceutical interventions targeted at individuals with variable risk of CVD classified as low, medium & high.	14 medical interventions of primary prevention of cardiovascular disease in Tanzania, including Acetylsalicylic acid, a diuretic drug (Hydrochlorothiazide), a ß-blocker (Atenolol), a calcium channel blocker (Nifedipine), a statin (Lovastatin) and various combinations of these, including a hypothetical polypill	DALYs averted over a lifetime	C/E ratio ranged from 85 USD per DALY for Hydrochlorothiazide to 4589 USD for a polypill in low risk Patients Therefore preventive cardiology not very CE in this setting	Representative of similar settings in SSA and modelling technique well-described
Amira et al.,2006 [151], Antihypertensive pharmacotherapy in a developing economy: pattern, acquisition costs and conformity to international guidelines in a tertiary-care setting	Nigeria, Cross-sectional descriptive study	Anti-hypertensive drugs to patients with HBP attending a tertiary centre between Oct 2002-Dec 2002	*Drug (no. taking it)* CCB (16) DV (8) -blockers (8) ACEI (10) -MD (8 Reserpine+clopamide (8) DV+ -MD (21) DV+CCB (24) DV+ -blockers (8) CCB+ACEI (24) CCB+ -blockers (13) CCB+ -MD (8) DV+CCB+ -blockers (12) DV+CCB+ -MD (9) CCB+ACEI+ -MD (11)	Cost-effectiveness assessed by determining annual cost of drugs divided by proportion of patients who are controlled on drug	Diuretics were most cost-effective but least prescribed. Brand name ACE-Is and CCB costs were prohibitively high and showed poor relative cost-effectiveness	Study duration very short and sampled a tertiary hospital where the most uncontrolled cases are usually referred & combination therapy advised
Gaziano et al., 2005 [154], Cost-effectiveness analysis of hypertension guidelines in South Africa: absolute risk versus blood	South Africa, modelling study	To determine cost-effectiveness of using absolute risk approach vs. blood pressure levels to manage CVD	Compared 6 strategies for initiation of drug treatment--2 different blood pressure levels (160/95 and 140/90 mm Hg) and 4 different levels of absolute CVD risk		Incremental cost-effectiveness ratios for treating those with 10-year absolute risk for CVD >40%, 30%, 20%, and 15% were 700 dollars, 1600 dollars, 4900 dollars, and 11,000 dollars per	

Authors, year and title	Setting, study type	Aim	Intervention Description	Study outcome	Main economic findings	Comments
pressure level.			over 10 years (40%, 30%, 20%, and 15%)--with one of no treatment		quality-adjusted life-year gained, respectively. Strategies using targeted blood pressure levels were costly and less effective compared to strategies based on 15% absolute CVD risk	
Caro et al., 1999 [152], International economic analysis of primary prevention of cardiovascular disease with Pravastatin in WOSCOPS	South Africa (as one of 5 countries studies. Others are UK, Canada, Sweden, Belgium), modelling study	To estimate the cost effectiveness of primary prevention with pravastatin compared to diet alone using a generalised cost-effectiveness model	Pravastatin for primary prevention in hypertensive or high risk males	Cost per life year gained	Pravastatin considered efficient as it fell below $25,000 per LYG. However, cost per LYG close to 3xGNI per capita for South Africa suggesting the intervention could have been cost ineffective	
Edwards et al., 1998 [153], Improving cost-effectiveness of hypertension management at a community health centre	South Africa, Observational Trial (before/ after study), conducted between Jan 1992-Dec 1992	Evaluate the impact of introducing treatment guidelines and restricting availability of less cost-effective antihypertensive drugs on prescribing patterns, costs of drug treatment and blood pressure (BP) control		1. Mean no. of drugs prescribed per patient. 2. Proportion of prescriptions for: each major class of antihypertensive drug; restricted availability and freely prescribable drugs; and more and less cost-effective drugs. 3. Mean monthly cost of drugs prescribed per patient. 4. Mean blood pressure and proportion of BP readings controlled (< 160/95 mmHg) or uncontrolled (> or = 160/95 mmHg)	Mean monthly drug costs per patient decreased significantly by R1.99 (24.2%) from R8.24 to R6.25 Prescribing of most cost-effective drug increased by 51% Proportion with controlled BP did not change significantly	Not a full economic evaluation. Because outcomes were virtually the same the study gives cost-minimisation results. Study population is mainly coloured population in Cape Town of lower SES therefore generalisability to the wider population likely low

Chapter 3 Methods

This chapter describes the overall methodological approach for the four inter-linked studies. Details on the specific methods are provided in the appended published papers (1, 2, 3), and in Paper 4 (manuscript under review).

3.1 Overview and summary of research methods

3.1.1 General Study Population

The population of interest in this study is the rural[10] population of South Africa [166]. The definition of "rural" employed in this study is based on the Municipal Infrastructure Investment Framework (MIIF) which divides local and metropolitan municipalities into five groups (Table 6). These are: metropolitan municipalities/large cities (A); secondary cities (B1); municipalities with a large town as its core (B2); municipalities with small towns (B3); and municipalities that are predominantly rural (B4) [167]. This study is concerned with B4 municipalities of which 70 municipalities, with a population of approximately 13 million people (quarter of total population), fall under this category (Table 7).

A visual presentation of the age and gender structure of the population of 'predominantly' rural South Africa is given in the population pyramid (Figure 5). When looking at the population in different age categories for this context of this study, it is useful to focus on four broad age categories: 0-14 years; 15-64 years; over 65 years and the group consisting of individuals 40 years and older. The 0-14 years and 65+ age groups (comprising 43% of the population) provide a proxy indicator of the burden of children and elderly in those who are potentially economically active (15-64 years old).

[10] Due to the large-scale re-demarcation of municipal boundaries that removed the administrative distinction between urban and rural areas after apartheid, there is no universally accepted definition for "rural" in South Africa.

Another age indicator of importance for this study is the size of the age category (40+ years) which comprises 24% of the population. Published guidelines for the cardiovascular disease risk assessment recommend systematic screening [168][11] for CVD begin at age 40 for men and 50 for women [169, 170] whilst other guidelines recommend commencing cardiovascular risk screening at 40 years for both men and women. Therefore, the importance of this age group lies in its resembling the population that may benefit from systematic screening of cardiovascular disease risk whilst flagging potential resource demands of doing so. Compared to the age-sex structure for the entire South Africa, rural South Africa tends to have a higher proportion of population that is dependent on the economically active. In 2011, approximately 30% of the population of entire South Africa was aged between 0-14 years whilst a further 5% was over 65years old (http://www.statssa.gov.za/census/census_2011/census_products/Census_2011_Census_in_brief.pdf). However, in both rural South Africa and the entire South Africa, men tend to live longer than women.

Table 6: Classification of municipalities in South Africa (National Treasury, 2011)

Class	Characteristics	Municipalities country-wide (N)
Metros	Category A municipalities	6
Secondary Cities	All local municipalities referred to as secondary cities	21
Large Towns	All local municipalities with an urban core. There is huge variation in population sizes amongst these municipalities and they do have large urban dwelling population.	29
Small Towns	They are characterised by no large town as a core urban settlement. Typically, these municipalities have a relatively small population, a significant proportion of which is urban and based in one or more small towns. Rural areas in this category are characterised by the presence of commercial farms, as these local economies are largely agriculturally based. The existence of such important rural areas and agriculture sector explains their inclusion in the analysis of rural municipalities.	111
Mostly Rural	These are characterised by the presence of at most one or two small towns in their areas, communal land tenure and villages or scattered groups of dwellings and typically located in former homelands	70
Districts	District municipalities that are not water services providers	25

[11] Systematic risk assessment is defined as a screening-like programme involving a predetermined selection process of people, compared with opportunistic risk assessment where case finding tends to happen among individuals already presenting at health facilities for other conditions.

Districts	District municipalities that are water service providers	21

Table 7: Total population figures by age and sex in 70 “mostly rural” municipalities of South Africa (Statistics South Africa, 2011)

Age Group	**Male**	**Female**	**Total**
0 – 4	861 642	850 647	1 712 289
5 – 9	781 287	771 497	1 552 784
10 – 14	788 169	743 658	1 531 827
15 – 19	814 390	792 860	1 607 250
20 – 24	593 558	630 462	1 224 020
25 – 29	424 774	515 353	940 127
30 – 34	312 116	401 640	713 756
35 – 39	262 005	360 947	622 952
40 – 44	215 597	323 176	538 773
45 – 49	199 145	316 641	515 786
50 – 54	176 989	274 667	451 656
55 – 59	156 852	233 453	390 305
60 – 64	134 876	200 053	334 929
65 – 69	92 362	153 551	245 913
70 – 74	77 401	138 986	216 387
75 – 79	41 936	104 697	146 633
80 – 84	29 739	83 493	113 232
85+	23 306	66 402	89 708
Total	5 986 137	6 962 183	12 948 320*

***Represents a quarter of the entire South African population in 2011; the latter was estimated at 51,770,560 in 2011.

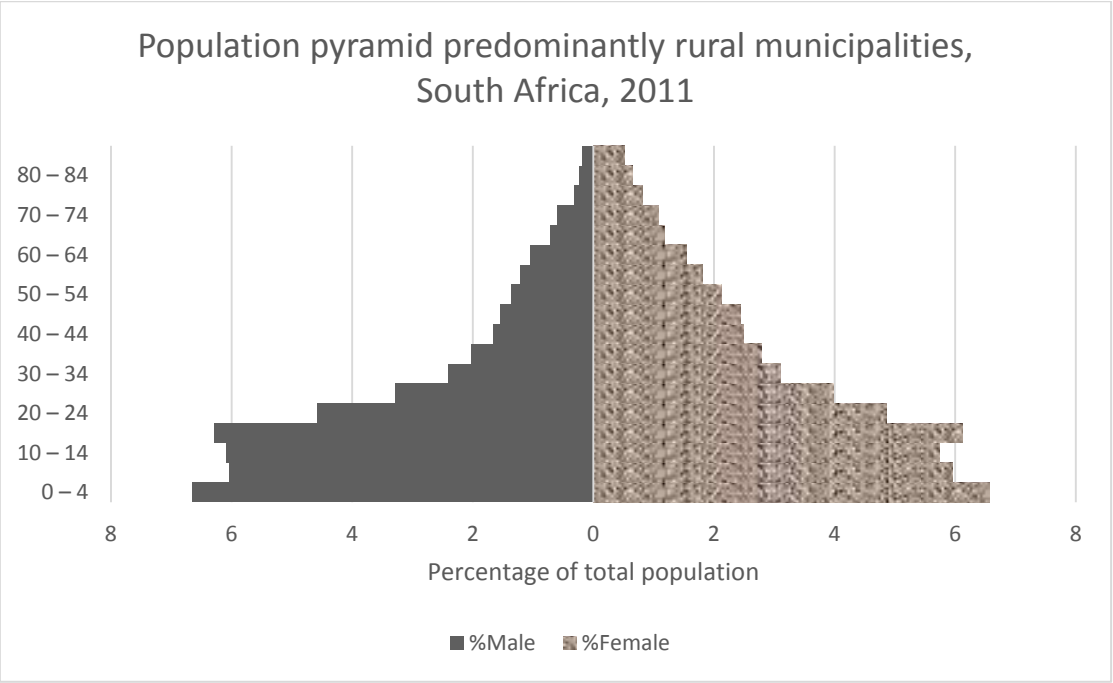


Figure 5: Population pyramid shows the age and gender population distribution of 'predominantly' rural South Africa, based on census 2011 estimates.

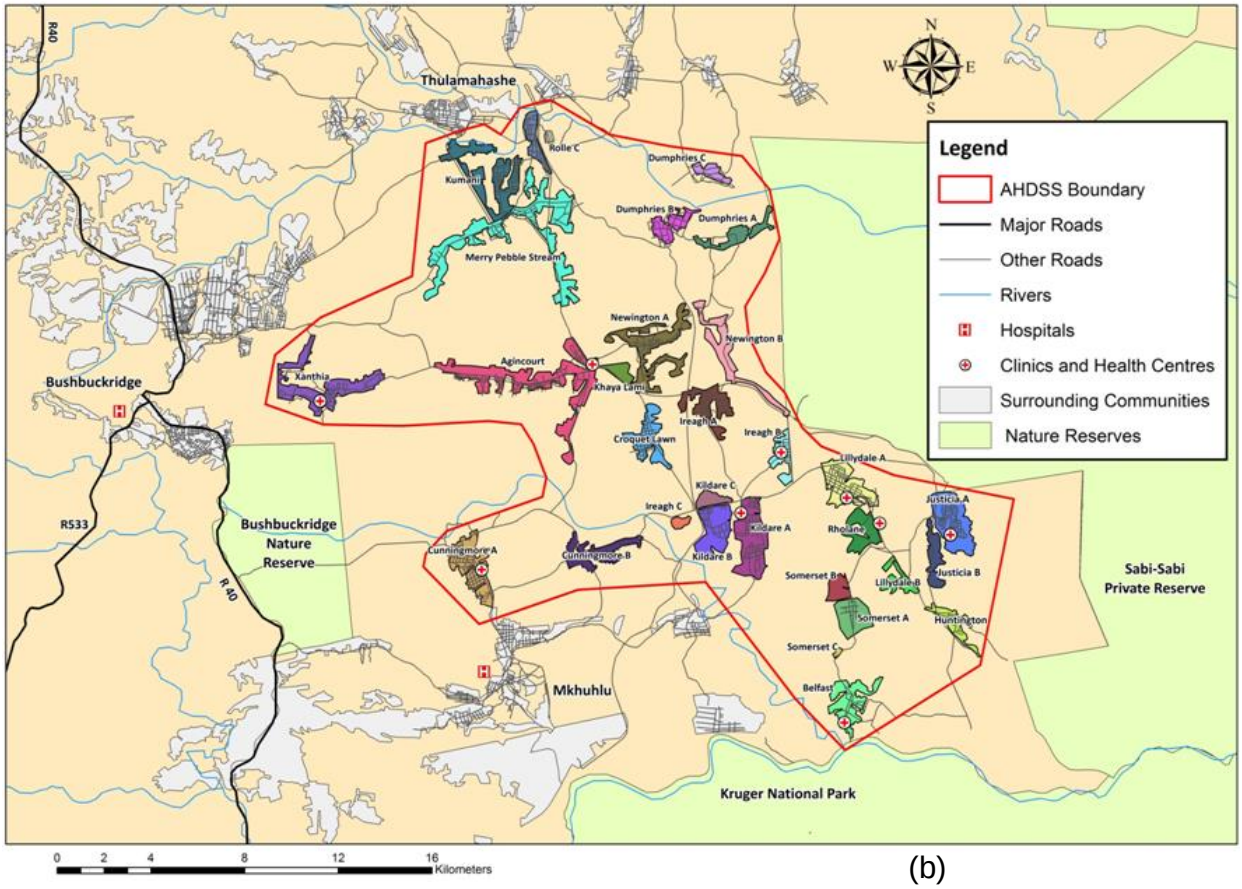
*The wider base indicates a population that is predominantly young and growing.

3.1.2 Specific Study Population

The Agincourt sub-district, measuring some 420 sq. km, and covering a population of approximately 116,000 people is the population upon which most of the analysis in this thesis is based (Figure 6; Figure 7). Agincourt sub-district falls under Bushbuckridge, a B4 municipality. Detailed descriptions of this study site have been given in each of the individual papers (1 to 4) and in other published papers [171].

(a)

Agincourt Study Site and Surrounding Area



(b)

Figure 6: Maps show (a) location of Agincourt study setting regionally in north-east South and Southern Africa and (b) boundaries of the study site/sub-district

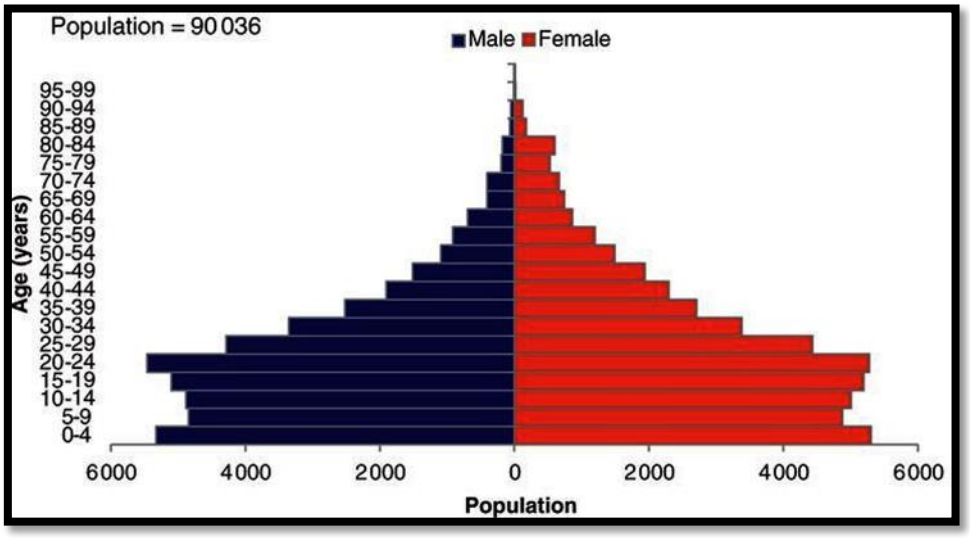


Figure 7: Population pyramid of the Agincourt HDSS population: de jure population, 1 July 2011; population = 90 036 (Adapted from Kahn et al, 2011)

*The population pyramid has a similar structure to that of 'entire rural South Africa' as shown in Figure 5 above

Agincourt sub-district has characteristics similar to many other rural South African populations. Despite improvements in the electricity grid and tarred road network, social infrastructure and utilities remain limited while schooling is sub-optimal. There is no formal sanitation, piped water to communal standpipes is erratic (despite commissioning of the Nyaka dam) and electricity which is available on a system of prepaid vouchers is affordable to a minority. The high unemployment within the HDSS results in temporary labour migration of both men and women. Temporary labour migration amongst adults aged 20-59 years was estimated at 25–35% amongst females and 50–70% amongst males [172]. There are two public health centres, one public-private health centre supporting community-based HIV/AIDS and TB management and seven satellite clinics in the site. The Agincourt community is served by three district hospitals that are approximately 25–60 km away.

The health profile of the Agincourt population is characterized by the "persistent burden of TB and HIV/AIDS, high maternal and child morbidity and mortality, and increasing non-communicable diseases" [173]. Using 2001–03 as the base year, the probability of dying from NCDs within the sub-district increased from 21.9% in 2001-03 to 36.5% in 2011-13 [174]. Mortality was higher amongst females compared to

males. On the other hand, deaths due to HIV/AIDS and TB have steadily declined over this period from 46.2% in 2001-03 to 26.6% in 2011-13. There are unprecedented levels of high blood pressure and obesity, particularly amongst middle aged women and this is fostered by lifestyle and dietary changes [108, 175].

3.1.3 Health and socio-demographic surveillance system (HDSS)

Agincourt sub-district is completely covered by a HDSS which has been in operation since 1992. Essentially, the HDSS provides data on who has lived in the study site since then, who has moved in (through birth or in-migration) and who has moved out (through death or permanent out-migration). This data is updated annually through a yearly census and vital events update. Verbal autopsies are also conducted using previously validated instruments to ascertain probable causes of deaths. The surveillance thus involves prospective follow-up of the entire population, which depending on research focus can allow analysis at the individual, household, or neighbourhood levels and permit disaggregated analysis by age-sex cohorts [173]. Additional data on labour participation and educational status have been collected at different time intervals to complement demographic data and provide contextual information. In addition to the annual censuses, the Agincourt centre's research infrastructure is used as a platform to 'nest' additional specialized studies that generate much-needed additional health data. Examples include the SASPI study on stroke [84] and the *Ha nakeke la* study on risk factors for CVD [175]. Box 1 below gives a summary of why the Agincourt HDSS is a strategic choice for embedding the work covered in this thesis.

Box 1

Overview - Agincourt HDSS as a strategic choice for embedding this work

- The geographically well-defined population has a known denominator; epidemiological rates are therefore reliable.
- Specialised ‘nested’ studies provide useful epidemiological input parameters on prevalence.
- Other data linkage initiatives, e.g. HDSS-clinic-linkage project that links individuals’ HDSS records with their clinic records producing an augmented data source on utilization of health facility services.
- It is possible to track changes in disease burden over time.

3.2 Data Collection and Analysis

Table 8 provides an overview of the data collection and analysis methods used in each of the four studies that are the basis of this thesis. Most of the data were requested from the Agincourt HDSS; the HDSS data is routinely entered through an MS SQL Server relational database management system. There are several quality control checks at different phases of the data collection process including fieldworker self-checks, supervisor random checks and verification of data by a dedicated quality checker before data entry within the HDSS. A data request form (appendix F) was completed for data for papers 1, 2 and 3 and this data was provided in Stata format. Data collection sheets were created for paper 4 (appendix G) to collect intervention effectiveness estimates and these data were identified through a systematic review of the literature.

Table 8: Overview of data collection and analytic methods employed in study

	Paper 1	**Paper 2**	**Paper 3**	**Paper 4**
Objective	Estimate burden of stroke in terms of incidence, mortality, disability adjusted life years (DALYs)	Estimate stroke burden attributable to high blood pressure, excess weight, raised blood glucose, elevated cholesterol	Estimate direct economic costs of stroke treatment in Agincourt HDSS	Determine cost-effectiveness of alternative CVD prevention interventions in a rural South African population
Data Collection - Data Received	Data requested - April 2013 Data received - February 2014	Data requested - April 2013 Data received - October 2014	Data requested - April 2013 Data received - February 2014	Data collected May 2013 – continuously updated till June 2016
Data Sources[12]	Agincourt HDSS census data; Agincourt cause of death data, SASPI study and secondary	Agincourt HDSS (*Ha Nakekela "We Care"* study) – a cross-sectional HIV/cardiometabolic risk factor survey in	SASPI study, South African medicine price registry, District Health Barometer[13]	Secondary literature

[12] An overview of the quality of data received is in the discussion section.
[13] An initiative of the national NGO, Health Systems Trust (HST), which works closely with the Department of Health.

	Paper 1	Paper 2	Paper 3	Paper 4
	literature sources	2010 – 2011 using an age-sex stratified random sample of those aged 15+ in the Agincourt sub-district		
Analytical approach	Followed World Health Organization's burden of disease analysis approach Dismod II software used to estimate incidence. Further analysis conducted in Excel	Used established WHO Comparative Risk Assessment Methods Analysis conducted in Excel, using add-in program for excel that performs numerical integration	Followed standard cost-of-illness methods based on bottom-up, prevalence-based costing. All analysis conducted in Excel	Developed mathematical model custom-designed for the population under study Model was spreadsheet based with add-in @Risk software for conducting monte-Carlo simulations

3.3 Ethical considerations

Ethical approval for the study was granted by the Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand, Johannesburg, South Africa for both the MRC/Wits Rural Public Health and Health Transitions Research Unit's (Agincourt) Health and Socio-Demographic Surveillance System, add-on modules and nested studies (Clearance certificate no. M131050; appendix H).

3.4 Applying existing methodological approaches and tools for addressing research objectives in papers 1 to 3

Standard, validated approaches for conducting burden of disease analyses, cost-of-illness analysis and comparative risk assessment were followed for each of the study papers 1-3. Existing modelling software and tools, most of which are freely available from developers were also utilised. The section below details these methodological approaches, with additional data provided in each of the appended published papers.

3.4.1 Burden of disease analytic approach to estimate incidence, mortality and disability-adjusted life years

The GBD approach, first published in 1996, that quantifies burden of disease in terms of both mortality and morbidity was used in this research. To capture the combined impact of mortality and morbidity, summary measures of population health including the Disability-Adjusted Life Year (DALY) were developed. The DALY is derived by summing years of life lost due to premature mortality (YLL) with years lived with disability (YLD) i.e.

DALY = YLL + YLD

Conceptually, the DALY addresses 2 critical questions: (i) how long people in good health "should" be expected to live, and (ii) how years lived with poor health or disability compare with years in good health [176].

The YLL metric is the sum of additional years that victims of disease would have lived if they had completed the life expectancy attributed to their age (as assessed by a standard population) at the time of their death. The GBD 2015 study takes a slightly different approach. It uses normative life tables based on the lowest death rates for each age group among geographies with total populations greater than 5 million [44]. Cause-specific YLLs are then constructed by multiplying cause-specific deaths by the life expectancy at the age of death (i.e., 86·59 years at age 0 years; 23·79 years at age 65 years). To reflect the notion that society prefers to benefit now rather than in the future, YLLs are discounted. To do this, the value of a year of life is generally decreased annually by a fixed percentage. For example, with a 3% discount rate, the YLL is:

$$YLL = \frac{N}{r}(1 - e^{-rL})$$

Where:

N = number of deaths.

L = standard life expectancy at age of death (years).

r = discount rate (e.g. 3% corresponds to a discount rate of 0.03)

Similarly, the YLD metric which expresses the consequences of living with less than perfect health conditions is derived as:

Where:

I = number of incident cases. *DW = disability weight.

L = duration of disability (years). r = discount rate.

$$YLD = \frac{I * DW * L(1 - e^{-rL})}{r}$$

* Stroke-specific disability weights covering 5 health states (of increasing severity) were adapted from the GBD 2010 study; the distribution of stroke by these levels was based on a South African study (table 1 in published manuscript paper 1).

These formulae have also been programmed into calculation spreadsheet templates for DALYs that are available at the WHO website (http://www.who.int/healthinfo/global_burden_disease/tools_national/en/). Additionally, a DALY package appears in the R statistical programming software and allows users to derive DALYs as well as perform sensitivity and uncertainty analysis. (https://cran.r-project.org/web/packages/DALY/index.html).

3.4.2 Derivation of incidence and duration through computer-based modelling

The input parameters for calculating YLD are not always readily available. Tools that estimate missing epidemiological parameters are therefore vital. Dismod II, a state transition disease modelling free software used in the GBD studies was used to calculate incidence and duration of stroke-related disability (http://www.epigear.com/index_files/dismod_ii.html).

The tool exploits the fact that disease incidence, prevalence, remission, case fatality, and mortality are not independent variables i.e. “a prevalent case must have been incident at some earlier time and age whilst an individual can only recover or die from a disease if they have had the disease first [177]”. In Dismod, “these logical relations are based on a set of differential equations which were solved numerically using an iterative approximation method, the finite differences method [177]”.

Dismod Conceptual framework

Conceptually, the DisMod II model is that of a multi-state life table (Figure 8). That figure shows that healthy people (S) of particular age (denoted by *a*) unaffected by the disease of interest (the disease being modelled) are subject to an incidence hazard *(i)* and may become diseased (C_a). When diseased they are subject to a hazard of dying from the disease, the case fatality (*f*), and to a hazard of recovery from the disease, called remission (*r*). Both healthy and diseased people are subject to the same mortality hazard from all other causes (*m*). D_a denotes the number of people of age (or age group a) who are dead from the disease.

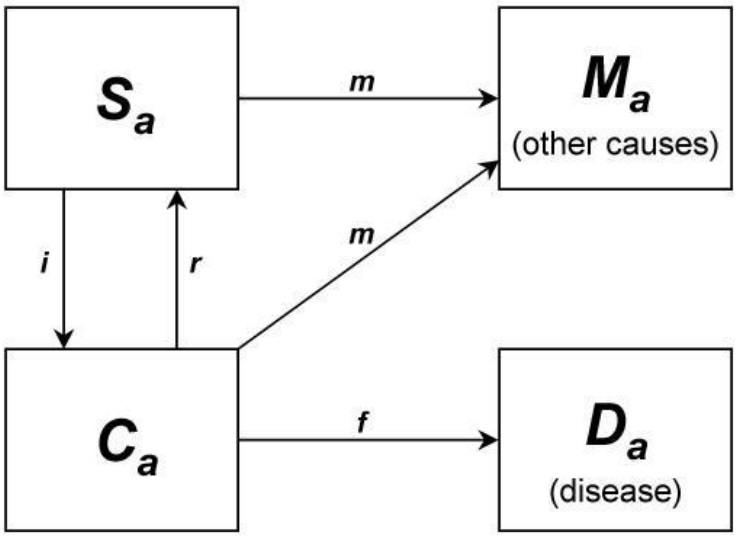


Figure 8: Conceptual framework of the Dismod II model (Adapted from Barendregt, 2003)

Advantages and limitations of the Dismod II approach

One of the main advantages of the Dismod II tool is its ability to map from incidence data to prevalence and vice versa; in many countries such as South Africa only one

of these parameters, prevalence in particular, is often available. In addition, Dismod II accepts input consisting of instantaneous rates for incidence, remission, and excess mortality, and is also able to use age-specific prevalence and cause-specific mortality rates, as well as incidence as a population rate [178]. Thirdly, Dismod II is able to minimize the weighted difference between the inputs and the output predictions by using the downward simplex method.

However, in spite of its usefulness the Dismod II model has some limitations worth noting:

- At least 3 transition hazards are required as inputs and single best estimates need to be produced for each. However this is a challenge: systematic review frequently finds multiple measurements of an age-specific rate, and yet only one could be the input to DisMod II. According to Flaxman, "transforming a large collection of measured values, often for incommensurate age intervals, to a single best estimate of disease prevalence was a difficult analytic challenge that was a necessary pre-processing step to do meta-analysis with DisMod II" [178].
- Secondly, it has been reported that in a bid to produce consistent output estimates that are as close as possible to the single-rate-type input estimates, the predictions from Dismod II showed oscillations as a function of age. Furthermore, other studies have shown that whilst global estimates of incidence that are derived through Dismod II are of similar magnitude to measured estimates, the tool over-estimated incidence for all but the oldest age groups i.e. Dismod II failed to show external validity for age-specific incidence rates [179].

Thus, whilst the Dismod II tool offered the "optimal" solution to analysis of the data that was available for this thesis, newer methods – Dismod MR in particular- should be considered as alternative approaches in future analyses. Briefly Dismod MR is "a Bayesian meta-regression tool that estimates a generalised negative binomial model for all the epidemiological data with various types of fixed and random effects" [180]. Examples include age fixed effects, fixed effects that predict variation across studies due to attributes of the study protocol [180]. As such, it addresses some of the highlighted limitations of Dismod II.

3.4.3 Cost-of-illness methods for estimating direct costs of stroke treatment in a rural South African setting

The study followed standard cost of illness (COI) methods to estimate direct costs of stroke treatment. Resource use associated with new and pre-existing stroke cases was estimated for the given year (2011) and this is termed a prevalence-based approach [181]. The resource categories included: inpatient stays, outpatient visits, general practitioner consultations, medications, diagnostic tests and clinic visits. A key assumption for this analysis was that nothing has to be known or assumed about the survival rate or course of the illness [182]. Further details are provided in Paper 3.

3.4.4 Comparative risk assessment methods to estimate burden of stroke attributable to physiological risk factors

A comparative risk assessment (CRA) was utilised to quantify contributions of the modifiable risk factors to stroke mortality and morbidity [183]. This methodology, developed by the World Health Organisation, is well established and has been applied in the global burden of disease (GBD) studies. Other studies that have utilised the approach include the South African national burden of disease study of 2000 and several other national and sub-national level studies [183-187]. CRA estimates the proportion of deaths attributable to a risk factor by combining local level data on risk exposures and cause-specific mortality with data from large scale prospective studies on risk factor–disease associations.

The outcome of CRA assessments are population attributable risks or fractions (PAFs) – defined as “the proportion of disease in a population that results from a particular risk to health”. A fundamental initial question when assessing the impact of a risk to health is to ask “compared to what?” Similar to the approach implemented in other studies, the research employs an explicit counterfactual approach, in which current distributions of risk factors are compared with some alternative distribution which confers the lowest population risk. For example, a systolic blood pressure distribution for a population with a mean of 115mmg and standard deviation 6mmHg, places the majority of the population within the confines of a physiologically favourable blood pressure distribution compared to a distribution with a mean of 130mmHg and SD of 10mmHg. The envisaged shift from current to counterfactual scenarios has been termed the distributional transition (Figure 9) and illustrates by

how much the disease of interest would be reduced under alternative counterfactual scenarios.

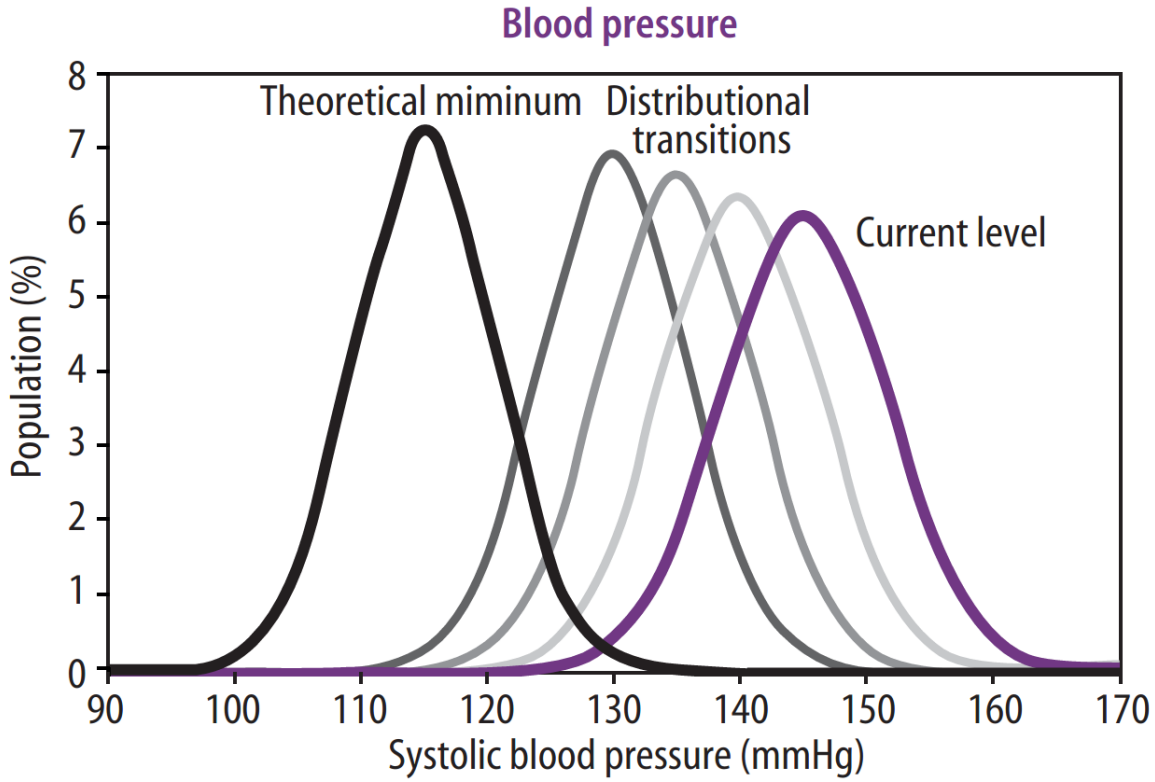


Figure 9: Illustrative example of 'distributional transition' for blood pressure

*The figure shows the current distribution of SBP within a population and the envisaged shifts from current to counterfactual distributions (termed distributional transitions) following intervention (Source: World Health Report 2002 [188]).

Estimating PAFs involves complicated numerical integration as shown in the equation below and detailed in appended publication (paper 2). However, excel-add ins to allow 'easier' numerical integration are now available as well as customised spreadsheets (http://www.epigear.com/index_files/risk_factor.html). The analysis was thus performed using Microsoft Excel 2013.

$$\text{Population attributable fraction} = \frac{\int_l^h RR\,(x)P(x)dx - \int_l^h RR(x)P'\,(x)dx}{\int_x^h RR\,(x)P(x)dx}$$

where: (i) $P(x)$ = Current population distribution of risk factor exposure ; (ii) $RR(x)$ = relative risk of mortality due to risk factor exposure; (iii) $P'(x)\ is$ an alternative exposure distribution

3.5 Developing and applying a cost-effectiveness model for CVD prevention

A cost-effectiveness model was developed specifically for this thesis and custom-built on the South African rural population of Agincourt sub-district. The following section gives an in-depth description of this model detailing the structure of the model.

3.5.1 Model Description

The mathematical model is a state transition Markov-type simulation model that describes how morbidity and mortality for stroke changes over time in the Agincourt sub-district population as a result of changes in absolute risk for stroke. The model simulates "cohorts of individuals" and their behaviours, states and actions over time. The main assumption behind the models is that individuals within each age-sex cohort, share the same characteristics hence average number of events can be computed. By necessity, multiple data sources are used to model individuals' health states (e.g. healthy, diseased, dead) and actions (e.g. adherent or non-adherent to treatment). These data sources include cross-sectional surveys, longitudinal surveys, randomized control trials and meta-analysis of published studies. The model can be 'updated' as better data become available.

3.5.2 Model Structure: Health states and transitions

The Stroke Prevention Model (SPM) has four discrete "Markov" states: "alive and free of stroke", "non-fatal stroke in first year", "alive with stroke after first year" and "dead" (Figure 10) and these states are defined for the absolute risk factor levels: <10%, 10-19%, and >20%. The risk factor levels were determined using the Framingham risk

prediction equation which was calibrated for the Agincourt sub-district population. The data used in the Framingham equation include age, sex, smoking status, total cholesterol level, and diabetes status derived from the “HIV/NCD risk factors” study - a nested study within the Agincourt HDSS [175].

In the starting year of the simulation, all cohorts are in the “alive and free of stroke” state. Then, in time steps of 1-year, cohorts of individuals move from one state to another. The transitions are governed by transition rates (T1-T5 in Figure 10). For example, incidence and case fatality rates between the states “alive and free of stroke” and “alive with stroke” govern the disease prevalence rates whilst case-fatality and all-cause mortality rates from the “Alive” states to the “Dead” state govern the final surviving population. The incidence of stroke victims who survive past 28 days (post-28 stroke survivors) was derived through modelling techniques with Dismod (paper 1). Cross-sectional prevalence data from the SASPI study; remission rates of zero; and case-fatality rates from a prospective population based study conducted in rural Tanzania were the 3 input parameters for the Dismod model. There were no population-derived estimates of case fatality rates of stroke in South Africa and the Tanzanian study (conducted in a similar rural HDSS) offered the best and most recent estimate of case fatality within a black, rural African setting [189] . Mortality from all causes, including stroke is calculated from the total number of deaths recorded within the Agincourt HDSS for the period 2007-11 (paper I).

It is important at this stage to specify one assumption of this model, the “markovian assumption”, which specifies that “the behaviour of the process subsequent to any cycle depends only on its description in that cycle.” That is, the process has no memory for earlier cycles [190]. Thus, in our example, if a proportion of the cohort is in the “Alive with stroke in first year” state after cycle n, the probability that they will end up in the “Dead” state after cycle n + 1 is constant. It does not matter how much time the cohort spent in the HEALTHY or “Alive without stroke” state before experiencing a stroke. This may not be the case in the “real world”. For example, a person who has been in a state for a long time may have a different transition probability to someone who has just entered that state. To illustrate, the probability that someone who suffered a first ever-stroke event dies is highest within the first year after the event and tends to decline gradually over time i.e. (lower probability 10-15 years after the event vs. 1-5 years after event) [191]. Therefore a person who has stayed for 4

years in the ‘alive with stroke after 1st year state will have a higher transition probability to the ‘death’ state compared to someone who has stayed in that state for 15 years. Because case fatality rates for stroke tend to be significantly high within the early years following a stroke event, the ‘Markovian assumption’ is unlikely to have a significant impact on results as the average length of stay in a particular state following a stroke is expected to be low. A prospective follow-up study of incident cases of stroke in Tanzania found that 83% of individuals had died by 7 years post-stroke [192].

This simulation is continued annually until every individual in the cohort has died or reached the age of 100. The simulation is done for both the intervention arm and baseline (no intervention) arm for each cardiovascular disease risk category. The main model outcome variables are incidence, mortality numbers specified by age and sex, life expectancy, disability adjusted life expectancy and lifetime costs. For the calculation of lifetime costs, the number of survivors and disease prevalence numbers of the different cohorts are used.

It is important to highlight that whilst ischaemic and haemorrhagic sub-types of stroke are not modelled as different states, their differential incidence and case fatality rates in the first year are taken into account in the transition probabilities. Similar to previous studies, incidence and case fatality for GI bleeds (a side effect of aspirin therapy) are accounted for in those who are receiving aspirin therapy in any state of the model [193].

3.5.3 Quality of life adjustment

In evaluating the Markov process, the patient is given credit for the time spent in each state such that if duration of survival is the only attribute of interest then adding together the average time spent in each state will give the expected survival. However, in reality the quality of life in each state (excluding death) is of the essence and each state is associated with a ‘quality factor’. That is, quality adjustments are made to reflect the number of years lived in optimal health and YLDs were used to make the quality adjustment in this study. We calculated an average disability weight for stroke in rural South Africa by combining disability weights obtained through the

GBD 2010 study with information on the proportion of the population with stroke that fell into each of the disability weight categories (table 1 in published manuscript paper 1). The latter was based on a South African-based study [194]. In contrast to previous GBD studies where disability weights were derived through a deliberative exercise by a panel of health experts, disability weights in the GBD 2010 study were derived through population-based surveys. The latter are thus more reflective of the public's average view of severity of different conditions and were selected as the most appropriate source of data. Furthermore, the GBD 2010 study was the most current study at the time of writing the published manuscript (paper 1).

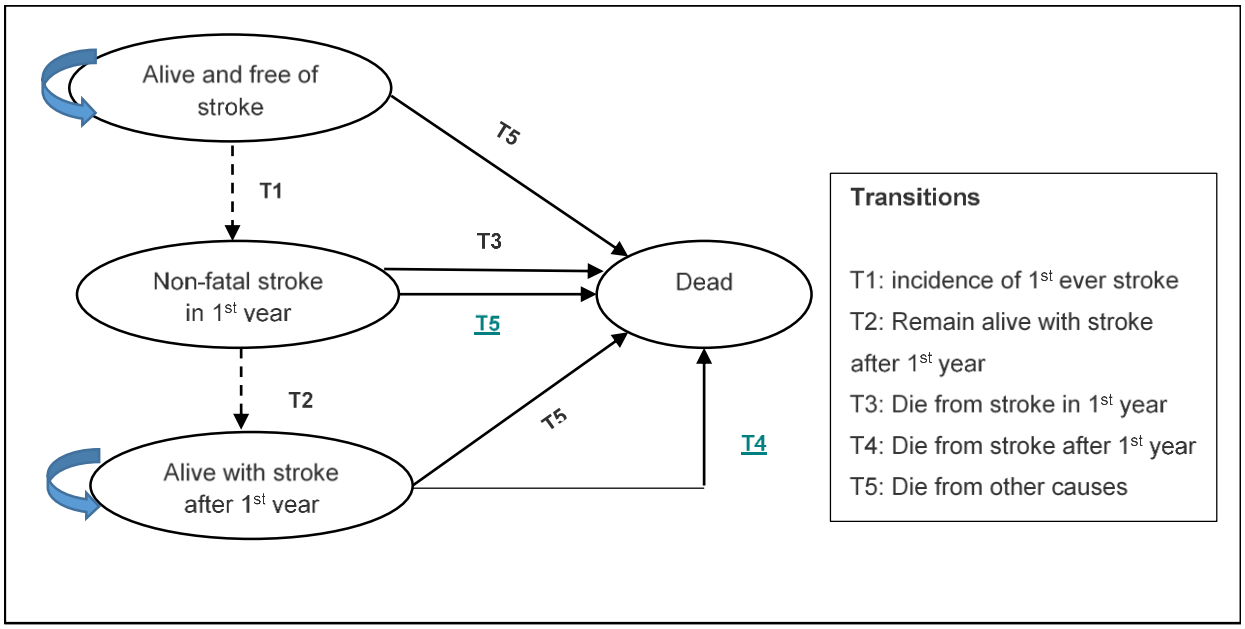


Figure 10: Simplified Stroke Prevention Model Structure where T_{1-5} represent yearly transitions from one state to another

3.5.4 Mathematical model equations

The model consists of three parts: initialization, simulation and post-processing. In the initialization part, we calculate the parameter values and the age-sex distribution of the population by risk factor categories. The population numbers are based on the 2012 figures from the Agincourt HDSS. In the simulation phase, 1-year changes in prevalence numbers are calculated. These changes are the results of transitions between states. The final transition numbers are the product of the transition rates

and prevalence numbers at each 1-year cycle. In the post-processing stage, the life expectancy and lifetime costs are calculated from the simulation part.

Model initialization

The first step involves determining how stroke risk is distributed within the population since not all preventive interventions will be delivered to everyone in the population. The distribution of stroke risk within the population is estimated using cross-sectional risk factor profiles based on data from the Agincourt HDSS.

10-year absolute risk of stroke

10-year risk of a stroke event is determined using a 're-calibrated'[14] Framingham equation for each individual who did not self-report stroke in the "Ha nakekela" HIV/NCD study. The Framingham risk equation is a predictive equation of CVD risk that was borne out of the long-term Framingham study. The Framingham study was carried out in the United States, in a small town (Framingham) near Boston, within a population of high background risk of cardiovascular disease [195]. Briefly, the Framingham Heart Study launched in 1948 aimed to identify the common factors that contribute to CVD through long-term follow-up of 5,209 men and women between the ages of 30 and 62 with no evident symptoms of CVD or who had not yet suffered a heart attack or stroke [196]. Every two years, subjects return to the study for a detailed medical history including physical examination, and laboratory tests [196]. The study continues to evolve: In 1971 a second generation - 5,124 of the original participants' adult children and their spouses – were enrolled to participate in similar examinations. In 1994, the first Omni cohort of the Framingham Heart Study was enrolled. The Omni cohort is "an ethnically and racially diverse population consisting of men and women of African-American, Hispanic, Asian, Indian, Pacific Islander and Native American origins, who at the time of enrollment were residents of Framingham

[14] Recalibration is premised upon one major assumption that the nature and strengths of the associations between risk factors and cardiovascular disease are constant across populations. Thus the equation is simply for different risk factor distributions and different background incidence of cardiovascular disease (Chow et al. 2009).

and the surrounding towns". In April 2002, a new cohort was enrolled - the grandchildren of the Original Cohort whilst in 2003, a second group of Omni participants was enrolled.

Nonetheless because the Framingham cohort is still primarily Caucasian, the risk equations emanating from that study have been shown to systematically overestimate risk in other populations, new equations based on local cohort data are considered the optimal solution [197]. However, due to the scarcity of such studies, an alternative approach is to recalibrate the Framingham equation using local risk data, and this method has been shown to give better estimates compared to those based solely on the original Framingham equation [197]. The latter approach is used in this study as local data on risk factors were more readily available and up-to-date.

Predictors of CVD in the equation include age, diabetes, smoking status, treated or untreated SBP, total cholesterol, HDL cholesterol and BMI. The HIV/NCD study conducted in Agincourt sub-district collected data on these risk factors on a sample population of 7,662 individuals aged 15 years and above [175]. In that study, information on smoking and hypertension treatment was collected using previously validated questionnaires. Point-of-care instruments were used to measure glycaemia, total cholesterol, blood pressure, weight and height. The 10-year risk of developing stroke was calculated for each individual based on information collected on these predictors. Programmed Excel spreadsheets that are available online were used to perform the calculations (https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php

The relative risk (RR) of stroke for each individual was then calculated by comparing the individual's stroke risk with all other individuals (without previous stroke) within the same sex and 10-year age group.

Transition probabilities for sub-groups

Risk of stroke within each 10-year age-sex subgroup varies over time. Hence it would be inaccurate to assume that the starting risk of stroke (in each age-sex group) remains constant over time and indefinitely into the future. To account for this varying distribution we performed the following:

1. Ranked individuals in each age and sex category (i.e. 15, 25, 35, 45, 55, 65 and 75 years) by risk of event as determined through Framingham equations and also by blood pressure treatment status.
2. Divided each age-year group into 20 equal sub-groups (vigintile) so that for each age group there were 20 cycles of changing risk that an individual passed through (i.e. the risk did not remain constant over time) (i.e. Table 9 and Table 10).
3. Calculated the mean risk per each age category and compared this with mean risk of each vigintile - this allowed computation of a RR measure by age and sex.
4. Cross tabulated the mean relative risk of the 10-year absolute risk groups with the relative risks by vigintiles in order to determine the vigintile to which the 10-year absolute risk group belong (Table 11 and Table 12).
5. Relative risks are multiplied by the corresponding age- and sex-specific population level probability of an event to determine the transition probability of the sub-group.

Table 9: Relative risk of stroke by age and vigintile[15] subgroup in males, Agincourt 2010

Risk Cycle	**Age Group (Years)**						
	15-24	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*
	Relative Risk of stroke						
1	0.286	0.373	0.310	0.363	0.354	0.380	0.463
2	0.372	0.452	0.463	0.461	0.446	0.465	0.536
3	0.428	0.501	0.544	0.543	0.497	0.531	0.582
4	0.469	0.562	0.613	0.607	0.542	0.592	0.651
5	0.525	0.602	0.650	0.661	0.604	0.682	0.718
6	0.580	0.632	0.685	0.692	0.655	0.760	0.754
7	0.634	0.686	0.730	0.744	0.714	0.817	0.786
8	0.695	0.735	0.775	0.799	0.775	0.867	0.852
9	0.753	0.780	0.824	0.833	0.848	0.897	0.925
10	0.828	0.844	0.870	0.872	0.912	0.921	0.953
11	0.895	0.903	0.932	0.919	0.969	0.963	1.004
12	0.975	0.969	0.970	0.981	1.051	1.012	1.062

[15] Vigintiles are 20 groups with equal population numbers (in this study equal population numbers within 20 cycles of changing risk).

Risk Cycle	Age Group (Years)						
	15-24	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*
	Relative Risk of stroke						
13	1.041	1.022	1.032	1.047	1.109	1.073	1.091
14	1.115	1.115	1.095	1.103	1.161	1.132	1.136
15	1.208	1.201	1.175	1.193	1.253	1.212	1.212
16	1.340	1.282	1.271	1.282	1.355	1.280	1.287
17	1.498	1.405	1.368	1.348	1.421	1.360	1.346
18	1.691	1.605	1.506	1.511	1.520	1.450	1.455
19	1.974	1.907	1.786	1.753	1.674	1.619	1.538
20	2.764	2.480	2.464	2.420	2.232	2.065	1.754

Table 10: Relative risk of stroke by age and vigintile[16] subgroup in females

Risk cycle	Age Group (Years)						
	15-24	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*
	Relative Risk of stroke						
1	0.286	0.317	0.330	0.283	0.332	0.299	0.287
2	0.385	0.404	0.425	0.366	0.415	0.395	0.406
3	0.431	0.461	0.486	0.432	0.455	0.469	0.484
4	0.482	0.512	0.532	0.483	0.506	0.542	0.542
5	0.540	0.556	0.575	0.533	0.554	0.622	0.573
6	0.587	0.597	0.613	0.571	0.602	0.668	0.629
7	0.642	0.640	0.654	0.606	0.633	0.700	0.671
8	0.708	0.680	0.693	0.639	0.663	0.739	0.706
9	0.769	0.733	0.728	0.681	0.718	0.785	0.746
10	0.834	0.799	0.776	0.730	0.776	0.818	0.822
11	0.897	0.861	0.830	0.806	0.824	0.860	0.890
12	0.957	0.941	0.894	0.886	0.891	0.942	0.966
13	1.012	1.029	0.967	0.946	0.994	1.016	1.028
14	1.097	1.119	1.024	1.025	1.073	1.084	1.097
15	1.164	1.200	1.107	1.174	1.209	1.169	1.232
16	1.278	1.292	1.213	1.310	1.331	1.313	1.376
17	1.424	1.406	1.383	1.514	1.439	1.440	1.557
18	1.631	1.556	1.591	1.711	1.688	1.619	1.705
19	1.943	1.756	1.980	2.027	2.053	1.874	2.008
20	2.986	3.199	3.198	3.335	2.924	2.794	2.450

[16] Vigintiles are derived by dividing participants into 20 equally sized groups (in this study 20 cycles of changing risk).

Table 11: Vigintile of risk by risk category, age and sex for males

Intervention target group	Age Group						
	15-24	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*
	Risk cycle that target group falls under						
<10% absolute risk	12	12	10	4	1		
10-19% absolute risk			20	19	13	5	2
>20% absolute risk				20	18	15	13
Stage 1 HT	15	14	12	13	11	11	13
Stage 2 HT	16	16	17	15	16	17	16

Table 12: Vigintile of risk by risk category, age and sex for females

Intervention target group	Age Group						
	15-24	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*
	Risk cycle that target group falls under						
<10% absolute risk		4	15	19	20	20	20
10-19% absolute risk		9	11	12	12	13	14
>20% absolute risk				11	12	12	13
Stage 1 HT			3	14	18	19	20
Stage 2 HT			3	13	18	19	20

3.5.5 Demonstrating the Stroke Prevention Model

The final part of the thesis seeks to demonstrate how the stroke policy model can be used to inform the development and evaluation of primary prevention interventions.

Selection and descriptions of interventions and their effects

The literature review established that the most effective methods for CVD prevention involve a combination of population-wide and individual-based interventions that respectively and in combination target the general population and individuals at high risk. In demonstrating the application of this model, individual interventions are divided into two sub-groups: individual treatment based on elevated levels of systolic blood pressure, and individual treatment based on the absolute risk of a

cardiovascular event in the next 10 years (Table 13). Within the Agincourt HDSS, approximately 40% of the stroke burden is attributable to systolic blood pressure (paper 2) amongst both males and females, suggesting that high blood pressure is the optimum individual risk factor to target. Amongst females, excess weight is also a concern since it is responsible for approximately 20% of the stroke burden in Agincourt HDSS. However, to-date there is limited data on the effectiveness of any culturally appropriate interventions that encourage weight loss and maintenance. There is opportunity in the future to analyse a randomised trial which will be implemented within the Africa Centre HDSS in KwaZulu Natal, South Africa (Sally van Wyke, personal communication). However, data for that will only become available within 5 years. The pharmaceutical interventions (commonly prescribed drugs for high blood pressure and cholesterol lowering) included in the analysis are based on international recommendations [198]; effectiveness estimates are based on pooled data from several randomised control trials [199]. Furthermore, we analysed the impact of the 'polypill'[17] – a single drug combining a statin and three antihypertensive agents at half standard doses (diuretic, calcium channel blocker and ACE-Inhibitor) - on stroke prevention. The polypill has been hailed as a promising concept in CVD prevention since 2001 and as such deserves particular mention. To date several randomised controlled trials (Table 14) have demonstrated that polypills can improve treatment adherence and reduce cardiovascular risk factors [200-202].Other major trials are underway to study the effect on clinical outcomes. Nonetheless, at the time of writing this thesis, there were no polypills being marketed for primary prevention of CVD. However, Fuster-CNIC-Ferrer CV polypill (marketed under the brands of Trinomia® and Sincronium®) and the Indian Polycap (marketed under the tradename (Cadila®) had received regulatory approval for secondary prevention of CVD.

[17] There is no single definition of the cardiovascular polypill. Originally proposed as an idea in 2001, the polypill was described as "consisting a combination of four drugs: a beta-blocker, an angiotensin converting enzyme (ACE) inhibitor, aspirin and a statin. Since then, the concept has evolved and the definition more flexible. The general consensus is that the polypill should target lipid lowering (statin) and blood pressure (ACE inhibitor, beta blocker), and, though controversial, potentially contain aspirin" (https://wellcome.ac.uk/sites/default/files/cardiovascular-polypill-feb17.pdf)

Table 13: Description of individual interventions and their effects[18]

Intervention Type	Target group	Intervention Description	Intermediate outcome affected
Individual targeted	140≤SBP<160	Counselling and individual treatment with diuretic, β-blocker, calcium channel blocker (CCB), ACE-Inhibitor and combination of β-blocker & Diuretic	Systolic Blood Pressure
	SBP≥160	Counselling and individual treatment with: β-blocker + Diuretic; CCB+Diuretic; ACE-I+Diuretic & ACE-I+CCB+ β-blocker+Diuretic	Systolic Blood Pressure
	Absolute risk of CVD in next 10 years: <10%; 10-19% and ≥20%	Combination treatment with β-blocker, statin, diuretic and calcium channel blocker (i.e. polypill); Counselling and individual treatment with: β-blocker + Diuretic; CCB+Diuretic; ACE-I+Diuretic & ACE-I+CCB+ β-blocker+Diuretic	Stroke

[18] Assumed 50% discontinuation rate in first year for pharmacotherapy. The exception was the polypill where adherence rates were higher and derived from systematic analysis of clinical trials.

Table 14: Principal clinical trials using a cardiovascular polypill[19]

Trial/Sample Size/ Principal Investigators	Population	Polypill Composition	Outcomes	Status
Primary prevention				
Indian Polycap Study (TIPS) n=2053 Yusuf S, Pais P	Men and women aged 40–80 years without CVD and with at least 1 CV risk factor in India	Aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, hydrochlorothiazide 12.5 mg, atenolol 50 mg	Feasibility; effect on risk factor levels; safety and tolerability	Completed
Poly-Iran: Phase II Study of Heart Polypill Safety and Efficacy in Primary Prevention of CV Disease n=475 Marshall T, Malekzadeh R, Malekzadeh F	Men and women aged 50–80 years without indications or contraindications for aspirin, BP-lowering drugs, and statins in Iran	Aspirin 81 mg, hydrochlorothiazide 12.5 mg, enalapril 2.5 mg, atorvastatin 20	Effect on risk factor levels; safety and tolerability	Completed
Combination Therapy Trial n=200 Furberg C, Mendis S, Soliman EZ.	Age >40 years without CVD and with estimated 10-year total CVD risk score >20% in Sri Lanka	Aspirin 75 mg, simvastatin 10 mg, lisinopril 10 mg, hydrochlorothiazide 10 mg (Red Heart Pill 2b)	Effect on estimated 10-year total CVD risk score	Completed
IMProving Adherence using Combination Therapy (IMPACT) n=497 Rodgers A, Selak A	Established CVD or 5-year risk ≥15%	Aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg with either atenolol 50 mg or hydrochlorothiazide 12.5 mg	Effect on adherence to recommended drugs and mean change in blood pressure and LDL-chol at 12 months	Completed
Indian Polycap Trial (TIPS)-3 n=5000 Yusuf S, Pais P, Xavier D, Liu L.	Primary prevention with estimated yearly CVD event rate of >1% using the INTERHEART risk score in China and India	Polycap; dose to be chosen after completion of the TIPS-K trials	Major CVD events; neurocognitive function	Estimated study completion date: January 2019
Heart Outcomes Prevention Evaluation (HOPE)-3 n=12,500 Yusuf S, Lonn E	Primary prevention in men aged >55 years and women aged >65 years with at least 1 CV risk factor and women aged >60 years with at least 2 risk factors and	Rosuvastatin 10 mg, candesartan 16 mg/ hydrochlorothiazide 12.5 mg (2×2 factorial design)	Major CVD events; study neurocognitive function; renal function	Completed

[19] Table 1 (Principal Clinical Trials using a Cardiovascular Polypill) was reproduced from Castellano et al. The publication is licensed under CC BY-NC-ND license for creative Commons.

Trial/Sample Size/ Principal Investigators	Population	Polypill Composition	Outcomes	Status
	with average BP and cholesterol levels in 22 countries			
Secondary prevention				
FOCUS Trial in Secondary Prevention Phase 1: n=2000, Phase 2: n=800 Fuster V	Survivors of myocardial infarction in Spain and Latin American countries	Aspirin 100 mg, simvastatin 40 mg, ramipril 2.5, 5, 10 mg (Trinomia)	Adherence; feasibility; effect on risk factor levels; safety and tolerability	Completed
Use of a Multidrug Pill In Reducing CV Events UMPIRE n=2000 Thom SA, Rodgers A	Established CVD or high-risk primary prevention (5-year CVD risk of >15%) in India, Netherlands, UK	Aspirin 75 mg, atenolol 50 mg, simvastatin 40 mg, lisinopril 10 mg (Red Heart Pill 1) or aspirin 75 mg, hydrochlorothiazide 12.5 mg, simvastatin 40 mg, lisinopril 10 mg (Red Heart Pill 2)	Adherence; effect on risk factor levels; safety and tolerability; CVD events (secondary outcome)	Completed
Patel n=623	Established CVD or high risk primary prevention (5-year CVD risk of >15%) Australia	Aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg and either atenolol 50 mg or hydrochlorothiazide 12.5 mg	Adherence to medications, systolic blood pressure and total cholesterol.	Completed
SECURE Trial n=3200 Fuster V, Castellano JM	Elderly population (>65 years) with a diagnosis of AMI	Trinomia (Aspirin 100, Ramipril 2.5, 5 or 10mg, Atorvastatin 40mg)	Composite primary endpoint of cardiovascular death, nonfatal MI, nonfatal ischaemic stroke and urgent revascularization	Ongoing. Estimated study completion date: April 2020.

Uncertainty analysis

Ninety-five percent uncertainty intervals are derived for all cost and health outcome measures by Monte Carlo analysis (2000 iterations) using the Excel Add-In programme @Risk (Palisade, Version 7.1). Through sampling different possible inputs, @RISK (Palisade version 7.1) computes thousands of possible future outcomes e.g. mortality, and the chances they will occur. The use of probability distributions ensures that variables can have different probabilities of different outcomes occurring; thus making probability distributions a much more realistic method of representing uncertainty.

Probability distributions that best characterised the data were selected by first plotting the data (when available) to check the distribution. In the event that data were not available e.g. relative risk of stroke incidence due to different pharmacotherapies, the probability distributions reported in the cited studies were selected. In addition, the following process proposed by Mun (2008) [204] was followed: i.e. “1. Examined the variable in question and listed everything known about the conditions surrounding this variable (some valuable insights were taken from historical published data). 2. reviewed the descriptions of the probability distributions, 3. Selected the distribution that characterized the variable”.

Table 15 shows the uncertainty distributions, sources and assumptions for the model input parameters.

Table 15: Model Parameters and their uncertainty distributions

Parameter	Value Mean (low; high)	Uncertainty distribution	Sources and assumptions
Diuretic			
Relative risk of stroke incidence with diuretic	0.62 (0.53; 0.72)	Triangle	Meta-analyses of primary prevention trials [205]
Annual cost of low-dose diuretic therapy	R164.25	–	Average annual cost for the standard daily dose of amiloretic and Ridaq, weighted by proportion on each medication in 2010 in Agincourt HDSS
Beta-blocker			
Relative risk of stroke incidence with beta-blocker -	0.83 (0.70;0.99)	Triangle	Meta-analyses of primary prevention trials [205]
Annual cost of beta-blocker therapy	R281.05	–	South African Medicine Price Registry (http://www.mpr.gov.za/)
Calcium channel blocker			
Relative risk of stroke incidence with calcium channel blocker	0.66 (0.58;0.78)	Triangle	Meta-analyses of primary prevention trials [205]
Annual cost of calcium channel blocker therapy	R332.15	–	
ACE inhibitor			
Relative risk of stroke incidence with ACE inhibitor	0.78 (0.66; 0.92)	Normal (lnRR)	Meta-analyses of primary prevention trials [206]
Annual cost of ACE inhibitor therapy	R1408.00	–	Average annual cost for the standard daily dose of enalapril and perindopril, weighted by proportion on each medication in 2010 in Agincourt HDSS
Statin			
Relative risk of stroke incidence with statin	0.70 (0.70; 0.87)	Normal (lnRR)	Meta-analyses of primary prevention trials [207]
Annual cost of statin therapy	R558.45	–	Average annual cost for the standard daily dose of simvastatin.
Aspirin			
Relative risk of disease incidence with aspirin - Stroke (ischaemic) - Stroke (haemorrhagic) - GI bleed	 0.86 (0.74-1.00) 1.32 (1.00 - 1.75)	 Normal (lnRR)	Meta-analyses of primary prevention trials

Parameter	Value Mean (low; high)	Uncertainty distribution	Sources and assumptions
	1.54 (0.13)		
Annual cost of aspirin therapy	R357.70	Uniform	Average annual cost of aspirin dispensed at primary health care
First year discontinuation with individually-targeted interventions	50% (8%)	Beta	
Treatment costs			
Stroke - First year - Subsequent years	 R 29,872 R 4,680	Uniform	Estimates derived from author's calculations based on actual resource use for hypertensive patients and stroke patients in Agincourt sub-district
GI bleed - Men - Women	 R4,616 R3,759	Uniform	Australian study (no data for South Africa)
NB. All costs adjusted to 2012 South Africa Rands using consumer price index and/or purchasing power parities where relevant. *Soluble aspirin cost (soluspirin) used in analysis *Average annual costs of drugs presented are unit costs for the drug only taken once daily over a 12 month period			

3.6 Budget impact analysis

Although this thesis chooses to explore cost effectiveness of a wide range of interventions for CVD prevention in its technical analysis, I recognize the stance in the literature that budget impact is an important criterion for funding new or scaling-up existing interventions. Within this study, I capture the budget impact considerations within the economic evaluation by conducting a budget impact analysis (BIA) from the perspective of the government as the payer of healthcare. By definition, a BIA is an economic assessment to establish whether a "cost-effective" intervention would be affordable if everyone in the target group received the intervention [208]. To contrast, a cost-effectiveness analysis evaluates whether an intervention provides better value compared with an existing intervention (with value defined as cost per unit of health outcome).

Chapter 4 Findings

4.1 Current epidemiological profile of stroke burden and trends in a rural South African setting

The burden of stroke in Agincourt sub-district as estimated in this study is considerable. Between 2007-2011, 394 deaths were assigned to stroke in Agincourt HDSS. This translates to a crude stroke-related mortality rate of 114 per 100,000 person years and age-standardised rate of 172 per 100,000 person years (paper 1). By considering analyses conducted within the same population in 1990-94, the current study establishes that stroke-related mortality has increased from 87/100,000 in 1990-94 to 114/100,000 in 2007-11.

If we conservatively assume that prevalence and distribution of risk factors across all municipalities that are considered 'mostly rural' is similar to that of Agincourt sub-district then the stroke burden across the entire rural South Africa is even more substantial. That is, approximately 33,500 strokes every year in a population of approximately 13 million people (Table 16). This translates to a crude incidence rate of 259 per 100,000 person-years and an age-adjusted incidence rate of 347 per 100,000 person-years. Comparison of these number of stroke deaths with country estimates produced through a similar mathematical modelling study indicate that the burden of new strokes within the South African context is disproportionately higher within rural communities. In the latter study, approximately 75,000 strokes occurred in 2008 in South Africa in a population of approximately 50 million people. Table 16 and Figure 11 place the age-sex incidence rates calculated in this study within the context of South Africa. As expected, risk of stroke increases with age for both males and females; incidence rates are highest in the '70-79' and 80+ age groups for both 'predominantly rural' and entire South Africa (Figure 11). Noteworthy is the increase in incidence rates amongst females in rural South Africa. Incidence rates more than double between the age groups: '15-29' to '30-44'; '30-44' to '45-59' and between '45-59' to '60-69'. This is in contrast to the modest increases observed nationally, suggesting that stroke burden peaks at much younger ages amongst females in rural South Africa. Furthermore, Table 16 indicates that in terms of absolute numbers, the

younger age groups bear a significant proportion of new stroke cases that occur yearly in rural South Africa. Premature mortality, measured as years of life lost due to premature mortality indicates that those who suffer a stroke are unlikely to survive it in 'predominantly' rural communities of South Africa. According to this study, approximately 90% of the DALYs lost are due to years of life lost due to premature mortality rather than years lived with disability (Table 17).

4.1.1 Baseline DALY estimates

Disability adjusted life years extend mortality measurements by incorporating premature mortality and disability. In the current study we establish the first baseline DALY estimates for stroke in rural South Africa and show that approximately 1,070 DALYs are lost due to stroke every year in Agincourt HDSS (Table 17). Premature mortality as opposed to years lived with disability is responsible for 90% of the DALYs loss. In contrast, national estimates indicate that YLDs comprise 17% of the DALYs lost due to stroke; pointing to the much higher premature mortality in rural communities of South Africa. Figure 12, places the estimates calculated in this study within the context of sub-Saharan Africa and other low and middle-income countries by making comparison with figures derived through the GBD 2010 study. Based on Figure 12, DALY loss rates in a rural setting of South Africa appears to be on the higher end of rates reported in SSA. However, the figures from GBD 2010 should be interpreted with caution since that analysis did not stratify between urban and rural settings; as such any urban-rural differences would be masked or averaged out. In addition, the GBD 2010 study calculated prevalent versus incident DALYs and did not discount years of life lost due to premature mortality.

Table 16: Incidence of stroke per 100,000 person years in 'mostly rural'[20] South Africa, 2011 compared with national estimates

Males				Females			Both sexes			South Africa, National estimates 2008 (Bertram et al. 2013 [5])	
Age	**Population**	**Incidence/ 100,000**	**Incidence (N)[21]**	**Population**	**Incidence/ 100,000**	**Incidence (N)**	**Population**	**Incidence /100,000**	**Incidence (N)**	**Incidence/ 100,000 Males**	**Incidence/ 100,000 Females**
0-4	861642	0	0	850647	0	0	1712289	0	0	0	0
5-14	1569456	0	0	1515155	12.6	191.2	3084611	6.2	191.2	0	10
15-29	1832722	91.9	1685.2	1938675	121.6	2357.2	3771397	107.2	4042.4	79	143
30-44	789718	332.9	2628.7	1085763	278	3018	1875481	301.1	5646.7	412	423
45-59	532986	772.8	4118.9	824761	691.1	5699.7	1357747	723.2	9818.6	665	384
60-69	227238	645.8	1467.4	353604	1204.9	4260.7	580842	986.2	5728.2	583	609
70-79	119337	1401.3	1672.3	243683	1341	3267.8	363020	1360.8	4940.1	595	826
80+	53045	2252.2	1194.7	149895	1320.1	1978.7	202940	1563.7	3173.4	1384	2520
Totals	**5,986,144**	**213.3 (198–243)**	**12,767.2**	**6,962,183**	**298.4 (296–372)**	**20,773.4**	**12,948,327**	**259**	**33540.6**	**465**	**615**

[20] Population figures for "mostly rural" South Africa are based on Census 2011 population estimates for 70 municipalities that fall under the B4 category of the Municipal Infrastructure Investment Framework. B4 municipalities are typically located in former homelands, have communal land tenue and characterised by presence of at most 2 small towns in the area.

[21] N is the number of incident cases.

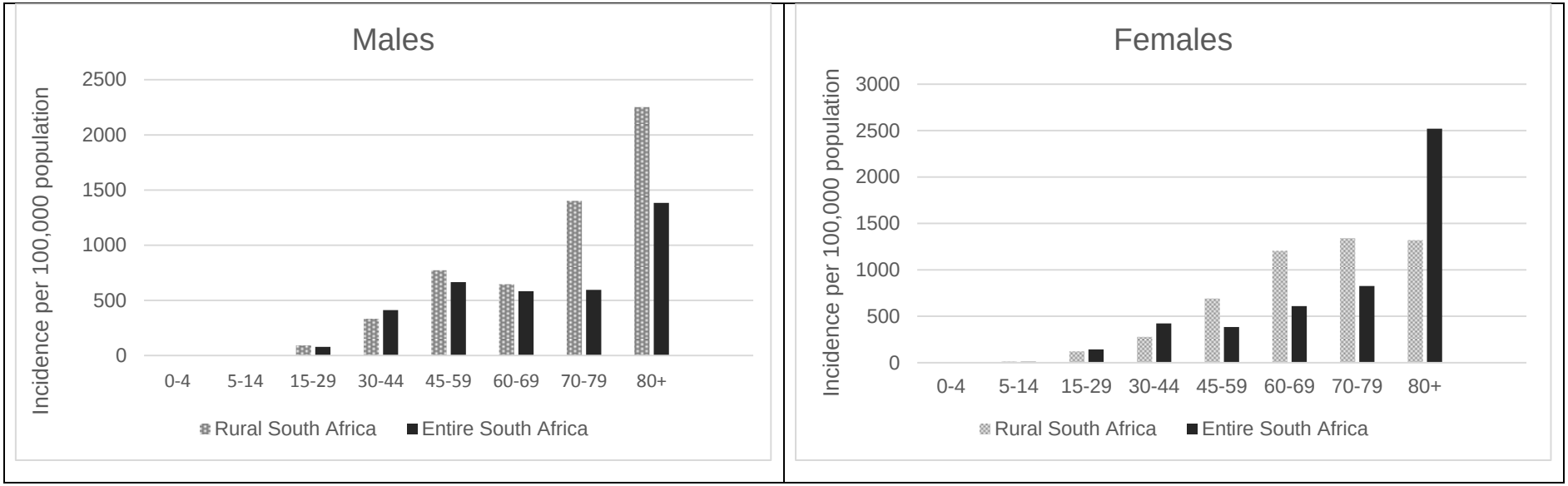


Figure 11: Incidence of stroke per 100,000 population by age and sex: 'mostly rural SA (2011) vs. entire South Africa (2008)

Table 17: Yearly DALYs lost due to stroke in Agincourt sub-district, rural South Africa (2007-11) using an incidence based approach

Age group	Population (% of total)	YLD	YLL	DALYs	Crude Rates (DALYs/100,000[22])	WHO standard population distribution [209] 23	Age-adjusted rates (DALYs/100,000)
0-4	22549 (33%)	0.0	0.0	0.0	0.0	0.09	0.0
5-14	16381 (24%)	1.1	0.0	1.1	6.7	0.17	1.2
15-29	11824 (17%)	10.4	76.6	87.0	735.8	0.25	181.0
30-44	7288 (11%)	13.8	153.3	167.1	2293.0	0.21	489.5
45-59	4631 (7%)	18.9	264.4	283.2	6115.9	0.16	976.1
60-69	2813 (4%)	12.9	174.9	187.8	6676.3	0.07	446.0
70-79	1793 (3%)	10.0	169.5	179.5	10011.2	0.04	373.4
80+	1664 (2%)	8.0	138.3	146.3	8791.4	0.02	135.4
Total	**68943 (100%)**	**93.6**	**977.0**	**1070.5**	**1552.8**	**1.00**	**2602.6**

[22] These are crude rates calculated by dividing the total DALY loss in each age group, over the period 2007-11, by the total number of persons in the population.

[23] The WHO standard population is used to adjust the crude-rates through a process of age-standardisation. Age standardisation is necessary if one needs to compare rates over time and across different countries. Most rates e.g. incidence and prevalence are age-dependent such that crude-age specific rates may be misleading if the underlying age composition differs between time points or in the populations being compared. The standard population for WHO is based on the average age-structure of the world population over the period 2000-2025.

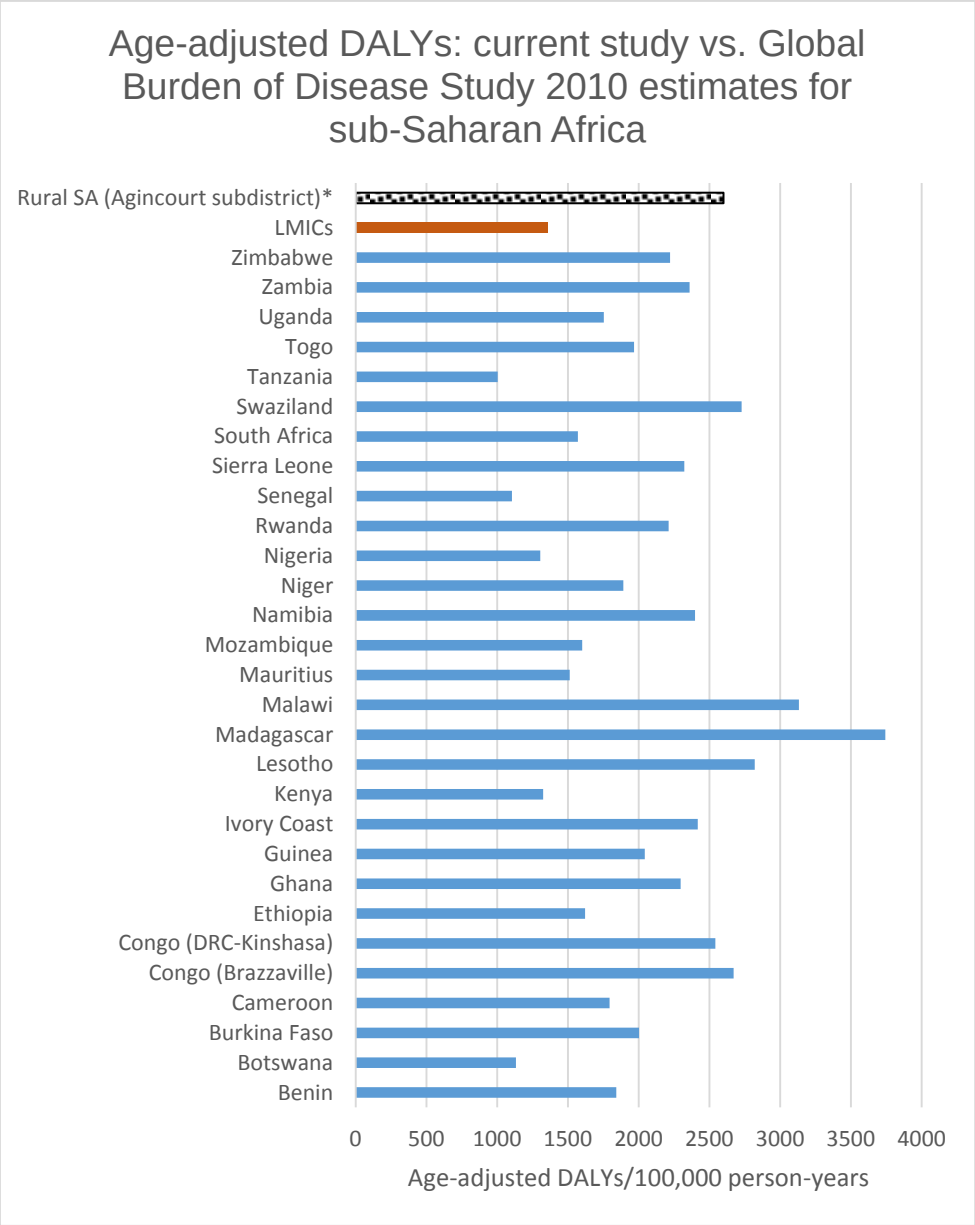


Figure 12: Comparison between age-adjusted DALY rates calculated in Agincourt sub-district, rural SA and estimates derived through the GBD 2010 study for Sub-Saharan Africa and all low and middle-income countries.

* Derived from HDSS data

4.2 Unique aspects of stroke burden in rural South Africa

The total age-adjusted incidence of stroke calculated in this study is lower than that reported for South Africa overall but with differing age patterns (paper 1). In this study

we indicate higher incidence rates at much younger ages compared to national figures [210] and a trend towards increased incidence with age particularly amongst females. This is in contrast to the modest increases observed nationally. The highest magnitude of increase amongst females at national level is observed between the last 2 age groups, where incidence increases from 826 to 2,520 per 100,000 person years but with marked uncertainty.

Compared to similar rural settings in SSA, we report a much higher incidence of stroke in Agincourt which is comparable only to urban settings that are at a more advanced stage of the epidemiological transition (Figure 13). Estimates derived from Hai district, a rural HDSS in Tanzania reported that in 2006, incidence of stroke was 108.6/100,000. This is 3 times less than estimates derived from this study. Our estimates are much closer to those derived from Dar-es-Salaam, an urban district in Tanzania, of 315 per 100,000 per person years [78].

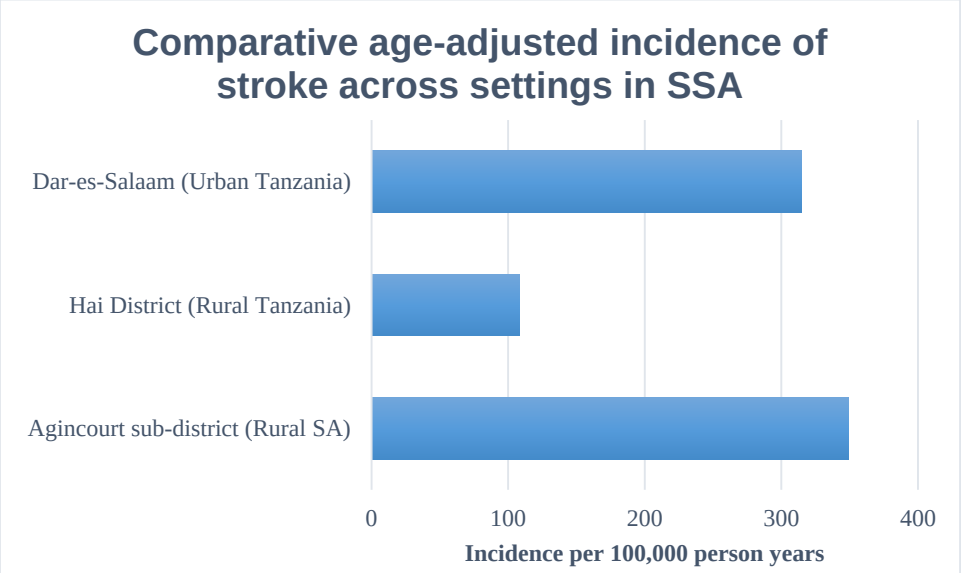


Figure 13: Comparison of age-adjusted stroke incidence rates calculated in the current study (Agincourt) with estimates from other settings in SSA

4.3 Detecting stroke burden attributable to modifiable risk factors

By using an established comparative risk assessment methodology, paper 2 illustrates that the high prevalence of known cardiovascular risk factors at younger

ages could partly explain the pattern of increased burden of stroke at younger ages in rural South Africa (Figure 14; Figure 15; Table 18). Based on this paper's analysis;

In females:

- Controlling systolic blood pressure levels within the Agincourt community such that the population distribution profile of systolic blood pressure has a mean of 115mmHg will potentially result in an approximately 50% reduction in burden of stroke at ages 55-59 years.
- Early onset obesity amongst younger age groups (25-49 years) is responsible for a third of the stroke burden in Agincourt sub-district. The peak of 35% occurs at age group 30-34 years. The trend of increased risk of stroke continues at older ages in women. It is important to note that the effects of BMI are partly mediated through blood pressure. Data from surveys conducted in different countries across socio-demographically diverse settings have consistently shown that, in most populations, blood pressure increases linearly with increasing relative body weight [11, 211, 212]. Nonetheless, the joint effects of high blood pressure and BMI were not examined in this thesis as the correlation between these risk factors is unknown and the grouped data could overestimate the burden from combined risk factors.

In males:

- The contribution of systolic blood pressure to the stroke burden is significant amongst the young adult males with more than 40% of the documented stroke burden in 2010 attributable to high SBP in the 25-39-year age groups.

In both males and females:

- The proportion of the stroke burden attributable to high systolic blood pressure is high across all age groups, and averages 35%.
- Notwithstanding the considerable uncertainty, diabetes was responsible for a relatively small proportion (<5%) of stroke DALYs in males and females aged between 65-75 years.

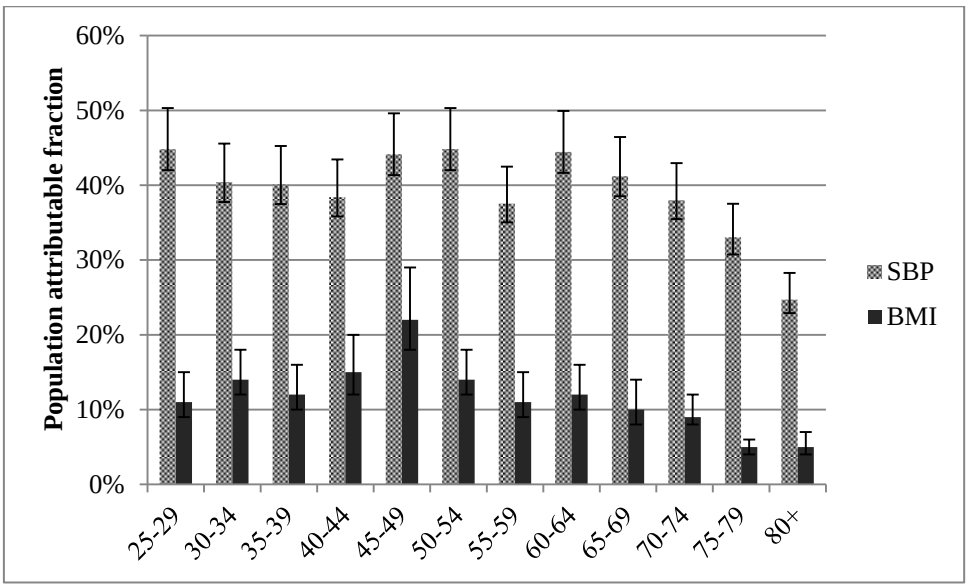


Figure 14: Distribution of population attributable fractions for stroke due to systolic blood pressure and body-mass index in adult males, Agincourt, South Africa, 2010

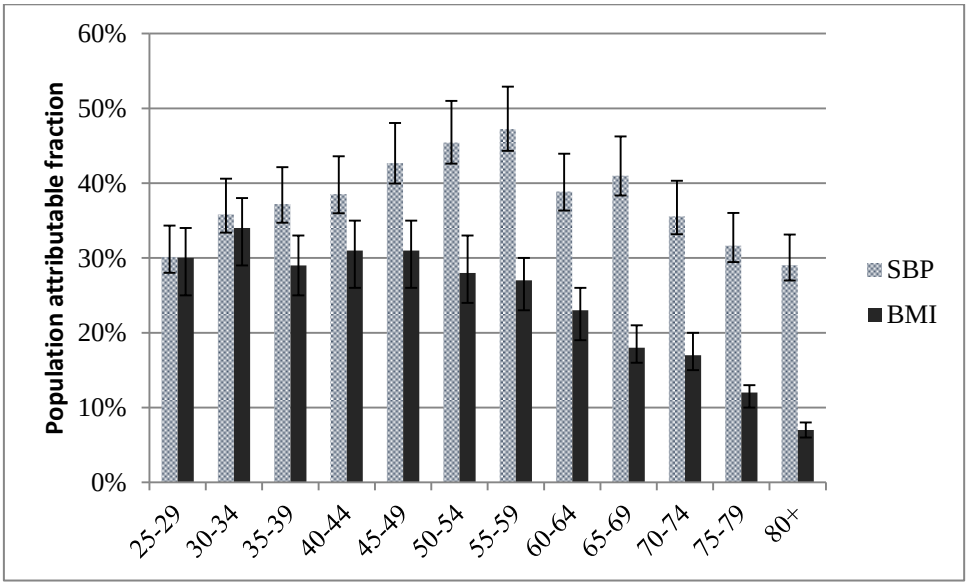


Figure 15: Distribution of population attributable fractions for stroke due to systolic blood pressure and body-mass index in adult females, Agincourt, South Africa, 2010

Table 18: Burden attributable to high blood pressure and excess body weight among adults aged over 25 years in Agincourt sub-district, rural South Africa (2007-11)

Adults 25+ years	Male	Female	Person
Total Stroke DALYs[24]	444.45	995.61	1440.10
% Attributable to high SBP	39.6	37.6	37.8 (23.8 - 49.8)
no. of DALYs attributable to SBP	176.00	374.35	544.40 (343 - 717)
Total stroke DALYs	444.45	995.61	1440.10
% Attributable to high BMI	11.4	22.5	19.2 (14.7 - 24.3)
no. of DALYs attributable to high BMI	50.67	224.01	276.5 (211 - 350)

It is important to reiterate that only metabolic risk factors have been assessed in this study; lifestyle factors such as tobacco, alcohol, salt and physical activity have not been considered. Furthermore, based on previous published studies, that showed that higher total cholesterol is less common in the Black African population[213], it was assumed that total cholesterol plays a limited role.

4.4 Economic consequences of an escalating stroke burden are significant

The increasing burden of stroke has placed additional economic strain on rural communities and health systems that are already suffering from HIV/AIDS and TB and traditional diseases of poverty. Paper 3 shows that, in Agincourt sub-district, the total direct costs of treating stroke cases (new cases plus existing cases) in one single year (2012) ranged between US$283,500 –US$485,000 depending on utilisation of health care services (Table 19). These figures represent 1.6-3% of the sub-district health expenditure. The lower figure of US$283,500 represents current

[24] Total stroke DALYs presented were calculated using a prevalence-based approach therefore values differ from those reported in Paper 1's abstract (the latter were estimated using an incidence-based approach). At the time of writing paper 2, the GBD 2010 study published by IHME had based the YLD calculation on prevalence rather than incidence and it seemed logical to follow the trend. Nonetheless, for reference, the main body of paper 1 also presents prevalence-based DALYs in addition to incidence-based DALYs.

extent of stroke management within the sub-district which falls well below the need for it.

By focusing on the breakdown of costs, we find that more than 80% of the costs in the first year post-stroke are attributable to inpatient care of stroke sufferers; thus suggesting that by preventing incidence of stroke within this community (possibly through targeting blood pressure and obesity as shown in paper 2), one can significantly reduce the economic costs of care. Though indirect costs (including gross loss of earnings) were not estimated in this study, they are likely to be significant. This is because younger individuals, who work as migrants and bread-winners are at high risk of suffering a stroke in rural South Africa.

Table 19: Total direct medical costs of stroke care in Agincourt sub-district, rural South Africa (2012), comparing the current (base case) scenario with a more optimistic best case scenario of improved health care coverage[25]

Cost items	**Cost — base case in Rands (US$)**		**Cost — best case in Rands (US$)**	
Diagnostic costs	R43,212	($4,967)	R265,984	($30,572)
Inpatient care costs	R2,164,000	($248,736)	R3,684,200	($423,471)
Outpatient care costs	R126,700	($14,563)	R126,700	($14,563)
PHC costs	R111,910	($12,863)	R111,910	($12,863)
Outpatient drug costs (11 months)	R12,629	($1452)	R3,026,200	($347,839)
Drug costs (1 month after stroke)	R7706	($886)	R13,342	($1534)
Total annual direct care cost	**R2,466,148**	**($283,465)**	**R4,215,780**	**($484,572)**

[25] Base case represents stroke management under current conditions whilst the best case scenario estimates the costs of stroke cases when coverage of all essential treatment and services is scaled up to 90%.

4.5 Cost-effective interventions can reduce the lifetime burden of stroke

4.5.1 Cost and effects of the interventions

The ‘polypill’ - a single drug combining a statin, aspirin 75mg and three antihypertensive agents at half standard doses (diuretic, calcium channel blocker and ACE-Inhibitor) - yields the highest number of healthy life years among all the alternatives. Within Agincourt sub-district, it is expected to avert 122, 128 and 205 DALYs per year when given to individuals at high, medium and low absolute risk of developing CVD in the next 10 years, respectively. Compared to other therapies assessed, the polypill results in the most DALYs averted among individuals with stage 2 hypertension. However, its benefits when targeted at the latter are lower than that observed when individuals are targeted based on their absolute risk of developing CVD in the next 10 years. Use of combination, rather than single therapies, is also associated with a greater number of DALYs averted across all target groups. The exceptions are combination therapies which include aspirin. Aspirin increases the risk of gastrointestinal bleeding and haemorrhagic strokes and this reduces in part, its overall additional health benefits, especially when other therapies are given first. The total incremental benefits (DALYs averted) within the sub-district as well as the incremental costs (cost of intervention less projected savings from reduced treatment costs) for all strategies are presented non-age weighted and discounted at 3% in Table 20.

4.5.2 Cost-effectiveness

Depending on the willingness to pay threshold chosen, pharmacotherapy could be a very cost-effective option even for people at low CVD risk (10-year risk of <10%). Average cost-effectiveness ratios fell within the range of US$160 to US$500 per DALY averted for all pharmacotherapies (figure 2, paper 4). Proposed thresholds in literature range from as low as US$150/DALY averted [214-216] to up to three times the GDP per capita of a country. Whilst ACERs provide useful background information, the optimal “intervention package” for each target group should be done after removal of dominated interventions to calculate incremental cost-effectiveness ratios

(ICERs). Interventions are strongly dominated if there is another competing alternative that costs less but is more effective. On the other hand, weakly dominated interventions have an incremental cost-effectiveness ratio that is greater than that of a more effective intervention. Weakly dominated interventions are ruled out to show that a combination of 2 strategies is better than a third alternative and that decision-makers generally prefer the more effective intervention with a lower incremental cost-effectiveness ratio.

Incremental cost-effectiveness

Table 20 shows the incremental cost-effectiveness of selected pharmacotherapies for all target groups for the 2012 Agincourt sub-district population. The incremental cost-effectiveness results are explained below for each target group.

Low risk

The results suggest that providing diuretics is the most cost-effective intervention; requiring US$228 to avert a DALY. The favourable price of hydrochlorothiazide is the major reason for this intervention showing such high cost-effectiveness in low-risk groups. Adding β-blocker to the diuretic is the next most cost-effective intervention, with an ICER of US$454 per DALY averted. Whilst combination of ACE-I and diuretic is cost-effective, it results in the highest ICER of US$2,752 per DALY averted. All the other strategies are dominated either by strong or extended (weak) dominance.

Medium-risk, high-risk and stage 2 hypertension

The combination of β-blocker and diuretic yielded the lowest ICER of US$173 in the medium-risk group. Providing this intervention averts a total of 109 DALYs per year at an additional cost of US$18,900 within the rural population of Agincourt sub-district. The polypill is the next most cost-effective intervention with an ICER of US$416 per DALY averted. It is worth mentioning that most of the benefit of the polypill is likely derived from the combination of 3 anti-hypertensives rather than the statin per se. As shown in Table 20, the combination of 2 antihypertensive medications and statin yields relatively fewer additional benefits (compared to 2 antihypertensive alone). The significant increase in life years that is seen with the polypill appears to be predominantly due to the addition of a third antihypertensive to the combination. This is unsurprising, and is in line with Paper 2 findings which

showed that cholesterol levels are probably not the biggest risk factors for stroke in Agincourt HDSS.

All other strategies were either weakly or strongly dominated. The optimal interventions are similar for the high absolute CVD-risk groups and for the group with stage 2 hypertension. Nonetheless the interventions have better cost-effectiveness in the higher-risk group i.e. those with ≥20% absolute risk of developing CVD in the next 10 years.

Using, as an alternative, the GDP per capita figure of US$7,548 (estimated for South Africa in 2012) [217] as the threshold for considering an intervention to be highly cost-effective, we found that all the interventions assessed met this criterion for all the risk groups and those with stage 2 hypertension. However, GDP based thresholds are generic and lack the necessary country specificity needed for them to be used in funding decisions and could lead to mistaken resource allocation decisions. This is further compounded when resource allocation decisions are at a sub-national level and focussed on deprived communities; in those settings the cost-effectiveness thresholds ca be anticipated to be much lower than that proposed by GDP based thresholds. The latter is supported in theory by a recent analysis on country-specific cost-effectiveness thresholds that showed that when opportunity costs rather than GDP are used as the basis for deriving cost-effectiveness thresholds, the willingness to pay in resource limited countries ranges between 1-50% of the GDP per capita of that country [218]. To circumvent the challenge that South Africa does not have its own willingness to pay thresholds, we construct cost-effectiveness acceptability curves. These indicate the probability of optimal interventions being cost-effective against a range of cost-effectiveness thresholds. According to that analysis the optimal strategies remain highly cost effective across the ranges of willingness to pay thresholds even after allowing for plausible variations in costs and effects.

One-way sensitivity analysis for the non-dominated interventions for all target groups showed that doubling the price of drugs and primary health care visits, reducing the intervention effectiveness to 50% of the point estimate and not discounting health benefits resulted in a change in ACER of more than 10% (table 4, paper 4). The average cost-effectiveness ratios were most sensitive to unit cost of drugs, with respective ACERs increasing by 50-75%. However, the results were less sensitive to

a change in drug effectiveness, to the lower boundary of effectiveness (the upper and lower boundaries of effectiveness estimates are shown on Table 15).

Table 20: Total annual cost, annual health benefits and cost-effectiveness ratio of selected pharmacotherapies for prevention of stroke in Agincourt sub-district, rural South Africa, 2012

Intervention	Life years saved	Years lived with disability averted	DALYs averted	Net costs (US$; 2012)	ACER	ICER
High absolute CVD risk (≥20%)						
Thiazide diuretics	53.8	34.5	88.3	15,500	176	Dominated
Aspirin + Diuretic*	51.7	33.1	84.8	14,700	173	Dominated
B-Blocker+ Diuretic	58.1	37.3	95.4	14,900	157	$ 156
B-Blocker+ Diuretic+Statin	60.3	38.6	98.9	16,800	170	Dominated
β-blockers	45.6	29.3	74.9	17,400	232	Dominated
PolyPill	68.3	43.8	112	21,100	189	$ 373
Calcium channel blockers	52.3	33.5	85.8	21,100	246	Dominated
Aspirin + B-Blocker	42.7	27.4	70.1	17,600	251	Dominated
Daily Aspirin	35.5	22.8	58.2	20,500	352	Dominated
ACEi / ARB	47.6	30.5	78.1	21,100	271	Dominated
ACE-I + Thiazide Diuretic	59.3	38	97.3	19,100	196	Dominated
Current Practice	40.2	25.8	65.9	26,800	406	Dominated
40mg/day statin (simvastatin)	43.3	27.8	71	28,200	397	Dominated
Medium absolute CVD risk (10-19%)						
Thiazide diuretics	67.5	33.6	101	19,700	195	Dominated
Aspirin + Diuretic	64.8	32.3	97.1	18,600	202	Dominated
B-Blocker+ Diuretic	72.9	36.3	109	18,900	205	$ 173
B-Blocker+ Diuretic+Statin	75.6	37.6	113	21,300	230	Dominated
β-blockers	57.3	28.5	85.7	22,100	248	Dominated
PolyPill	85.6	42.6	128	26,800	266	$ 416
Calcium channel blockers (CCBs)	65.6	32.6	98.2	26,800	273	Dominated
Aspirin + B-Blocker	53.6	26.7	80.2	22,300	275	Dominated
Daily Aspirin	44.5	22.2	66.7	26,000	279	Dominated
ACEi / ARB	59.7	29.7	89.4	26,900	300	Dominated
Current Practice	50.4	25.1	75.5	24,100	320	Dominated
ACE-I + Thiazide Diuretic	74.4	37	111	34,000	321	Dominated
40mg/day statin (simvastatin)	54.3	27	81.3	35,600	331	Dominated

Intervention	Life years saved	Years lived with disability averted	DALYs averted	Net costs (US$; 2012)	ACER	ICER
Low absolute CVD risk (<10%)						
Thiazide diuretics	133	29	162	36,900	228	$ 228
Aspirin + Diuretic	128	27.8	155	38,200	246	Dominated
B-Blocker+ Diuretic	144	31.3	175	42,800	244	$ 454
B-Blocker+ Diuretic+Statin	149	32.4	181	49,100	271	Dominated
β-blockers	113	24.6	137	41,400	302	Dominated
PolyPill	169	36.8	205	63,300	309	$ 683
Calcium channel blockers (CCBs)	129	28.1	157	50,700	323	Dominated
Aspirin + B-Blocker	106	23	128	42,500	332	Dominated
Daily Aspirin	87.7	19.1	107	36,800	344	Dominated
ACEi / ARB	118	25.6	143	50,700	354	Dominated
ACE-I + Thiazide Diuretic	146	31.9	178	66,200	372	$ 2,752
Current Practice	99.2	21.6	121	46,300	383	Dominated
40mg/day statin (simvastatin)	107	23.3	130	50,900	392	Dominated
Stage 2 Hypertension (BP>160/90mmHg)						
B-Blocker+ Diuretic	45	31	76.3	20,900	274	$ 274
Thiazide diuretics	42	29	70.6	19,800	280	Dominated
B-Blocker+ Diuretic+Statin	47	32	79	27,100	343	Dominated
Aspirin + Diuretic	40	28	67.8	23,300	344	Dominated
PolyPill	53	36	89.7	35,400	395	$ 1,082
β-blockers	36	24	59.9	23,700	395	Dominated
Calcium channel blockers (CCBs)	41	28	68.6	27,200	397	Dominated
Aspirin + B-Blocker	33	23	56	22,900	408	Dominated
Daily Aspirin	28	19	46.6	19,400	417	Dominated
ACEi / ARB	37	25	62.4	27,200	437	Dominated
Current Practice	31	21	52.8	25,200	477	Dominated
ACE-I + Thiazide Diuretic	46	32	77.8	37,100	477	Dominated
40mg/day statin (simvastatin)	37	21	58.1	27,900	481	Dominated

Values are rounded to 3 significant figures
DALYs – Disability adjusted life years are the sum of years lived with disability and years of life lost due to premature mortality
Net Costs – Intervention costs less projected savings from reduced treatment costs.
ACER - average cost-effectiveness ratio are median values and represent the cost-effectiveness of intervention against the alternative of doing nothing. ICER – incremental cost-effectiveness ratio is the ratio of

Intervention	Life years saved	Years lived with disability averted	DALYs averted	Net costs (US$; 2012)	ACER	ICER
the incremental costs and incremental effects of moving from one intervention to the next more effective intervention starting from the most cost-effective intervention. ICER – where ratio is dominated, the intervention costs more and is less effective than an alternative strategy *Combination therapies which include aspirin yield lower DALYs than expected due to the assumed increase in deaths due to GI bleeding and the increased mortality among those with haemorrhagic stroke						

4.6 The most cost-effective interventions are potentially affordable

In 2012, there were approximately 4.3 million people over the age of 30 residing in predominantly rural communities of South Africa (Table 7). Assuming that the same pattern of CVD risk observed in Agincourt sub-district exists throughout the entire rural South Africa, the number of people with low, medium and high absolute CVD risk would be 4.1million, 132,000 and 55,000 respectively. The budget impact, per year, of giving the optimal interventions of β-blocker/Diuretic and polypill to at least 90% of individuals with high CVD risk was estimated. The findings show that the government would need approximately $4.06 million and $ 6.28 million each year to cover these drug costs for the β-blocker/Diuretic and polypill respectively. These figures need to be understood in the context of budgetary constraints within the Department. In 2012/13 the health care budget for the country was R121 billion (US$13.9 billion). Based on this figure, the annual costs of providing β-blocker/Diuretic or polypill to individuals with high absolute CVD risk in predominantly rural communities of South Africa correspond to less than 0.1% of the total health care budget.

4.7 Synthesis of findings on CVD prevention in Agincourt sub-district, South Africa

The accumulated evidence from this work suggests that stroke prevention is urgently needed. The significant premature mortality which is a consequence of increased stroke risk largely due to modifiable risk factors of high blood pressure and excess weight amongst younger adults provides compelling evidence to spur action. This is consequent on the high prevalence of largely modifiable risk factors of high blood pressure and excess weight, in particular amongst young adults. Current systems for primary prevention do not appear adequate. The proportion of people with untreated high blood pressure, particularly stage 2 hypertensions is testimony to this. Furthermore, the finding that treating these individuals with low cost thiazide diuretics and β-blockers is a highly cost-effective strategy for CVD prevention highlights a missed opportunity for action.

The cumulative and still growing burden of lifestyle risk factors has further increased the likelihood that individuals in this community will experience a stroke event, and this can only be averted by instituting effective primary measures (paper 4). By maintaining status quo, we show that the economic burden of stroke treatment will be considerable for the health system that is still grappling to deal with HIV/AIDS and other diseases of poverty. However, such costs can be considerably reduced through a combination of population-based and individual-based interventions selectively targeted at high risk individuals.

Through an understanding of the epidemiological burden (paper 1), economic burden (paper 3), attributable burden from key risk factors (paper 2), the thesis highlights that it is possible to develop and model disease projection within this rural population and demonstrate the extent to which such mathematical models can identify optimal prevention interventions. Through paper 4, we derive important findings for policy. The main ones are:

- a systematic, localised understanding of mortality and cause-of-death data which together with, risk factor data, at a time of rapid health transition, can provide the basis for developing projection models that can give us outcome-oriented information necessary to inform CVD prevention in our setting. Such data is available within the health and demographic surveillance site. Moreover, our findings will adaptable to similar rural settings of South Africa and other HDSS sites within the sub-Saharan African region.

The availability and richness of data to characterize the changing and evolving burden in Agincourt sub-district highlight strengths of the Agincourt HDSS at a time when the imperative for a knowledge base could not be greater.

Chapter 5 Discussion and Conclusions

The body of work covered in this thesis describes the current and future epidemiological and economic burden of CVD in rural South Africa using stroke as the marker condition. It presents a model calibrated for the Agincourt sub-district population that can project future burden of stroke, and demonstrates that this is a potential tool to aid priority setting and resource allocation. By aggregating evidence from a well-defined setting on the epidemiological burden of disease (paper 1), risk factor profile (paper 2) and economic costs (paper 3), the thesis highlights that it is possible to derive context-specific and outcomes-based solutions to CVD prevention (paper 4). To date, the biggest challenge in primary prevention of CVD has been the lack of reliable population data and this thesis strengthens the evidence base and the scope for contribution to provincial/national policy and programme development.

This section will demonstrate the plausibility of results by discussing the methods used and highlighting key findings within the context of national and international literature. Furthermore, it draws out implications for priority setting.

The discussion will be organized into three thematic areas:

- The ongoing health transition in rural South Africa
- Implications of a rapidly rising CVD burden
- Policy and practice: Locally generated evidence and tools to support priority setting adapted to the local South African context

5.1 Health transition in a rural South African setting

There is growing literature suggesting that rural South Africa is undergoing an epidemiological transition that is a consequence of urbanisation, an ageing population and a nutritional transition [116, 172, 219]. By computing epidemiological estimates for stroke (paper 1) and contrasting with local and international settings, this thesis broadens the evidence base to determine the extent to which such transition is indeed occurring within a well-defined rural setting.

Stroke incidence that is similar to the incidence in 'urban' settings at more advanced stages of epidemiological transition point to a disease burden that is tending towards diseases of lifestyle. Taking these findings together with those of paper (2) which showed that at least 40% of the documented stroke burden in Agincourt is due to raised blood pressure and excessive weight, this thesis highlights that the increase in CVD is propagated by an increase in lifestyle risk factors. Kimani-Murage et al have documented a nutritional transition in this community that has seen adolescent obesity on the rise [116]; a finding confirmed by the higher risk of stroke associated with excess weight amongst young adults in our study. The findings from this work confirm those of other studies that have shown that in settings where obesity is on the rise, CVD, specifically stroke increases.

The findings of this thesis have far-reaching consequences within the Agincourt community:

- The apparent increase in CVD comes at a time when age-standardised prevalence of HIV/AIDS stands at 26% in men and 19 % in women [175] and average under-5 mortality rate stood at 62 per 1,000 live births (between 1992 and 2013) [220]. This depicts the multiple health challenges the community faces.
- Not only is the incidence of stroke high in comparison to other settings in SSA, mortality due to stroke has increased within the Agincourt sub-district community. This suggests that current systems are inadequate to prevent CVD. If the current trend continues, the efforts made to reduce premature mortality from HIV/AIDS may be seriously undermined if countered by increased premature mortality from CVD.
- The large burden of stroke that is attributable to excess BMI in young and middle-age females is occurring in a community where hunger, food insecurity, micronutrient deficiency, and excessive intake of calories co-exist [116]. Tackling this double burden of malnutrition will require creating an enabling environment that will facilitate the implementation of interventions focused towards both undernutrition and overweight and obesity [221].
- The over-representation of older women in rural South Africa is noteworthy; it has social and healthcare implications, some of which have already been

documented. For example, older women in rural South Africa are assuming the role of primary caregiver due to labour migration, non-marital child-bearing, and the increase in the number of children left orphaned by HIV/AIDS [222]. At the same time, the increase in prevalence of HIV/AIDS and in cardiovascular diseases, namely stroke (as indicated in this thesis) among adults aged 50+ years are leaving older women in need of care themselves. It is thus important to understand whether available policy programmes e.g. “cash assistance to older persons’ homes shape not only their carework, but also their own health and well-being” [223]. Similarly, but most often overlooked, is the availability of psychosocial support programmes that can provide older carers with support to help them carry out their caring duties whilst ensuring that they look after their own physical and emotional well-being

Studies that evaluate the theory of demographic and epidemiologic transitions are based on longitudinal assessment of empirical data. This thesis attempts to bring together actual longitudinal mortality and cause-of-death data with data on metabolic risk factors in order to create a holistic picture of epidemiological transition in the Agincourt HDSS. Is this approach valid? This question can better be answered by highlighting the strengths of the HDSS and the methodological approaches adopted in this study. Agincourt HDSS characterizes a well-defined population (contextual strengths), and supports acceptable analytic designs and studies carried out within the same population. These are scientifically complementary to create an integrated picture on socio-economic and health transitions in the community. Secondly, the methodologies that were utilised in this study to measure incidence and attributable burden have been validated and accepted internationally (methodological strengths). A key message from this section is that an epidemiological transition seems to be well underway in rural Agincourt and likely in other similar settings. Unless curbed, through targeting modifiable risk factors such as high blood and obesity, the consequences for a community that is still grappling with traditional disease of poverty could be severe.

To expand our understanding of epidemiologic and health transitions beyond health and demographic surveillance sites to national and sub-national levels, future research will require: (i) “reliable unbiased documentation of age- and sex-specific mortality, including the major causes of deaths in the population and (ii) periodic

documentation of exposure to the major risk factors of mortality by age and sex (via periodic population-based surveys)"[224]. The latter has been particularly lacking in low and middle-income countries. This has forced researchers to rely on a series of random snapshots from studies that utilise methodologies that are not always comparable.

5.2 Implications of CVD burden

Communicable diseases, which are high in Agincourt sub-district and many rural settings of South Africa impose not only heavy human costs in terms of suffering and death, but also heavy financial costs on poor households. As CVD burden (morbidity and mortality) increases, the costs to governments are significant (paper 3). Health transition in rural South Africa, described in the section above, represents an enormous challenge to the country where resources to implement an effective response are reducing in absolute terms.

In section 5.1 above and paper 1, a picture of increasing stroke mortality and high incidence of stroke due to modifiable risk factors is presented. The high incidence of stroke can be expected to increase demand on health services particularly at hospital level. Paper 3 shows that even though the proportion of stroke cases that reach hospitals is modest in Agincourt sub-district, the inpatient care costs are significant – i.e. more than 80% of the total direct costs of care. Owing to the disabling nature of stroke, substantial costs to livelihood and the local economy due to productivity losses can be anticipated. Though such costs were not calculated in this study, estimates derived from other developing country settings suggest that productivity losses are highest in countries where people delay seeking care. Studies from other settings have indicated that productivity losses make up a significant part of total costs of care [25].

The findings that burden of stroke - both morbidity and mortality - is high amongst prime age adults has severe social implications within the community. Whilst not the focus of this thesis, it is important to mention that according to other studies conducted within the Agincourt HDSS, households that have experienced an adult death suffer greater consequences: increased deaths of infants and children in the

family and greater use of natural resources e.g. firewood to compensate for the loss of an adult household member [225]. In addition, death of prime age adults imposes a huge burden on the elderly who are left to tend to the younger children (including widespread fostering) contributing towards a complex social transition.

5.3 Implications for health system organization

The demand to re-organise health services on the premise of increasing CVD disease becomes more urgent (Figure 16). Until recently, the health system has been designed to cater mainly to communicable diseases and maternal and child care and was biased towards acute, curative rather than preventive and long-term continuing care. Though effective control of communicable disease remains important, re-designing health services to prevent onset of stroke by managing risk factors such as high blood pressure, or managing stroke (so as to limit premature mortality) is critical. As such, chronic-care programmes that are developed to function alongside existing services for acute care, maternal health and child health could prove more effective than the situation currently [226]. The integrated approach that is currently being piloted at the Agincourt HDSS - that aims to ensure that all chronic disease patients (hypertensives, HIV/AIDS, diabetics) are managed within the same health care platform - offers hope for CVD prevention into the future [162].

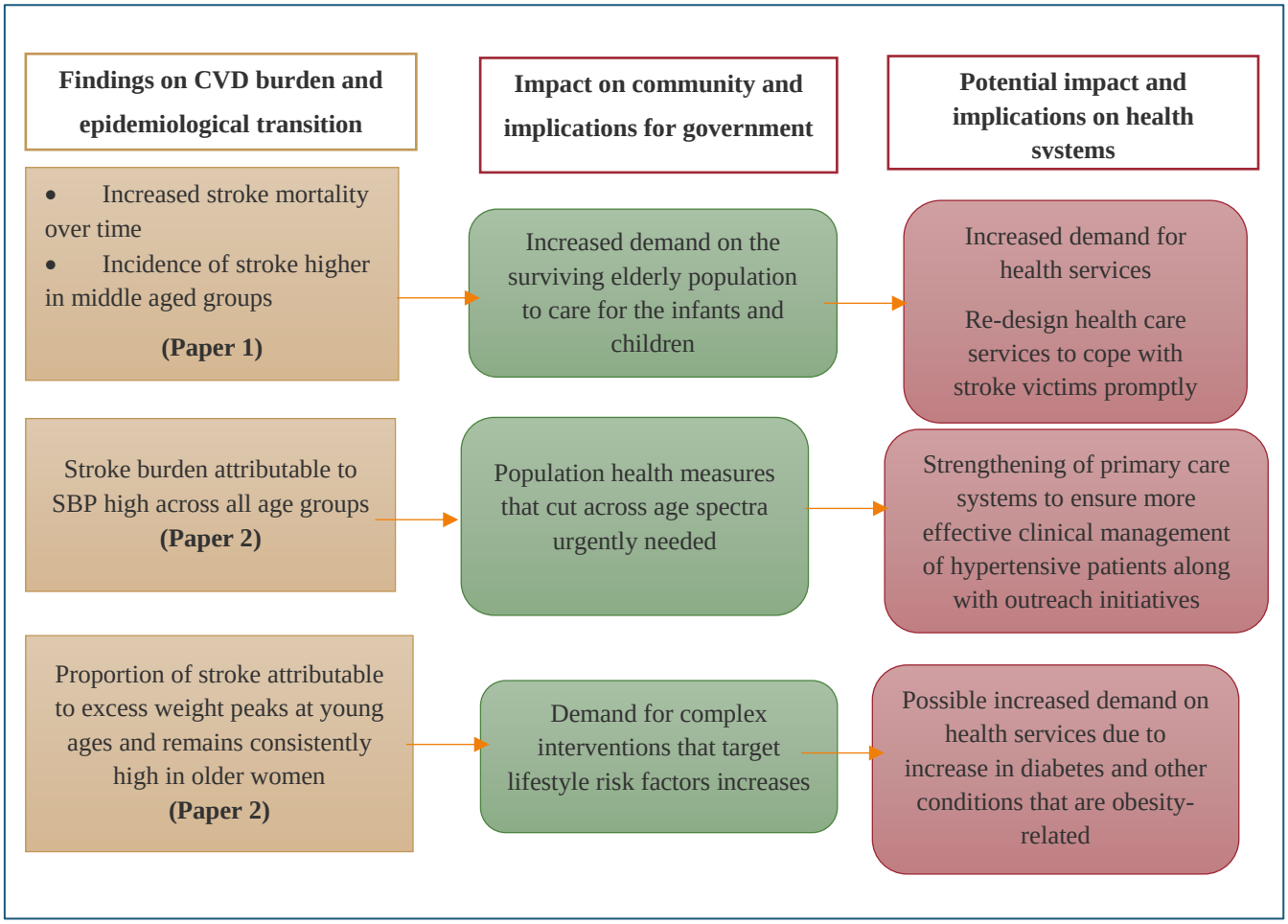


Figure 16: Potential impact of CVD burden and epidemiological transition on health system services and community

5.4 Implications outside the health system

It is commendable that policy-makers in South Africa are already acknowledging that a multi-faceted approach that includes non-health sector specific interventions is needed to ensure optimal CVD prevention [129]. Whilst two legislative interventions for salt [227] and sugar [228] have already been drafted, there is still room to curb unhealthy foods through a fat tax that targets unhealthy fats in processed foods. There is cumulative evidence in South Africa that a legislated salt intervention is not only cost-saving but will potentially prevent catastrophic health spending though this was not, as yet, specifically assessed within a rural population [22, 29]. The finding potentially applies to other population-wide interventions, such as those targeting sugar consumption [156]. The impact of using a multi-pronged approach that includes amongst others, pharmacotherapy and population-wide interventions such as salt reduction cannot be over-emphasized.

5.5 Policy and practice: Locally generated evidence and tools to support priority setting

This body of work adds to the portfolio of priority setting initiatives and data sources in South Africa, each of which has its strengths and limitations. These include initiatives focused on priority setting on the basis of burden of disease as along lines of the *Global Burden of Disease, Injuries and Risk Factors* study [229]. This initiative, championed by the World Health Organization and Institute of Health Metrics and Evaluation (IHME) in Seattle uses a standardized measure of disease burden - the disability adjusted life year (DALY) metric – to compare and track burden across disease categories. The overall intent is to identify a region's burden of disease profile to ensure continued prioritization of resources to address these causes of death and disability. Other initiatives such as the *WHO CHOICE (Choosing Interventions that are Cost-effective)* focus on cost-effectiveness analysis to facilitate comparison of interventions on the basis of their "value for money" [230]. Yet another group of initiatives have concentrated on quantifying the number of lives that are potentially saved when coverage of key essential interventions is increased, and these include the *Lives Saved Tool* (LIST) developed at Johns Hopkins University, in Baltimore [231]. Though the overall goal of these initiatives is the same: to provide better, scientifically valid information regarding a decision issue so as to contribute towards better informed and more rational decision-making, they still face several methodological challenges that can limit their use at a local or sub-national level. These include: absence of local specific data in analyses and inability to capture heterogeneity that exists within marginalized communities. An appreciation of the strengths and limitations of these sources is needed in order to assess the value-add of this thesis.

5.5.1 Generating baseline DALY estimates on the basis of mortality and morbidity

Information on the baseline and future trends in burden of diseases and related risk factors is needed for planning and monitoring local, national and international CVD prevention responses. This was true of the Millennium Development Goals (MDGs) and is equally relevant to the Sustainable Development Goals (SDGs). One of the

main obstacles in developing appropriate disease prevention strategies at country level is a lack of high quality health information [129]. While many countries in Africa have well established information systems for communicable diseases, in general, the burden of NCDs including CVD is not as well documented [232]. For example, between 1960 and 2014, less than 20 published studies reported on stroke incidence [82]. Out of these, 7 were from Egypt, 2 from Tanzania and 2 from Nigeria suggesting the narrow scope of the information base. Thus certain assumptions that have informed modelling and forecasting exercises for the Africa region had major limitations. By deriving estimates of incidence, mortality and disability-adjusted life years (DALYs) using predominantly local data, we increased the degree of confidence in the assumptions that inform modelling efforts in South Africa. Data currently emerging from Tanzania indicates the potential of conducting economic and modelling-based studies of stroke, once baseline incidence estimates are established.

In addition, this work has begun to contribute towards a systematic way of measuring disease burden using a comparable metric measure - the DALY. For example, within the Agincourt HDSS, Wagner et al (2015) reported that DALYs lost to convulsive epilepsy in 2008-2012 were 332 [233]. Using a similar time period, we reported a DALY loss of 1,070 DALYs in Agincourt [210] suggesting that on the basis of a combined morbidity and mortality measure, stroke imposes a larger burden on the Agincourt sub-district population. Thus, even in the absence of other data, we can begin to rank diseases (by priority) on the basis of epidemiological burden. Whilst our study and the study by Wagner et al are the only studies yet to have measured disease burden in DALYs in Agincourt sub-district, they have paved the way for future studies to adopt similar approaches since the data to conduct the requisite analysis is readily accessible within the HDSS. To summarise, empirically derived HDSS data could, and should, be integrated into national information systems, by calibrating the many ‘light’ surveys with the greater depth of information from the HDSS.

At a national level, it remains critical to monitor acute stroke and its care by setting up national stroke registries. From this thesis, we learn that mortality is unacceptably high following a stroke and this contributes to the estimated high DALY loss. By understanding the incidence of acute stroke policies to improve care can be

developed that are appropriate to context and better targeted at the stroke survivors, in the process being equity enhancing.

5.5.2 Mathematical model as priority setting tool

Even with the knowledge regarding the diseases or conditions to target, local decision making on how to intervene is usually difficult. Until recently, most of the evidence base on cost-effectiveness was derived from regional estimates which, as noted, are limited by the data that is used as input in analyses [144]. By taking advantage of the "data wealth" of the Agincourt HDSS, including prevalence of risk factors it was possible to develop a mathematical model customised to the Agincourt population that can assist and support local decision makers in this regard. We demonstrated the capability of the model (paper 4) and selected several pharmaceutical interventions to assess population effects. Thus explored the capacity of the model to characterize interventions that could be a priori on the basis of costs and health outcomes. It is important to note that the model is not limited to assessing pharmacotherapies only but can be used to evaluate cost-effectiveness of population-wide preventive or behavioural interventions. As more effectiveness evidence for other interventions becomes available in the future, these can also be assessed. Of particular note is the Nkateko trial, implemented in Agincourt sub-district in 2014, which ran until March 2016 [8]. This intervention works with lay health workers to identify new (untreated) and manage existing hypertensive patients within the primary care clinical setting [8]. Once the primary cost-analyses are finished and outcomes data published, the model built in this thesis will be used to project the lifetime costs and benefits of this locally-relevant intervention. The findings of this thesis have demonstrated that targeting medical treatment at patients with stage 2 hypertension is a less cost-effective strategy for stroke prevention compared to targeting individuals with a high absolute risk of developing CVD in the next 10 years. This finding is reinforced by the recently-released Joint National Committee (JNC) guidelines which now propose a lower cut-off for blood pressure compared with JNC 7 guidelines [234]. According to the updated guidelines, adults with an average systolic blood pressure of 130 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg are categorized as having stage 1 hypertension; these were previously classified as prehypertension in JNC 7 [234]. It will be important to establish if the Nkateko trial, with its locally relevant and more up-to-date data, will corroborate or contradict these

findings. Within the Agincourt sub-district, 50% of people with hypertension are on treatment, whilst in total only 23% have optimally controlled hypertension [235].

The approach that was used to develop the mathematical model is scaleable beyond the Agincourt HDSS and sub-district, as well as South Africa. Since most of the INDEPTH Network centre sites collect comparable data, it would be possible to integrate information from other HDSS so that a “true” regional picture of cost-effectiveness of CVD interventions can be derived on the basis of locally derived data. By doing this, it becomes possible to validate the model (expected outcomes) against data that has been collected prospectively (observed outcomes), for example incidence data in Tanzania. Ultimately, this could lead to a tool that is generated regionally and is highly context-specific.

The results should be considered in light of model limitations. Interactions of HIV/AIDS treatment with CVD risk factors and CVD outcomes were not assessed. This is despite the high prevalence of HIV/AIDS in South Africa and the emerging evidence that HIV and highly active antiretroviral therapy could affect CVD outcomes [236, 237]. A more complete single model that is capable of simultaneously dealing with all cardiovascular risk factors and HIV interactions is needed. However, current empirical data on HIV/CVD interactions to support the development of such a model are still scarce and based on small scale studies in high-income countries [238].

The modelled economic evaluation results should be used as a guide for decision makers and are not prescriptive, since other factors—such as implications for equity of the intervention, feasibility of implementation and financial burden to the government—should be taken into account. Moreover, health systems usually have other resource-competing “very cost-effective” interventions that have not been completely scaled-up e.g. childhood interventions which, when compared with interventions assessed in this study, could prove ‘better’ value for money. No explicit value has yet been set for the cost-effectiveness threshold in South Africa; without this value interpretation of what is cost-effective remains debatable. Future research should focus on developing a threshold that clearly incorporates budget constraints and opportunity costs in South Africa.

Personal note:

A major strength of this thesis is that costs and disease parameters were based on local data. This approach has already appealed to the National Department of Health which recently approached me (together with other researchers) to be part of a team of analysts to conduct a cost-effectiveness analysis of statin treatments (at different doses) on cardiovascular disease prevention in the country. This analysis (coupled with, and compared to, other mathematical-based models) would assist in the process of revising the essential medicines list for the country and thereby contributing to establishing South Africa's nascent NHI system. It is my hope that this would be the beginning of sharing evidence on what therapeutic interventions would be most appropriate in rural and marginalised communities of South Africa.

5.5.3 HDSS as a platform for generating data

The thesis demonstrates repeatedly that data from the Agincourt HDSS was key in informing more advanced modelling approaches. By implication, demographic surveillance sites are well positioned to generate reliable estimates that can be used in forecasting or model-based analysis. On its own, the Agincourt HDSS data has limited generalisability capacity. However, if data from the other two health and demographic surveillance sites in South Africa (Dikgale in Limpopo province and Africa Health Research Institute (AHRI) in KwaZulu-Natal province) are pooled with Agincourt data, together they can inform a national picture of disease burden and approaches to addressing this within marginalized communities. This potential is now within reach given the recent formation of SAPRIN – the South African Population Research Infrastructure Network – a new "national research infrastructure" based on an innovative partnership of the Department of Science and Technology (DST) with the Medical Research Council (MRC) and contributing HDSS centres/universities (Agincourt, AHRI and Dikgale (http://saprin.mrc.ac.za/).

5.5.4 Data quality

High quality data is a pre-requisite for accurately evaluating and monitoring the burden of disease in populations and the impact of public health interventions. This section provides an overview of the quality of data received from the Agincourt HDSS

focussing where possible on six main attributes of data quality i.e. completeness, accuracy, timeliness or up-datedness, validity, reliability and relevance.

Mortality and cause of death data - Within the Agincourt HDSS, completeness of death registration averaged 90% in 2007-11 and this increased to 96% in 2013-14 [239]. Information from verbal autopsy interviews (for cause of death) was available for 87% of these deaths, of which the InterVA-4 model classified 6% as indeterminate. Whilst there is no gold standard against which HDSS data can be measured, useful insights can derive from comparing findings with national data. For example, in a study by Kabudula and colleagues, at least 80% of deaths recorded in the HDSS were matched to the civil registration system. Records that were not matched belonged to more vulnerable people, including poorer persons, young children, and non-South Africans [240]. Similarly, it is challenging to state with certainty the accuracy of cause-of-death data that is derived through verbal autopsies. For example, operational factors such as yearly data collection can result in a time lag - from death to VA interview—which influences how terminal events are recalled, which in-turn affects cause-of-death assignment [241]. Nonetheless, a recent study, based on 10,882 deaths from the Agincourt Health and Demographic Surveillance System (HDSS) showed that recall period did not have a significant impact on cause-of-death assignment [241]. The researchers considered two recall periods: within six months of death and verbal autopsies undertaken from six to 12 months of death. The exceptions were neonatal deaths where the cause-specific mortality fractions ratio between 2 recall periods were significantly greater than one. Other than recall bias, there are concerns that automated interpretation of verbal autopsy data into cause of death information using tools such as InterVA-4 results in misclassification of deaths. However, a secondary data analysis of verbal autopsy archives covering 54,182 deaths from five African (including South Africa) and Asian countries showed strong concordance between InterVA–4 and physician–coded verbal autopsies (concordance correlation coefficient was 0.83 (95% CI 0.75 to 0.91)) [242]. Whilst the strong concordance does not imply that cause of death ascertainment is completely accurate it shows that interVA-4 used for cause of death ascertainment is consistent with other methodological approaches for converting verbal autopsy data into cause-of-death data. It is important to note that there are several quality control checks at different phases of the data collection process including fieldworker self-checks,

supervisor random checks and verification of data by a dedicated quality checker before data entry within the HDSS.

Prevalence of stroke – One of the key strengths of the prevalence data used in this study is the accuracy of the denominator as the SASPI study was conducted within a surveillance site, with a well-defined population. Nonetheless, seventy-four percent of individuals who screened positive for stroke based on the 2 screening questions: "Has (person) ever had weakness down 1 side of the body?" and "Has (person) ever had a stroke? were available for clinical assessment. This means that data was not available for at least 25% of individuals. The study authors made an assumption that stroke prevalence was equal in those examined and not examined. However, baseline characteristics of unexamined individuals were not provided; it is therefore challenging to comment on the validity of that assumption. The SASPI study was a cross-sectional study thus events were not captured as they occurred. However, accuracy of stroke diagnosis was enhanced through detailed clinical assessments performed by a neurologist and clinicians trained in stroke diagnosis.

Prevalence of cardiometabolic and lifestyle risk factors (diabetes, hypertension, obesity, high triglycerides, smoking, and waist circumference): Complete covariate data were available for 3,641 individuals out of a total of 4,362 individuals who consented, i.e. 83% completeness. The study was conducted in 2010 and at the time of analysis provided more up-to-date estimates of cardiovascular risk factors within the Agincourt sub-district. Nonetheless, approximately 43% of eligible individuals who were randomly selected for the study refused to consent. Because data on the baseline characteristics of those who refused to consent were not available, it is difficult to comment on whether consent bias was an issue in the study i.e. those who consented differ significantly on some characteristics compared to those who did not. Nonetheless, as a preliminary analysis, this thesis compared the baseline characteristics of the individuals whose data were available for analysis to that of the general population of Agincourt sub-district and the results indicated that the characteristics were broadly similar. Therefore, based on that analysis it is likely that the analysed population sample was representative of the general population.

To summarise the major strengths and potential weaknesses with the quality of data received for this study: timeliness and or updatedness was one particular challenge.

Some of the issues related to data quality were addressed statistically through sensitivity and uncertainty analyses to assess the impact of parameters with a degree of uncertainty on outcomes. For example, @Risk 6.3 Professional for excel was used to conduct uncertainty analysis for population attributable fractions through Monte Carlo simulations. Through this approach, models of possible results were built by substituting a range of values—a *probability distribution*—for any parameter that has inherent uncertainty. Results were recalculated several times, each time using a different set of random values from the probability functions. For each of the output variables (for example attributable burden due to BMI or high blood pressure), 95 % confidence intervals were calculated bounded by the 2.5th and 97.5th percentiles of the 1000 iterations generated.

5.6 Gaps Identified and Limitations

It is worth noting some of gaps and limitations arising from this research effort.

- The data for this study were predominantly from Agincourt HDSS – a single ecologic area that is relatively ethnically homogeneous[26] - and cannot be representative of all 69 other municipalities in rural South Africa. It is important to reiterate that all projections to rural South Africa were based on the conservative assumption that prevalence and distribution of risk factors across all municipalities that are considered 'mostly rural' is similar to that of Agincourt sub-district. However, Agincourt HDSS is a research site, where few intervention studies with the potential to alter lifestyle choices have been implemented over time. Because such interventions are not widely available in districts where research is not actively carried out, it is possible that awareness of risk factors may in fact have lowered CVD risk factors in the Agincourt population compared to other rural settings.

- Even in a community such as Agincourt sub-district where there are various nested studies in which lifestyle health education is offered coupled with promotion and prevention initiatives, prevalence of lifestyle risk factors remains unacceptably high. This raises the big questions – Is the Agincourt HDSS with governmental and non-governmental partners maximizing the potential of these studies and taking full advantage to educate individuals within the community?; what efforts are being made to ensure that lifestyle interventions extend beyond the length of research studies. The latter is currently a focus area in the Agincourt HDSS.

- There is scope for much more to be done within the Agincourt HDSS and other centre sites in South Africa, particularly where evaluating lifestyle interventions is concerned. Currently, there is limited evidence on what lifestyle interventions are effective in such settings. This is against a backdrop

[26] A third of the Agincourt population are former Mozambican refugees.

of increasing literature that obesity is increasing, hypertension prevalence is unacceptable and lifestyle risk factors are increasing within the sub-district. Generating this information would contribute towards a missing yet key aspect of evidence in literature [243]. Worldwide the evidence on weight-loss interventions is mixed [244, 245]. Ideally, the HDSS would inform us on: (i) how lifestyle interventions should be designed in rural African settings where nutritional patterns are complex, and (ii) how effective lifestyle interventions are [246]. It is encouraging to note the recent efforts to identify critical factors that need to be considered in the development of effective and culturally-appropriate lifestyle interventions in rural communities. Published studies from Agincourt HDSS have focussed on healthy eating practices and physical activity, mostly among adolescent girls in rural South Africa [247-249]. Data emanating from these studies indicate that there are major overriding, and most often inter-linked contextual issues that could challenge the implementation of lifestyle interventions in rural communities. These include: gender inequality, rapid social transitions, and chronic poverty [247]. For example, gender bias in the way in which sports competitions are organised and funded, and in the physical condition of sporting facilities (better for boys) influences the extent to which girls are physically active [247]. On the other hand, despite the widespread knowledge about healthy eating practices within the sub-district, poverty, was consistently found to be a barrier to healthy eating as access to healthy (most-often pricey) food options remains limited [248]. Furthermore, socio-economic transitions and greater exposure to "western media" influenced adolescences' perception of body image, eating habits and physical activities. By synthesizing the data from these studies, there is an opportunity to develop models for lifestyle risk interventions that are better-suited to adolescents in disadvantaged rural communities. From an intervention perspective, it is encouraging that there are proposals to develop a church-based weight management programme with the AHRI HDSS (Sally Wyke, personal communication).

- Emerging data in rural KwaZulu Natal suggests that IHD, which was low in rural settings (but high in urban settings) at the time this study was conceptualized is on the rise. Stroke and IHD share similar risk factors. Targeting the main behavioural risk factors namely; tobacco use[27] (in men), high blood pressure, high body mass index (BMI), high cholesterol, high blood glucose, and physical inactivity will assist in reducing both stroke incidence and IHD. It is possible that the economic evaluation underestimated the health benefits of CVD prevention strategies as stroke was the only outcome assessed and future analysis should include impact of interventions on ischaemic heart disease.

- Whilst acknowledging the emerging literature on stroke/HIV interactions, the evidence base on the nature of pathophysiologic mechanisms and their effects is still limited. As such, it was not possible to explore the impact of this relationship within the study and this remains a critical area of future research in high HIV-prevalent settings. There are studies underway in Agincourt HDSS that could generate data relevant to such analysis.

- The conclusions of our cost-effectiveness analysis are subject to important limitations reflecting the nature of the model. Most of the treatment effect data was derived from meta-analysis of randomised control trials. Many of these trials are based on populations in developed countries and treatment effect could differ in our population thus affecting cost-effectiveness of interventions as evidenced by the sensitivity analysis. Furthermore RCTs are conducted in controlled settings and the effectiveness in real life could be lower than assumed in our model. One of the key findings of the cost-effectiveness analysis was that the polypill was highly cost-effective. However, effectiveness estimates were conservatively assumed to be the multiplicative effect of individual therapies. It will be important to re-analyse this data once empirical data from longer-term follow-up studies become available. Furthermore, we

[27] Tobacco use is currently very low among rural women.

did not stratify our population based on diabetes status. However, there is evidence to suggest diabetes incidence increases in patients treated with thiazide diuretics or β-blockers compared with other classes of antihypertensive drugs [250]. Thus, future efforts of this modelling exercise will attempt to incorporate diabetes risk.

- This study utilised the traditional cost-effectiveness analysis approach of determining the optimal interventions based on the value per dollar spent. However there are recent advances to the 'traditional' CEA, namely the extended cost-effectiveness analysis (ECEA) approach [143] that could go beyond CEA by explicitly considering the multiple dimensions and outcomes that ensue from health policies such as: 1) the health gains; (2) the financial risk protection benefits; (3) the total costs to the policy makers; and (4) the socio-economic distribution of health gains. Performing ECEA was beyond the scope of this study as it requires disaggregated inputs per specific population subgroups and out-of-pockets costs borne by individuals and their families [143] . Much of this data is not readily available in low and middle-income countries.
- Lastly, whilst reflecting on the process of conducting the cost-effectiveness analyses I believe that though these models are useful it is important for us to invest in calculating what each service in the country (treating a hypertensive patient etc. costs us). Without accurate cost estimates of how much the government is paying for such services, it is challenging to conduct cost-effectiveness analyses in a timely manner. In high-income countries such as the United Kingdom, analysts use pre-defined Healthcare Resource Groups (HRGs)[28] to estimate unit costs of treatment for health conditions. Though, there are some controversies surrounding the accuracy of some of the HRGs, the availability of unit cost data across all diseases have enabled timely cost-effectiveness analyses.

[28] HRGs are standard groupings of clinically similar treatments which use common levels of healthcare resource. HRGs are currently used as a means of determining fair and equitable reimbursement for care services delivered by providers. Their use as consistent 'units of currency' supports standardised healthcare commissioning across the service (http://content.digital.nhs.uk/hrg).

This thesis covered cost-effectiveness assessments for stroke. However, ideally one would like to easily compare the stroke figures against those of treating other conditions in the country. Whilst the evidence base for cost-effectiveness analyses is increasing in general in the country, the efforts are still disaggregated into small-scale efforts. This challenge can be bridged by better collaboration among academic, government, research and non-governmental institutions. Such collaboration may lead to data repositories of economic evaluation data that are better poised to answer questions of cost-effectiveness at national and sub-national levels.

5.7 Future work

Improving estimation of burden of risk factors: alternative methodological approaches

This thesis utilised the population attributable fraction (PAF) methods to estimate burden of risk factors. This approach was appropriate at the time of analysis as individual-level, population based data were available on risk factors but could not be directly linked to health outcomes within the Agincourt HDSS. Specifically, we could not link the majority of individuals who were sampled *in Ha Nakekela* study with those who have reported suffering a stroke at some point (including those from SASPI study). Thus, the risk factor profiles (from *Ha Nakekela*) were in fact absent for most of those individuals with a known stroke in Agincourt. Secondly, efforts to link individuals who had information on risk factor profiles with those that subsequently died were equally futile as only 8 individuals had subsequently died. The latter was unsurprising as *Ha Nakekela* study was conducted in 2010 and the mortality data that was being analysed spanned the period 2007-11 i.e. the years overlapped.

However, it is important to acknowledge the limitations of the PAF methods which stem primarily from combining ecological, summary measures of exposure, outcome and hazard, across different sources of data. In particular, definitions of exposure categories tend to differ across data sources (exposure mismatch). Furthermore, heterogeneity amongst available studies complicates choice of hazard rates. Even when meta-analytic techniques are used to adjust hazards, the application of external summary hazards to the population may be imprecise as potential confounders in the population of interest are ignored [251].

There are opportunities in the future to improve estimates of risk factor burden within the Agincourt HDSS by linking the rich individual-level population-based exposure data (e.g. collected through *Ha Nakekela*) to outcomes (e.g. through tracking cause specific mortality of the same individuals over time). “When such data are available it becomes possible to directly estimate, through multivariable models, the incidence of disease in exposed and unexposed individuals, opening up opportunity to measure attributable burden without relying on PAF methods” [251]. By way of example, a statistical model (e.g. Cox proportional hazard) can be used to estimate an individual’s probability of outcome given a set of exposures (e.g. BMI and SBP). By including interaction terms within the model, interactions between risk factors (for example BMI and SBP can be explored more precisely. Thus, it will be worthwhile, if in the near future, the wealth of data within Agincourt HDSS is subsequently used to derive more precise estimates of the population burden of risk factors.

5.8 Conclusions

The thesis commenced by highlighting the “information paradox”: lack of data in settings where the need for such data to enable priority setting is vital. By highlighting the data needs, the body of work covered in this thesis that “generated” this data was documented with an intent to broaden the evidence base for CVD prevention. Through a stepwise process, baseline epidemiological estimates for stroke (incidence and DALYs) were estimated as well as costs of stroke treatment. In addition, outcomes-based solutions to stroke prevention were established on the basis of a projection model. By developing a mathematical model that is calibrated for the Agincourt sub-district population, the thesis demonstrated the untapped potential of the Agincourt HDSS in informing comprehensive modelling efforts that can be further integrated into national systems of planning and service delivery. The Agincourt HDSS covers a sub-district. This facilitates both local/ decentralised intervention development and should contribute to intervention scale up.

Cardiovascular disease prevention within the context of rural South Africa is urgent. However, a structured approach to prevention demands that the information or evidence base upon which local decision-making is made be broadened. There is opportunity to expand the analysis of this study by pooling data from the other heath

and demographic surveillance sites in the country. Exploiting the data-wealth of the three existing HDSS could lead to a better understanding of CVD burden in rural South Africa and to what is cost-effective in these diverse communities.

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Appendices

Appendix A: Paper 1

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BMC Neurology

RESEARCH ARTICLE Open Access

Disease burden of stroke in rural South Africa: an estimate of incidence, mortality and disability adjusted life years

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Abstract

Background: In the context of an epidemiologic transition in South Africa, in which cardiovascular disease is increasing, little is known about the stroke burden, particularly morbidity in rural populations. Risk factors for stroke are high, with hypertension prevalence of more than 50%. Accurate, up-to-date information on disease burden is essential in planning health services for stroke management. This study estimates the burden of stroke in rural South Africa using the epidemiological parameters of incidence, mortality and disability adjusted life year (DALY) metric, a time-based measure that incorporates both mortality and morbidity.

Methods: Data from the Agincourt health and socio-demographic surveillance system was utilised to calculate stroke mortality for the period 2007–2011. Dismod, an incidence-prevalence-mortality model, was used to estimate incidence and duration of disability in Agincourt sub-district and 'mostly rural' municipalities of South Africa. Using these values, burden of disease in years of life lost (YLL), years lived with disability (YLD) and DALYs was calculated for Agincourt sub-district.

Results: Over 5 years, there were an estimated 842 incident cases of stroke in Agincourt sub-district, a crude stroke incidence rate of 244 per 100,000 person years. We estimate that 1,070 DALYs are lost due to stroke yearly. Of this, YLDs contributed 8.7% (3.5 – 10.5%) in sensitivity analysis). Crude stroke mortality was 114 per 100,000 person-years in 2007–11 in Agincourt sub-district. Burden of stroke in entire rural South Africa, a population of some 13,000,000 people, was high, with an estimated 33, 500 strokes occurring in 2011.

Conclusions: This study provides the first estimates of stroke burden in terms of incidence, and disability in rural South Africa. High YLL and DALYs lost amongst the rural populations demand urgent measures for preventing and mitigating impacts of stroke. Longitudinal surveillance sites provide a platform through which a changing stroke burden can be monitored in rural South Africa.

Keywords: Stroke, DALY, Incidence, Rural, South Africa, Agincourt health and socio-demographic surveillance site

Background

Stroke is the second-leading cause of death worldwide after ischaemic heart disease [1]. In 2010, stroke was responsible for 5.3 million deaths or 1 in 10 deaths worldwide. The absolute number of people affected by stroke has been increasing yearly since 1990, along with the numbers of disabled stroke survivors and deaths related to stroke [2]. It is estimated that, if current trends continue, by 2030 there will be 20 million annual stroke deaths and 70 million stroke survivors worldwide.

More than 80% of stroke burden occurs in low and middle-income countries (LMICs), yet reliable data on stroke epidemiology, particularly incidence and morbidity is scarce in these settings [3]. The paucity of data is even more pronounced in rural parts of Africa. This is a critical gap for a variety of reasons. Epidemiological data is required to better describe trends, and to develop appropriate cost-effective, prevention and treatment strategies. In the absence of up-to-date estimates on epidemiological

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burden of stroke, the economic impacts due to stroke are likely underestimated. Global estimates show that 3% of total health care system resources are devoted to stroke [4]. However, much of the data is derived from developed countries.

In South Africa (SA), stroke is responsible for some 25,000 deaths annually and 95,000 years lived with disability [5] yet a few published studies report on the epidemiology of stroke in rural parts of the country [6-8]. Whilst out-of-date, the evidence from these studies indicates that as far back as the 1990s, stroke was an important cause of death in rural South Africa. Analysis based on data for the years 1992–1995 indicated that stroke was responsible for 6% of total deaths in the Agincourt sub-district, rural North-Eastern South Africa [8]. A 2001 study, based on the same population, found a crude stroke prevalence of 243 per 100,000 [6], which is twice as high as rates reported for a rural Tanzanian district [9]. Recent evidence from an incidence-based study points to a high incidence of key risk factors for stroke in rural North-West Province. This study showed that a quarter (n = 84) of adults aged ≤35 years whose blood pressure was optimal at baseline in 2005, developed hypertension at 5 years of follow-up [10]. Similarly, consumption of sugar-sweetened beverages, doubled during the same period. Given the increase in risk factors and the implications for stroke, it is critical to understand the current burden of stroke in rural South Africa.

Empirical observation is the gold standard for obtaining epidemiological information. However, much of the available data in South Africa is on mortality with incidence and morbidity data almost lacking. Incidence-Prevalence-Mortality (IPM) models such as Dismod II can assist to fill this information gap by exploiting the causal structure of disease processes: incidence has to precede prevalence, and cause-specific mortality follows being diseased [11]. With at least 3 available input parameters such as case-fatality, remission, and prevalence the model can back-calculate incidence. In addition, these models allow one to check for the internal consistency of observations. A validation study of Dismod showed that provided past trends in disease epidemiology did not differ significantly from future trends, the model calculates correct results [11]. The Dismod models have been used in the global and national burden of disease studies to circumvent the challenge of incomplete data [12,13].

The primary aim of this paper is to contribute towards the practical understanding of stroke burden in rural South Africa. The analysis utilises population-based data from the Agincourt sub-district population of some 70,000 people, for the period 2007–2011, coupled with some modeling techniques [14]. Stroke incidence is assessed using Dismod II software, and total burden captured using the DALY metric. The DALY is a summary measure of population health that captures, into a single measure, both the mortality and severity of the morbidity associated with a disease. The DALY metric has been implemented in several studies including the Global Burden of Disease (GBD) studies and subsequent WHO updates [12,13,15] and the South African National Burden of Disease (SA NBD) Study of 2000 [16].To the authors' knowledge, there are no published studies to-date that have examined the epidemiology of stroke in rural South Africa using the most recent available data on morbidity and mortality. Information generated from this research is intended to guide the planning of health services for stroke prevention and management.

Methods

Definition of a rural area

The term 'rural' suggests many contrasting images to people, such as agricultural landscapes, isolation, small towns, and low-population density [17]. We use the classification by Palmer Development Group (PDG), a public sector consulting firm which classifies rural areas as either 'small towns' or 'mostly rural' municipalities (Additional file 1: Table S2 and Table S3) [18]. The Agincourt sub-district falls under Bushbuckridge municipality 'mostly rural'; in this study, 'rural' refers explicitly to such municipalities.

Setting and population

This analysis is based on a population of approximately 70,000 people residing in the Agincourt sub-district of Mpumalanga province, north-eastern of South Africa between 2007 and 2011 (Figure 1) [19]. The area is completely covered by a health and demographic surveillance system (HDSS). Comprehensive data on mortality and causes of death, births, and inward and outward migration have been collected through a yearly census update since 1992. Additional data on labour participation and educational status have been collected at different time intervals to complement demographic data and provide contextual information. Agincourt sub-district has characteristics similar to many other rural South African populations. Though the sub-district's socio-economic status has improved since 1994, the majority of the population relies on social assistance grants particularly pension and child care grants. Labour migration is high, with approximately 50-70% of men aged 20–59 years migrating to work outside the study area in 2011 [20]. The proportion is lower for women but increasing over the years with 25-35% of women considered a temporary migrant in 2011, an increase from 20-25% observed in 2000 [20].

The health status profile in the area is characterized by the persistent burden of TB and HIV/AIDS, maternal and child health problems, and emerging non-communicable

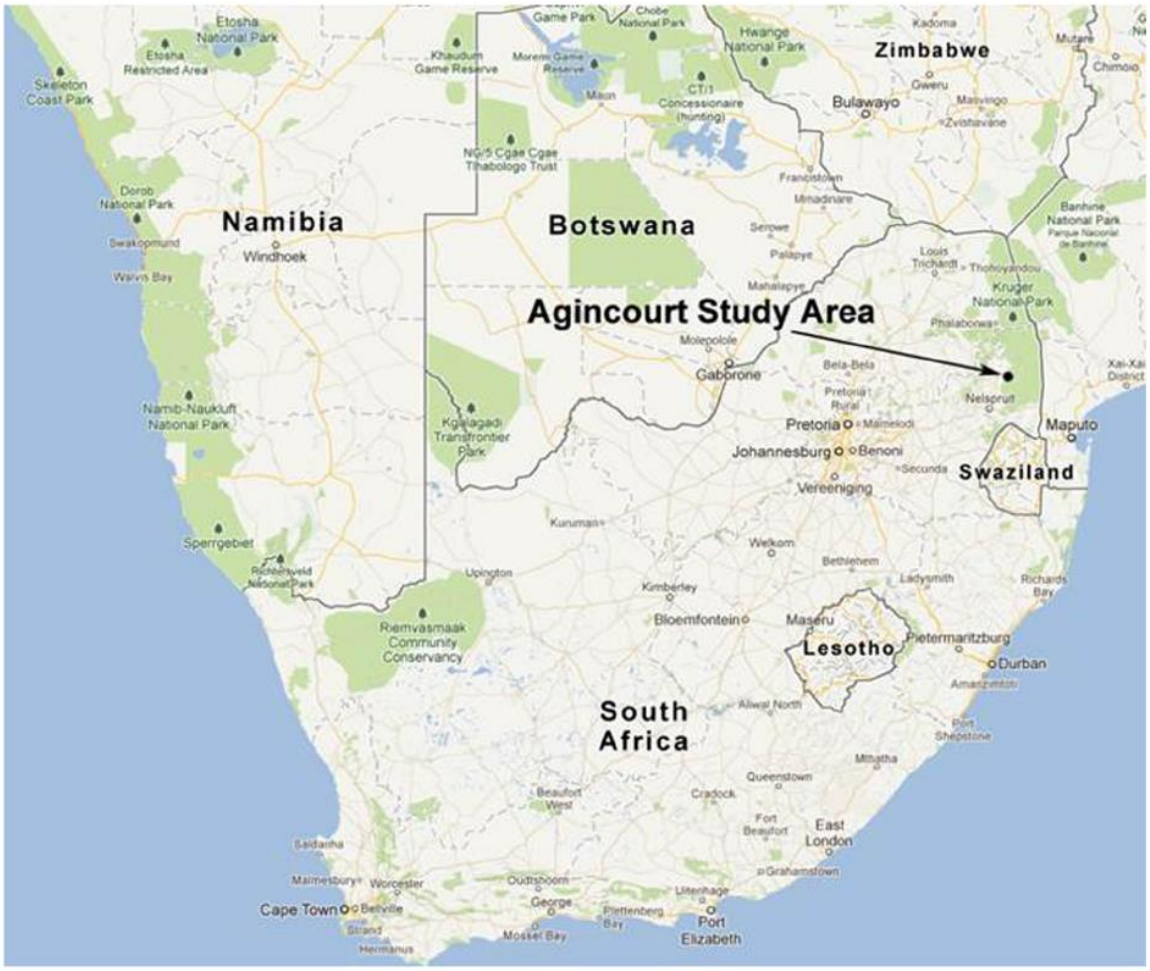

Figure 1 The map of Agincourt HDSS, located in rural North-Eastern South Africa. As of 2013, the surveillance site covered 32 villages and a population of more than 100,000 people.

diseases. Data from the HDSS suggest that between 1992 and 2005, cardiovascular disease (CVD) remained the top cause of death amongst women 50–64 years old [21]. In men, CVD showed a sustained increase. By 2002 it was the third-leading cause of death in men aged 50–64 and second-leading cause of death in men 65 years and above. The sub-district, measuring some 420 km^2 is served by six clinics and one health centre. Hospital services are provided by three hospitals situated between 25 km and 45 km from the Agincourt study site. Imaging equipment for the diagnosis of stroke is lacking within the district but accessible at the provincial capital, Nelspruit, some 120 km south of Agincourt. At the time of this study, the stroke register set up in the early 2000s as part of the Southern African Stroke Prevention Initiative (SASPI) was no longer functional and there were no dedicated stroke units in the South African public health system.

Ethics approval

Ethical approval for the study was granted by the Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand, Johannesburg, South Africa for both the MRC/Wits Rural Public Health and Health Transitions Research Unit's (Agincourt) Health and Socio-Demographic Surveillance System and add-on modules (Clearance certificate no. M131050).

Computation of DALYs

DALYs were calculated by predominantly applying the methodological principles employed in the Global Burden of Disease Studies (detailed description in Additional file 1).

DALYs are the sum of years of life lost due to premature mortality (YLL) plus years of life lost due to time lived in states of less than optimal health, loosely referred to as "disability" (YLD) [22]. YLL due to stroke among all persons that die of stroke is the sum of years that victims would have lived if they had completed the life expectancy attributed to their age (as assessed by a standard population) at the time of their death. In this study, the reference life table used in GBD 1990 study was chosen to ensure comparability with previous burden of disease studies. This was based on the highest life expectancy at the time, Japanese females with a life expectancy at birth of 82.5 years. YLLs measure the fatal burden of disease. The YLD figure expresses the consequences of living with less than perfect health conditions. It is an estimate based on the length of time that a condition persisted along with any accompanying disability and thus is an indicator of the non-fatal burden of disease. YLD can be calculated from an incidence perspective as the product of incidence, disability weights and average duration of disease. Alternatively YLD can be measured from a prevalence perspective as the product of prevalence of disease and disability weights.

To ensure consistency with the YLL calculation, which takes an inherently incidence perspective, and for comparison with earlier GBD studies, we compute incidence YLDs. Prevalence-based YLDs were calculated mainly for comparison with the GBD 2010 study. To be consistent with GBD 2010, we did not discount or apply age weighting in computing prevalence- based DALYs but apply discounting when YLDs are calculated using incidence. The latter allows comparison with earlier studies that discounted DALYs. Comparative analysis of the incident and prevalence YLDs is warranted as the two are not directly comparable. The incidence approach does not reflect the current prevalent burden of disabling sequelae for a condition for which incidence might have been substantially reduced. Secondly, in an incidence perspective, all YLDs for a condition are assigned to the age-groups at which the condition is incident, whereas in many cases for health policy-making, the ages at which the loss of health is experienced are of most interest.

Data sources for calculating YLD

Prevalence of stroke

We conducted a systematic literature search of studies conducted in rural South Africa on prevalence of stroke. The search yielded one study; the Southern African Stroke Prevention Initiative (SASPI) study conducted in 2001 within the Agincourt population [6]. In that study, fieldworkers questioned each household informant, systematically reviewed every individual in the household using a previously validated questionnaire, and asked the following question: "Has (person) ever had weakness down one side of the body?" and "Has (person) ever had a stroke?" If either question was answered positively, a clinician/neurologist visited individuals aged >15 years to clinically assess the possible diagnosis of stroke by performing a detailed assessment of the patient. Clinical assessment of possible stroke victims was lowest amongst migrant males 25–44 years. To account for this non-contact, the investigators adjusted the stroke rates in each 10-year age stratum and assumed the same proportion of stroke survivors in employed men as among predominantly unemployed men. Migrant labourers were included in the local population denominator as they consider the sub-district home and return to seek health care when too ill to work [23]. Given the rising trend in risk factors, notably hypertension, and the potential impact of such changes in prevalence on YLD within the population, a sensitivity analysis was conducted around the point estimate, using a range of ±15%.

Disability weights

Disability following a stroke spans a wide spectrum. Most contemporary stroke research has assessed disability using the modified rankin scales (MRS), a commonly used ordinal scale that measures disability or dependence in conducting activities of daily living in stroke victims [24]. In the GBD 2010 study, five sequelae of stroke were assessed and disability was ranked according to the lay definitions shown in Table 1 [25]. The disability weights were calculated based on personal interviews in Bangladesh, Indonesia, Peru, and Tanzania; telephone interviews in the USA; and an open access web-based survey. To identify the distribution of the severity of stroke within the Agincourt population, we used Hoffmann's study (2000) carried out in KwaZulu Natal, South Africa [26]. In the study, patients were recruited into a stroke database from 1992–1998 and a retrospective analysis undertaken of all patients aged 15–40 to establish whether their disability resulted from stroke. Though disability was assessed based on the MRS, similar distribution of severity on the basis of the GBD sequela definition was assumed in this study. The slight difference between the definition of disability on MRS and categories in GBD 2010 was regarded as acceptable by a consensus of members of an international collaborative stroke expert group. A weighted disability weight (DW) was calculated by multiplying each disability weight by the proportion of the population it represented.

Derivation of incidence and duration through computer-based modelling

Dismod II was used to calculate incidence and duration of stroke-related disability. It models transitions from being healthy, to the incidence of a specific disease, to death

Table 1 Disability weights for stroke at each disability level, South Africa

GBD 2010 stroke sequale	Definition of score	% of stroke population in SA (Hoffman et al. 2000 [26])	Disability weight associated with score (95% CI)
0	No symptoms	2	0
1	long-term consequences, mild	40	0.021 (0.011-0.037)
2	long-term consequences, moderate	23	0.076 (0.050-0.110)
3	long-term consequences, moderate plus cognition problems	12	0.312 (0.363-0.705)
4	long-term consequences, severe	15	0.539 (0.363-0.705)
5	long-term consequences, severe plus cognition problems	8	0.567 (0.394-0.738)

Weighted average disability weight across all disability levels: 0.18.

from the disease under study or death from other causes. Given three input parameters such as remission, case fatality and prevalence, DisMod II can generate age-specific and sex-specific estimates of disease incidence. Because remission is defined as 'cure' in Dismod, no remission (i.e. improvement from the input condition) is possible when modelling stroke survivors. Consequently, prevalence (from SASPI study 2001), post-28 day relative risk of mortality, and a remission rate of zero were used to yield estimates of incidence and duration as outputs.

Post 28-day stroke mortality

Due to the high risk of mortality in the first 28 days following a stroke, prevalence reflects only those who survive this period; there is thus a need to calculate mortality post-28 days. We could not identify South African specific studies that assessed post-28 day mortality amongst stroke survivors. The best available data chosen as input parameters was based on a prospective study conducted in a rural demographic surveillance site in Hai district, Tanzania between June 2003 and June 2006 [27]. The results of post-stroke case fatality relate to follow up until June 2009, which is at least 3 years of follow-up amongst the cases (Additional file 1: Table S6 and Table S7) [28]. To the best of the authors' knowledge this is the first published data of post-stroke mortality in Sub-Saharan Africa, based on an incident population and that reports on long-term case fatality.

Mortality rate at 28 days post-stroke (28-day case fatality)

Incidence calculated through Dismod reflects those who survive the high mortality period (first 28 days after stroke) since the prevalence of stroke that was used as input data also reflects those who survive the high mortality period. To show incidence of all cases (those who die within 28 days plus those who survive past 28 days), equation 1 is used to make an adjustment.

Equation 1:

$$\textit{Incidence of stroke amongst those who survive the first } 28\textit{days } (\textit{calculated in Dismod}) = \textit{All incident cases} * (1 - 28\textit{ day case fatality rate})$$

In South Africa, two hospital-based studies found case fatality rates of 33% and 34%, the weighted average of which is 33% [29,30]. Because the studies are hospital based and many people die before they reach facilities, we elected to use the mortality rates at 28 days post-stroke from the study described above conducted in Tanzania [28].

Extrapolating incidence and disability to entire rural South Africa

Incidence and YLD of stroke in the whole of rural South Africa were extrapolated based on mortality rates and prevalence observed in Agincourt sub-district. The total population for rural South Africa was based on 2011 estimates by Statistics South Africa for the 'mostly rural' municipalities (Additional file 1: Table S2).

Results

In 2007–11, 394 deaths were assigned to stroke in Agincourt HDSS, a crude stroke-related mortality rate of 114 per 100,000 person years (Additional file 1: Table S1). Of these, 30% were in males. When age-standardised to the WHO population [31], stroke mortality was 172 per 100,000 person years.

We estimate that 168 cases of stroke (72.7 males) occur every year in Agincourt sub-district (Table 2). This translates to a crude-incidence rate of 244 per 100,000 person years and age-adjusted rate of 349 per 100,000 person years. Table 3 shows the extrapolated incidence of stroke to the entire rural South Africa, a population of approximately 13 million people (Additional file 1: Table S2). It shows that at least 33,500 strokes occurred in 2011. This gives a crude incidence rate of 259 cases per 100,000 person years (age adjusted incidence of 347 per 100,000 person years). Of these, 20,800 were in females.

Table 2 Yearly YLL, YLD and DALYs in Agincourt sub-district calculated using an incidence-based approach

	Age	Average yearly population	Incidence/ 100,000	Incidence (N)	Duration of disability (Years)	YLD/ 100,000	YLD (N)	YLL	DALYs	DALYs/ 100,000
Males	0-4	11212.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	5-14	8202.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	15-29	5848.2	109.6	6.4	2.9	57.1	3.3	10.8	14.1	241.8
	30-44	3389.8	332.6	11.3	2.7	160.0	5.4	66.2	71.7	2113.9
	45-59	2019.8	780.8	15.8	3.5	489.6	9.9	94.5	104.4	5170.5
	60-69	1230.4	647.2	8.0	2.8	326.4	4.0	65.0	69.0	5610.2
	70-79	677.6	1394.2	9.4	1.8	453.5	3.1	41.9	45.0	6636.5
	80+	446.6	2283.9	10.2	1.1	464.7	2.1	21.5	23.6	5286.6
	Total	**33027.4**	**220.2**	**72.7**	**2.7**	**108.6**	**35.9**	**300.0**	**335.9**	**1017.0**
Females	0-4	11336.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0
	5-14	8178.4	13.0	1.1	5.8	13.5	1.1	0.0	1.1	13.5
	15-29	5976.0	127.2	7.6	5.2	118.7	7.1	65.8	72.9	1219.3
	30-44	3897.8	274.1	10.7	4.3	214.5	8.4	87.1	95.4	2448.7
	45-59	2611.2	675.0	17.6	2.8	343.8	9.0	169.8	178.8	6847.1
	60-69	1582.6	1219.5	19.3	2.6	560.8	8.9	109.9	118.8	7505.2
	70-79	1115.4	1327.9	14.8	2.6	621.6	6.9	127.6	134.5	12061.3
	80+	1217.4	1312.0	16.0	2.1	485.5	5.9	116.8	122.7	10077.2
	Total	**35915.6**	**266.6**	**95.7**	**3.3**	**160.7**	**57.7**	**676.9**	**734.6**	**2045.5**

Comparison of stroke incidence rates in 'mostly rural' South Africa with national figures produced using similar modelling techniques shows that, incidence follows a similar pattern amongst males (Table 3). In females, incidence doubles from age group 30–44 to 45–59 in rural South Africa and follows a similar trend from age group 45–59 to 60–69. This is in contrast to the modest increases observed nationally amongst these age groups. The highest magnitude of increase amongst females at national level is observed between the last 2 age groups, where incidence increases from 826 to 2520 per 100,000 person years. However, results of uncertainty analysis (Additional file 1: Table S11 and Table S12) show that because the confidence intervals overlap from age 45–59 to highest age group there is no significant difference in incidence across these age groups.

Burden of stroke in YLLs, YLDs and DALYs

Tables 2, 4, and 5 show the calculated YLLs, YLDs and DALYs lost in Agincourt sub-district for the period 2007–11. We present average yearly figures since burden of disease estimates are typically done for a year. In Tables 2 and 4, YLD estimates were produced using the incidence based approach with YLLs discounted to 3% as done in the global burden of disease study of 1990 and subsequent WHO updates. Table 5 presents DALYs calculated using the prevalence based approach, with no discounting (hereafter simplified DALY approach).

We estimated that total DALYs lost due to stroke were 1,550 per 100,000 from an incidence-based perspective (Table 1). When the simplified DALY approach was used, DALYs lost due to stroke increased to 2,200 per 100,000 person years (Table 5). In both scenarios, YLDs comprised less than 10% of the DALYs lost. However, the ratio was much lower for prevalence-based YLD (3.3%) than for incidence-based (8.7%).

Sensitivity analysis

Additional file 1: Table S8 shows the results of the sensitivity analysis. It highlights that case fatality rate has the most significant impact on overall crude incidence rate. Varying the 28 day case-fatality rate from 0.238 to 0.33 resulted in an increase in incidence rate of approximately 13.5%. 0.238 was the case-fatality rate reported by Walker and colleagues and used in this study, whilst 0.33 was the average case-fatality rate from 2 published hospital-based studies in South Africa [29,30]. Nonetheless neither case-fatality rate nor disability weight had a significant impact on overall DALYs lost. This is because both parameters predominantly affect YLD which in turn comprises a very small proportion of DALYs lost in Agincourt sub-district.

Discussion

Emerging evidence suggests that rural South Africa is experiencing dramatic epidemiological changes characterised by an increase in non-communicable diseases

Table 3 Incidence of stroke per 100,000 person years in 'mostly rural' South Africa, 2011 compared with national estimates

Males				Females			Both sexes, Agincourt			South Africa, National estimates 2008 (Bertram et al. 2013 [5])	
Age	**Population**	**Incidence/ 100,000**	**Incidence (N)**	**Population**	**Incidence/ 100,000**	**Incidence (N)**	**Population**	**Incidence (N)**	**Incidence/ 100,000**	**Incidence/100,000 Males**	**Incidence/100,000 Females**
0-4	861642.0	0.0	0.0	850647.0	0.0	0.0	1712289.0	0.0	0.0	0	0
5-14	1569456.0	0.0	0.0	1515155.0	12.6	191.2	3084611.0	191.2	6.2	0	10
15-29	1832722.0	91.9	1685.2	1938675.0	121.6	2357.2	3771397.0	4042.4	107.2	79	143
30-44	789718.0	332.9	2628.7	1085763.0	278.0	3018.0	1875481.0	5646.7	301.1	412	423
45-59	532986.0	772.8	4118.9	824761.0	691.1	5699.7	1357747.0	9818.6	723.2	665	384
60-69	227238.0	645.8	1467.4	353604.0	1204.9	4260.7	580842.0	5728.2	986.2	583	609
70-79	119337.0	1401.3	1672.3	243683.0	1341.0	3267.8	363020.0	4940.1	1360.8	595	826
80+	53045.0	2252.2	1194.7	149895.0	1320.1	1978.7	202940.0	3173.4	1563.7	1384	2520
Totals	**5986144.0**	**213.3 (198–243)***	**12767.2**	**6962183.0**	**298.4 (296–372)**	**20773.4**	**12948327.0**	**33540.6**	**259.0**	**465**	**615**

Table 4 Yearly DALYs lost due to stroke in Agincourt sub-district, rural South Africa for both males and females based on incidence based approach

Age group	Population (% of total)	YLD	YLL	DALYs	DALYs/100,000	WHO standard population	Age-adjusted rates
0-4	22549.0 (33%)	0.0	0.0	0.0	0.0	0.09	0.0
5-14	16381.2 (24%)	1.1	0.0	1.1	6.7	0.17	1.2
15-29	11824.2 (17%)	10.4	76.6	87.0	735.8	0.25	181.0
30-44	7287.6 (11%)	13.8	153.3	167.1	2293.0	0.21	489.5
45-59	4631.0 (7%)	18.9	264.4	283.2	6115.9	0.16	976.1
60-69	2813.0 (4%)	12.9	174.9	187.8	6676.3	0.07	446.0
70-79	1793.0 (3%)	10.0	169.5	179.5	10011.2	0.04	373.4
80+	1664.0 (2%)	8.0	138.3	146.3	8791.4	0.02	135.4
Total	**68943 (100%)**	**93.6**	**977.0**	**1070.5**	**1552.8**	**1.00**	**2602.6**

Table 5 Yearly YLL, YLD, DALYs lost due to stroke in Agincourt sub-district, rural South Africa calculated using simplified DALY approach

	Age	Population	Prevalence	Disability weight	YLD /100,000	YLD (N)	YLL	DALYs	DALYs/100,000
Males	0-4	11212.2	0.0	0.2	0.0	0.0	0.0	0.0	0.0
	5-14	8202.8	0.0	0.2	0.0	0.0	0.0	0.0	0.0
	15-29	5848.2	143.2	0.2	25.8	1.5	22.2	23.7	405.2
	30-44	3389.8	706.2	0.2	127.1	4.3	115.8	120.1	3543.1
	45-59	2019.8	1933.2	0.2	348.0	7.0	137.1	144.1	7134.6
	60-69	1230.4	2599.0	0.2	467.8	5.8	82.6	88.4	7183.5
	70-79	677.6	2854.2	0.2	513.7	3.5	49.1	52.6	7758.7
	80+	446.6	2839.7	0.2	511.1	2.3	23.1	25.3	5673.6
	Totals	**33027.4**	**471.9**	**0.2**	**84.9**	**28.1**	**429.8**	**457.9**	**1386.4**
Females	0-4	11336.8	0.0	0.2	0.0	0.0	0.0	0.0	0.0
	5-14	8178.4	17.1	0.2	3.1	0.3	0.0	0.3	3.1
	15-29	5976.0	319.9	0.2	57.6	3.4	138.6	142.1	2377.6
	30-44	3897.8	988.5	0.2	177.9	6.9	155.8	162.7	4174.9
	45-59	2611.2	1479.6	0.2	266.3	7.0	262.6	269.6	10324.5
	60-69	1582.6	2655.0	0.2	477.9	7.6	145.9	153.5	9698.4
	70-79	1115.4	3229.7	0.2	581.3	6.5	153.2	159.7	14317.8
	80+	1217.4	3208.1	0.2	577.5	7.0	128.5	135.5	11132.4
	Totals	**35915.6**	**680.6**	**0.2**	**122.5**	**44.0**	**984.7**	**1028.7**	**2864.2**
Overall	0-4	22549	0	0.2	0	0	0	0	0
	5-14	16381.2	17.1	0.2	1.5	0.3	0	0.3	1.5
	15-29	11824.2	463.1	0.2	41.9	4.9	160.8	165.8	1402
	30-44	7287.6	1694.7	0.2	154.3	11.2	271.6	282.8	3881
	45-59	4631	3412.8	0.2	301.9	14	399.7	413.7	8933.2
	60-69	2813	5254	0.2	473.5	13.3	228.6	241.9	8598.4
	70-79	1793	6083.9	0.2	555.8	10	202.3	212.3	11839
	80+	1664	6047.8	0.2	559.7	9.3	151.6	160.9	9667.3
	Totals	68943	1152.5	**0.2**	104.5	72.1	1414.5	1486.6	2156.3

(NCDs), persisting HIV/AIDS and TB and maternal and perinatal health issues [32]. During the period 1994 – 2009, NCD deaths increased amongst people under the age of 60 in Agincourt sub-district. At the same time, deaths due to HIV/AIDs initially decreased, then plateaued at high levels. To effectively address the colliding epidemics and intervene at a population level, empirical information about the scale of burden is required. However, there is a dearth of information, particularly incidence and morbidity of non-communicable diseases in rural South Africa.

This is the first study to calculate the burden of stroke in terms of both morbidity and mortality in rural populations of South Africa. The study begins the process of stratifying burden of the disease by urban and rural areas. Although the spectrum of urban to rural is clearly a continuum, a working approach to rural can support greater awareness and better targeted policy towards traditionally neglected populations with less functional health systems. Previous studies indicated that the burden of stroke might be lower in rural areas but the comparison was based on mortality and prevalence only and the data used is now out of date [5]. The major strength of this study is its use of predominantly local data from the Agincourt HDSS and from South Africa, with the exception of relative risk data.

Our findings indicate that the burden of stroke has increased over time in Agincourt sub-district. The observed stroke mortality rate of 114 per 100,000 person years in 2007–11 was significantly higher than the 87 per 100,000 person years observed in 1990–94 within the same population [8]. This trend towards an increased mortality rate is in contrast with what was reported in the GBD 2010 study for LMICs [2]. According to this study, mortality rates for ischaemic and haemorrhagic strokes declined between 1990 and 2010 in LMICs. Our findings could thus be reflective of the continual challenges that populations in rural South Africa face when accessing acute care services. Currently, imaging equipment for the diagnosis of stroke is accessible at the provincial capital, Nelspruit, some 120 km south of Agincourt and barriers to accessing care including the costs of transportation are well documented [33].

The burden of stroke seems to be disproportionately higher amongst rural populations in South Africa. According to Bertram et al. 2013 who used similar modelling techniques to measure incidence, approximately 75,000 strokes occur yearly in South Africa [5]. Our estimate of 33,500 strokes per year thus suggest that, despite comprising one-fifth of the total national population, "mostly rural" South Africa carries at least half of the stroke burden. However, it is important to mention that the national study was based on 2008 population estimates whilst our study was based on 2011 census estimates. We estimated a crude stroke rate of 244 per 100, 000 person years (CI: 110–122) within Agincourt sub-district. This is significantly higher than 108.6 per 100,000 person years reported for a Tanzanian rural demographic surveillance site [27]. Differences in incidence of stroke could indicate that rural SA is indeed in a health transition due to a higher level of lifestyle risk factor exposure [7]. However, other factors such as methodological differences in the 2 studies could explain the differences. When compared to global estimates from GBD 2010 study which ranged from 60 cases (Kuwait) to 504 cases (Lithuania) per 100 000 person-years [34]; our estimate falls within the middle of the range and these findings are consistent with the theory of an epidemiological transition occurring in rural South Africa.

We compared the age-adjusted incidence results for "mostly rural" South Africa with rural settings from middle –income countries for which data was available. The comparative analysis reveals that age-standardised incidence of stroke of 347 per 100,000 person years was higher than both West Bengal (262 per 100,000 person-years) and Trivandrum in rural India [35,36]. There are important differences between the Indian and rural South African settings that could account for the differences. In West Bengal, as in the rest of India, smoking is still a critical challenge and higher than optimal blood pressure was also evident amongst stroke survivors. It is estimated that smoking increases the odds of a stroke event by four. In South Africa, high blood pressure could be the most important underlying risk factor. According to the SASPI study, 43% of stroke survivors were hypertensive in Agincourt sub-district (BP greater than 140/90 mmHg). Though not examined in this study, the high HIV/AIDs prevalence in rural South Africa could account for some of the stroke cases. Emerging literature suggests that HIV infection can result in stroke via several mechanisms, including opportunistic infection, vasculopathy, cardioembolism, and coagulopathy [37]. HIV prevalence is highest in South Africa, with prevalence rates in Agincourt of 19.4% across all ages in 2010; peaking at 45.3% among men and at 46.1% among women, both at ages 35–39 [38]. This dual stroke/HIV burden reinforces the need to understand the underlying etiology of stroke in populations living with HIV/AIDS, particularly the younger age groups in which risk factors for stroke are seldom evident.

DALYs which have now been widely accepted by public health experts as suitable for measuring disease burden were also higher than most countries' estimates. According to the GBD study, in 2010, DALYs lost due to stroke ranged from 398 (Australia) to 5227 (Afghanistan) per 100 000 people [34]. In LMICs, DALY loss rate per 100,000 person years amongst all ages was 1821 (1589–1925), and this was twice as high as the estimates produced

for high income countries. During that period, DALY loss rate per 100,000 person years for the whole of South Africa was estimated to be 1,570 (1,381.20-1,926.24). This places our estimated DALY loss rate in rural Agincourt of 1,552 per 100,000 person years within the upper range and suggests a significant burden due to stroke.

Comparing the DALYs computed based on the GBD 2010 methodology where time discount of 0% and no age-weighting were applied, we observed a substantial increase in the absolute number of DALYs lost (Table 5). Time discounting places less importance on health benefits that occur in the future and as such its removal will result in the observed increases in DALYs lost, particularly if the stroke death occurred amongst younger age groups. These findings are in line with what was reported in a recent WHO analysis [39]. These differences in methodological approaches warrant caution when conducting cross-country comparisons of DALY results and reinforce the need to explain in depth the methodological approach taken when calculating DALYs.

The high fatal burden of stroke warrants urgent measures for population-wide stroke interventions. Potential interventions include lowering sodium content of processed foods. This intervention could prevent 7 400 CVD deaths and 4 300 non-fatal strokes per year in South Africa and initiatives are underway to implement this policy [40]. In a setting where 30% of people with diagnosed hypertension are on correct medication and have controlled blood pressure [41], personal interventions are equally important. Such approaches could include pharmacological treatment of individuals with global risk of CVD [42]. There are other novel initiatives that are currently being explored in rural SA. The Nkateko (Hope) trial is one such example [43]. This cluster randomised trial, focused on integrated chronic care will evaluate clinic-based lay health worker support for community health worker efforts to manage NCDs, hypertension in particular. . Future analyses should thus focus on estimating the cost-effectiveness of strategies to reduce the stroke burden. This study provides a platform through which such analyses can be made.

Despite the strengths of our analysis, there are a number of limitations in the data used. The data did not distinguish between haemorrhagic and ischemic stroke. This requires radiological imaging which is costly and not readily accessible. The inability to distinguish between stroke subtypes makes it difficult to accurately determine the appropriate epidemiological parameters to use particularly regarding case fatality. Different pathological subtypes result in different prognoses and knowledge of the pathological type of stroke is important for targeted country-specific health-care planning.

Cause of death was ascertained through verbal autopsy in Agincourt HDSS, not physician coding [19]. Verbal autopsy would tend to misclassify deaths. However, we do not believe that this omission had a significant impact on the results of this analysis because verbal autopsy methods for assigning stroke deaths have been well validated, particularly for assigning fatal stroke deaths [44].

Conclusions

By utilizing population-based data from a well characterised research setting, coupled with modelling techniques, we were able to derive the first estimate of total burden of stroke in a rural South African population. The findings provide further evidence on the dynamic health transition underway, and suggest that stroke is on the increase in rural areas of South Africa despite the immense impact of HIV/AIDS. In the absence of health system interventions, rural South Africa appears at risk for a stroke epidemic. Furthermore, the study highlights the critical role played by indepth studies in understanding the burden of disease in countries where health information systems are not adequate. Agincourt's longitudinal research platform can monitor the evolution of stroke mortality in rural South Africa, particularly the impact of targeted interventions. This study is well positioned to advance the health policy agenda of South Africa, in particular as outlined in the 'South African Declaration on the Prevention and Control of Non-communicable Diseases' adopted in 2011. One of the key objectives of that strategic plan was to develop an integrated and inter-sectoral plan for a coordinated response to prevention of non-communicable diseases. While noble, this goal cannot be accomplished without proper baseline data and information on high burden non-communicable diseases.

Recommendations

Future research in South Africa should focus on obtaining population representative data on stroke incidence to strengthen burden-of-disease analysis. Such studies will allow derivation of missing epidemiological parameters, particularly incidence and case fatality, and will enable a fuller understanding of stroke epidemiology in rural areas. It would be worthwhile to conduct such studies within health and demographic surveillance sites in which mortality data and/or prevalence data can be readily sourced. In addition, a follow-up study to SASPI would enable South Africa to track the extent to which prevalence of stroke has increased in rural areas. Data on disability is very difficult to obtain with completeness and reliability and stroke registers are vital.

Additional file

Additional file 1: Supplementary appendix with detailed methodology including population figures, data sources and results of uncertainty analysis.

Abbreviations
CVD: Cardiovascular diseases; DALY: Disability adjusted life year; DW: Disability weight; GBD: Global burden of disease; GDP: Gross domestic product; HDL: High density lipoprotein; HDSS: Health and socio-demographic surveillance system; IPM: Incidence-prevalence-mortality; LMICs: Low- and middle-income countries; MRS: Modified ranking scales; PDG: Palmer development group; PURE: Prospective urban rural epidemiology; SA: South Africa; SA NBD: South African national burden of disease; SASPI: Southern African stroke prevention initiative; SSBs: Sugar sweetened beverages; TB: Tuberculosis; YLD: Years lived with disability; YLL: Years of life lost.

Competing interests
All authors declare that they have no competing interests.

Authors' contributions
MM, MYB and ST contributed towards the conceptualization of the study. MM carried out all the initial analysis and drafted the manuscript. MYB assisted with the statistical analysis. ST critically appraised the manuscript for intellectual content and assisted with interpretation of data. All authors edited subsequent drafts and approved the final manuscript.

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RESEARCH ARTICLE Open Access

Burden of stroke attributable to selected lifestyle risk factors in rural South Africa

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Abstract

Background: Rural South Africa (SA) is undergoing a rapid health transition characterized by increases in non-communicable diseases; stroke in particular. Knowledge of the relative contribution of modifiable risk factors on disease occurrence is needed for public health prevention efforts and community-oriented health promotion. Our aim was to estimate the burden of stroke in rural SA that is attributable to high blood pressure, excess weight and high blood glucose using World Health Organization's comparative risk assessment (CRA) framework.

Methods: We estimated current exposure distributions of the risk factors in rural SA using 2010 data from the Agincourt health and demographic surveillance system (HDSS). Relative risks of stroke per unit of exposure were obtained from the Global Burden of Disease Study 2010. We used data from the Agincourt HDSS to estimate age-, sex-, and stroke specific deaths and disability adjusted life years (DALYs). We estimated the proportion of the years of life lost (YLL) and DALY loss attributable to the risk factors and incorporate uncertainty intervals into these estimates.

Results: Overall, 38 % of the documented stroke burden was due to high blood pressure (12 % males; 26 % females). This translated to 520 YLL per year (95 % CI: 325-678) and 540 DALYs (CI: 343-717). Excess Body Mass Index (BMI) was calculated as responsible for 20 % of the stroke burden (3.5 % males; 16 % females). This translated to 260 YLLs (CI: 199-330) and 277 DALYs (CI: 211-350). Burden was disproportionately higher in young females when BMI was assessed.

Conclusions: High blood pressure and excess weight, which both have effective interventions, are responsible for a significant proportion of the stroke burden in rural SA; the burden varies across age and sex sub-groups. The most effective way forward to reduce the stroke burden requires both population wide policies that have an impact across the age spectra and targeted (health promotion/disease prevention) interventions on women and young people.

Keywords: Comparative risk assessment, Stroke, Rural, Body-mass index, Systolic blood pressure, South Africa

Background

Stroke is the second most common cause of death in South Africa, after HIV/AIDS and the leading cause of disability [1]. Recent estimates suggest that at least 30,000 strokes occur yearly in rural South Africa [2]. The major risk factors for stroke are common to other non-communicable diseases (NCDs) and are modifiable with effective interventions. They include high blood pressure, tobacco use, high blood glucose, physical inactivity, and overweight and obesity [3]. In an environment where health system resources to manage stroke victims are severely limited, consistent and up-to-date information on the number of premature deaths potentially prevented by changing the profiles of modifiable risk factors in a population is needed [4]. Such information will enable effective targeting of efforts and community oriented health promotion.

Increasing the nation's life expectancy through prevention of premature deaths from NCDs and related lifestyle risk factors is a key health agenda for the South African government. This is the driving principle behind the five-year strategic plan called "Strategic Plan for the Prevention and Control of Non-Communicable Diseases

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2013-17", released in 2013 [5]. In that plan, 3 major components are identified to achieve this goal, including: healthy lifestyle promotion, health systems strengthening, and monitoring cases and risk factors to evaluate where the most population health improvements can be achieved. This study speaks to the third component. It builds on our previous work that showed that stroke as a marker condition for cardiovascular disease has increased significantly over the years in rural South Africa [2]. In that study, stroke related mortality of 114 per 100,000 person-years was significantly higher than that reported for comparable settings of sub-Saharan Africa (SSA) as was the morbidity as measured using the disability adjusted life year (DALY) metric [6]. Few other studies corroborate these findings and indicate that in general, NCDs as well as risk factors have increased rural South Africa [7, 8].

In the present study, we assess the relative contribution of key risk factors on stroke burden in a rural setting of South Africa. The intent is to identify the most important risk factors for stroke deaths and morbidity at the population level. Whilst useful data exists through the global burden of disease study of 2010 [9], it is aggregated at a regional level. The extent of cross-country and inter-country variations in risk factor exposure profiles warrant sub—national analyses that utilize best available and up-to-date local data. In South Africa, the most comprehensive attempt to quantify the impact of modifiable risk factors on disease including stroke was through the national burden of disease study of 2000 [10]. However, the analysis was not stratified by rural and urban and the data used is now out-of-date.

We employed a comparative risk assessment (CRA) strategy developed by the World Health Organization to quantify contributions of the modifiable risk factors to stroke mortality and morbidity [9, 11]. This methodology is well established and has been applied in the global burden of disease (GBD) studies, the South African national burden of disease study of 2000 and few other national and sub-national level studies [9–16]. CRA utilises local level data on risk exposures and cause-specific mortality, supplemented by data on risk factor –disease associations from large scale prospective studies to identify the proportion of deaths attributable to a risk factor. We derived the local data from the Agincourt Health and Demographic Surveillance System Site (HDSS), rural North-Eastern South Africa [17]. Data on risk-factor disease associations was derived from the GBD 2010 study [9]. To our knowledge, our results provide the first estimates of the stroke burden (mortality and morbidity) that could be averted by controlling the selected risk factors in rural areas of South Africa and provide crucial information that policy makers could use to determine the best course of action to effectively reduce the stroke burden in such settings.

Methods

Population and setting

This study was based on the Agincourt sub-district, a population of approximately 90,000 people, located in rural North-Eastern South Africa adjacent to Southern Mozambique [17]. The Agincourt sub-district is entirely covered by a health and socio-demographic surveillance system which has been in operation since 1992. Comprehensive data on deaths, migration and vital events, i.e. the underlying population denominator, has been collected through a yearly census for over 20 years. Detailed description of the study site is available elsewhere [17]. Agincourt sub-district is fairly typical of many of the rural communities of South Africa with high unemployment, high levels of labour migration, high HIV prevalence and low socio-economic status. The emerging evidence from the sub-district indicates that the population is undergoing a rapid health transition, characterised by an increase in non-communicable diseases (NCDs), stroke in particular [18]. Risk factors for NCDs are also on the rise with 40 % of women (30 % men), 15 years and older classified as hypertensive [8].

Ethics approval

Ethical approval for the study was granted by the Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand, Johannesburg, South Africa for both the MRC/Wits Rural Public Health and Health Transitions Research Unit's (Agincourt) Health and Socio-Demographic Surveillance System and for specific add-on survey modules (Clearance certificate no. M131050).

Selection of risk factors

Our key criteria for selecting risk factors followed those of the WHO CRA project [11]: (i) availability of reasonably complete data on risk factor exposures within the Agincourt sub-district, (ii) availability of data from high quality epidemiological studies that indicates the causal association of risk factor exposure to stroke mortality, and (iii) a potential for modification. We excluded risk factors such as total cholesterol for which the population mean was below the theoretical minimum for all age groups. Systolic blood pressure (SBP), body-mass index (BMI) and fasting plasma glucose were the risk factors chosen for final assessment.

Estimating population attributable fractions

We estimate the number of stroke deaths and disability adjusted life years (DALYs) that would have been averted

in 2007-2011 in Agincourt sub-district if the current distribution of selected modifiable risk factors were shifted to an alternative optimal 'counterfactual' distribution as illustrated in Fig. 1 (using systolic blood pressure as an example). In that figure, the study population has an exposure distribution with a mean of $\bar{x}$ and a standard deviation of s, compared to the 'optimal' (counterfactual) distribution with a mean of μ and standard deviation of σ. The non-zero standard deviation of the theoretical-minimum-risk distribution reflects the reality that there always is some inter-person variability within any given population, even after hypothetical reductions [11]. The lower part of Fig. 1 shows the distance (in SBP units) that random subject x travels on the exposure axis in moving to his or her corresponding position on the counterfactual distribution. This distance times the slope of log relative risk on SBP gives the proportional reduction in risk (i.e. the distance travelled on the 'log RR' axis), equivalent to the potential impact fraction (PIF) for this individual [19]. Summing the PIFs for all individuals gives us the population attributable fraction.

Mathematically the PAF for continuous risk factors is calculated as shown below:

Equation 1:

$$\text{Population attributable fraction} = \frac{\int_l^h RR(x)P(x)dx - \int_l^h RR(x)P'(x)dx}{\int_x^h RR(x)P(x)dx} \quad [9, 19]$$

where: (i) $P(x)$ = Current population distribution of risk factor exposure; (ii) $RR(x)$ relative risk of mortality due to risk factor exposure; 0(iii) $P'(x)$ is an alternative exposure distribution

Numerical integration was conducted in Excel, using customised spreadsheets as done in previous studies [19] and the spreadsheets are provided as (Additional file 1).

Input data for PAFs

From Fig. 1 and equation 1, calculation of PAF requires four key input data:

Estimates of relative risk of stroke occurrence by risk factor

Age-specific relative risks for stroke occurrence by raised SBP, BMI and fasting glucose for South African population

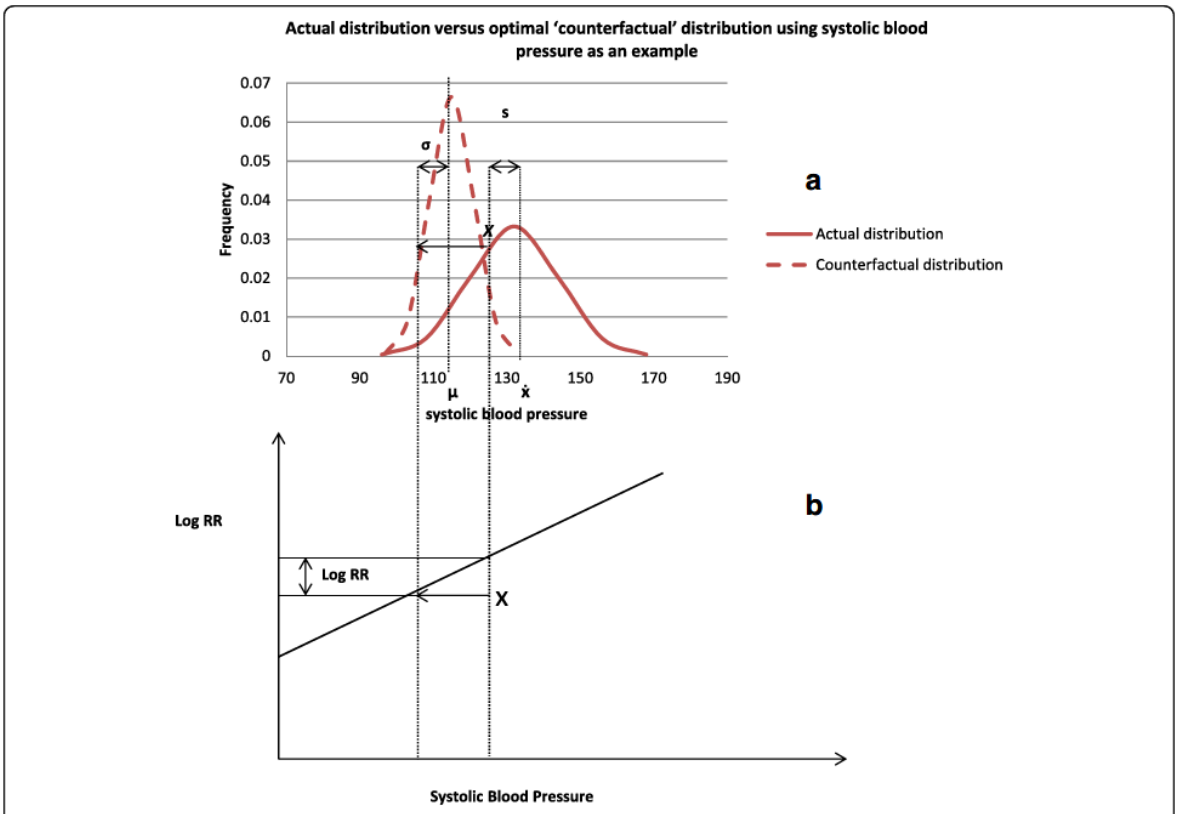

Fig. 1 CRA methodology – comparison of population of interest with actual (factual) exposure distribution versus corresponding theoretical optimum distribution (the counterfactual) (**a**) and impacts on relative risk of disease occurrence (**b**)

were extracted from the Global Burden of Disease study (Amy VanderZanden, personal communication). These estimates were derived by systematically reviewing and synthesising published and unpublished data. We assumed the same relative risks observed in South Africa would apply for the Agincourt population (Table 1).

Prevalence estimates for the risk factors

We derived prevalence estimates from the HIV/NCD study "Ha Nakekela" - a cross-sectional study of 4,362 adults >15 years conducted in Agincourt HDSS in 2010 (Table 2) [8]. In that study, a team of experienced local fieldworkers collected the data on cardiometabolic risk factors using validated questionnaires and standardised measurement instruments. Physical measurements included height, weight and waist circumference using a flexible stadiometer (Seca, Hamburg, Denmark); and Analysis Scale Body Check (Seca, Hamburg, Denmark). Blood pressure was taken from an average of the last 2 measurements out of 3 readings taken 2 to 3 min apart using Boso blood pressure instrument (BOSCH + SOHN, Jungingen, Germany). Random blood glucose was measured with a Caresens POP blood glucose meter (i-Sens, Nowon-gu, Seoul Korea) [8].

Because the number of individuals with blood glucose measures was small, we collapsed the age groups to form larger age bands (Table 3). Relative risk estimates are based on meta-analyses of prospective studies. This is the same data used by the global burden of disease study in 2010 [20].

Estimates of theoretical minimum for the optimum 'counterfactual' distribution

For our base case, we have followed the GBD 2010 study in assigning exposure [9]. Based on previous meta-analyses of population-based studies, the mean (± standard deviation) of the optimal exposure distributions were chosen to be 23 (±1) kg/m^2 for body mass index, 115 (±6) mmHg for systolic blood pressure and 4.9 (±0.9) mmol/l for fasting plasma glucose [9]. These are selected as the clinically meaningful exposures to minimize risk but these choices can be varied easily within the model. Worth noting is that the levels of blood pressure are consistent with levels reported in populations which have low cardiovascular disease, namely the Yanomamo Indians and rural populations in Kenya and Papua New Guinea [21].

Estimates of total stroke burden in study population

We obtained data on the number of stroke deaths by age and sex in 2007-2011 from the Agincourt HDSS. Cause of death in this sub-district is assigned through verbal autopsy, a process of interviewing a care–giver, relative or witness after a death, using a locally validated instrument [17]. The interview is conducted 1–11 months after a death and then reviewed independently by two medical doctors who assign probable underlying, immediate and contributory causes-of-death. When diagnoses differ and the physicians fail to reach a consensus, the verbal autopsy is reviewed by a third physician blind to the others' assessments [17]. Further we calculated yearly incidence of stroke, years of life lost (YLL) due to premature mortality and disability adjusted life years (DALYs). The comprehensive details of this analysis are available elsewhere [2]. Further, based on estimates from a prospective community-based study conducted in rural Tanzania, we assumed 82.5 % of strokes were ischaemic [22] and focus on ischaemic strokes for this analysis. Because haemorrhagic stroke may well prevail in Agincourt sub-district, we vary this estimate in uncertainty analysis using data from Connor (2007) [23]. That study indicated that ischemic strokes comprise 71 % of total strokes in rural South Africa but this was a hospital-based study.

Uncertainty analysis

We conducted statistical simulation to deal with uncertainty introduced by input parameters, namely relative risks estimates and prevalence of exposure data. We used @Risk 6.3 Professional for excel which allows multiple recalculations of a spread sheet, each time randomly choosing a value from distributions specified for input parameters (@RISK 6.3 Industrial) . We assumed that mean SBP, BMI and fasting glucose follow a normal distribution. Similarly relative risks followed a normal distribution, with the logarithm of the relative risks as the mean of the distribution. For each of the output variables (namely attributable burden due to BMI or high blood pressure), 95 % confidence intervals were calculated bounded by the 2.5th and 97.5th percentiles of the 1000 iterations generated.

Results

Quantification of the contribution of risk factors on stroke occurrence in this analysis represents the effects of individual risk factors, holding other factors constant. The effects of multiple risk factors are not a simple addition of the individual effects and this should be borne in mind when interpreting the following results.

The actual exposure distribution for SBP amongst individuals 25 years and older in Agincourt sub-district is shown in Fig. 2a. That distribution has a mean and standard deviation of 128 and 18 mmHg respectively. In accordance with the comparative risk methodology, 'shifting' this distribution to one that is clinically more beneficial (counterfactual) would have potentially avoided 40 % of the stroke burden (both mortality and morbidity) i.e. the population attributable fraction of SBP on stroke occurrence was 40 % in 2010 for both males and females. Similarly, 'shifting' the BMI distribution' towards the counterfactual distribution (Fig. 2b) would have potentially

Table 1 Age-specific relative risks of stroke occurrence due to raised systolic blood pressure (SBP) and body mass index (BMI) (GBD 2010 study estimates for South Africa, Amy VanderZanden - personal communication)

Risk factor	RR	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80+
SBP	RR for 10 mmHg increase	2.17	2.07	1.97	1.88	1.8	1.71	1.64	1.56	1.49	1.42	1.36	1.26
	RR for 1 mmHg increase	1.08	1.08	1.07	1.07	1.06	1.06	1.05	1.05	1.04	1.04	1.03	1.02
	95 % CI	(2.03–2.31)	(1.95–2.20)	(1.87–2.09)	(1.79–1.99)	(1.71–1.89)	(1.64–1.79)	(1.57–1.71)	(1.50–1.62)	(1.44–1.54)	(1.38–1.46)	(1.32–1.39)	(1.24–1.29)
BMI	RR for 5 kg/m2 increase	1.88	1.81	1.74	1.68	1.61	1.55	1.49	1.44	1.38	1.33	1.28	1.21
	RR for 1 kg/m2 increase	1.13	1.13	1.12	1.11	1.10	1.09	1.08	1.08	1.07	1.06	1.05	1.04
	95 % CI	(1.69–2.08)	(1.64–1.99)	(1.59–1.91)	(1.54–1.82)	(1.49–1.74)	(1.45–1.67)	(1.40–1.60)	(1.36–1.53)	(1.31–1.46)	(1.27–1.40)	(1.23–1.33)	(1.17–1.25)

Table 2 Prevalence estimates by sex and age group for systolic blood pressure (SBP) and body mass index (BMI) in Agincourt sub-district, South Africa, 2010 [8]

	Males			Females		
Age group	n	SBP	BMI	n	SBP	BMI
		Mean (SD)			Mean (SD)	
25–29	181	127.7 (9.7)	22.6 (3.6)	312	120.7 (10.1)	26.7 (5.6)
30–34	171	126.4 (10.6)	23.3 (4.3)	323	124 (11)	28.1 (6.3)
35–39	197	127.3 (11.8)	22.9 (4.4)	345	125.7 (12.1)	27.4 (6.1)
40–44	113	127.5 (13.7)	23.8 (4.8)	213	127.5 (14.1)	28.4 (6.4)
45–49	134	132.8 (13.9)	25.6 (7.9)	238	131.8 (13.3)	28.9 (7.6)
50–54	73	135.4 (10.5)	24.4 (4.9)	127	135.8 (13.6)	28.9 (7.2)
55–59	83	131.9 (14.1)	23.7 (5.1)	121	139.8 (14.7)	29.2 (6.6)
60–64	111	140.4 (13.6)	24.5 (5.2)	132	135.5 (12.2)	28.5 (6.8)
65–69	87	140.6 (15.9)	24.3 (4.5)	124	140.5 (14)	27.8 (5.7)
70–74	86	141.3 (13)	24.3 (5)	67	138.8 (11.4)	28.1 (6.8)
75–79	36	140.3 (13.5)	22.5 (4.3)	67	138.8 (12.4)	26.4 (5.3)
80+	52	137.9 (11.3)	23.7 (4.1)	66	143.7 (13.5)	25 (5.7)

Table 2 shows the prevalence of risk factors in Agincourt sub-district, South Africa, in 2010. The sample size (n) shown is for participants whose blood pressure was measured; this varied slightly more than the sample size for body-mass index

prevented 22 % of the total mortality and morbidity burden experienced in Agincourt over the same time period.

Population attributable fractions varied by age and sex within the sub-district (Figs. 3 and 4); this was more pronounced for SBP amongst females where PAFs increase steadily, peaking at 47 % at age 55-59, and then declining. For males, the distribution is less clear. However the proportion of stroke deaths/ DALYs due to high blood pressure is consistently high across all age groups, and average 35 %.

We used the same age-specific relative risk ratios for males and females for each risk factor. However, when comparing the burden attributable to BMI, there is a stark difference between males and females. Whereas the peak value for PAF in males was 22 % and occurred at ages 45-49 years; amongst females, PAFs for BMI were greater than 25 % for all ages less than 60 years. Worth noting is that in the younger age groups PAFs for BMI were more than double in females compared to males (11 % versus 30 %) in the age group 25-29 years. A similar pattern is observed up to age group 35-39 years. Overall, the proportion of deaths attributable to excess weight is highest in theage band 25-49 years amongst females compared to older age groups. However, because few deaths were classified as stroke-related in that age group in Agincourt in 2007 -11, the absolute number of stroke deaths attributable to BMI was small (i.e. 12 out of 38 deaths).

Table 3 Mean plasma blood glucose levels and relative risk estimates by age and sex, Agincourt sub-district, 2010

Age group	Male	Females	
	Mean in mmol/L(SD) [8]		Relative risk of stroke occurrence(CI) [20]
35–44	4.32 (1.14)	4.26 (1.21)	1.19 (0.91–1.53)
45–54	4.43 (1.13)	4.64 (1.25)	1.16 (0.97–1.39)
55–64	4.26 (1.03)	5 (1.45)	1.14 (1.01–1.29)
65–74	5.26 (1.05)	5.04 (1.25)	1.14 (1.08–1.20)
75–84	4.70 (1.13)	4.75 (1.42)	1.1 (1.06–1.15)
85+	4.98 (2.48)	3.77 (1.77)	1.06 (0.98–1.16)

The PAFs for raised blood glucose were more erratic and comprised less than 5 % of the total burden of stroke. Challenges of measuring the fasting plasma blood glucose in the original study were documented and could partly explain this [8]. The results are thus not included here but shown in the Additional file 1; even so they should be interpreted with caution.

In terms of absolute numbers for the period 2007-11, high blood pressure was responsible for 520 YLL due to premature mortality (95 % CI: 325-678), of which 355 YLL (95 % CI: 221-467) occurred amongst females. Similarly, high blood pressure was responsible for a further 545 DALYs lost due to stroke (CI: 343-717). The burden attributable to high blood pressure was almost twice that of BMI (Table 4). Overall, there were more attributable YLLs and DALYs in females compared to males, meaning that by controlling high blood pressure and excessive weight, it is possible to markedly reduce the premature mortality from stroke amongst females.

Discussion

To the best of our knowledge, this is the first study to estimate the burden of stroke attributable to raised blood pressure, excess weight and raised blood glucose in rural South Africa, using an established methodology. Notwithstanding the inter-relationships between risk factors, the key strength of this approach is that it allows comparison of the relative contribution of modifiable risk factors on stroke burden thereby aiding public health prevention and promotion efforts. In addition, the analysis was based largely on local data derived from recent studies [8] with the exception of relative risk data which was based on meta -analyses of large prospective studies [20].

We have highlighted the very substantial burden of stroke incurred by increases in systolic blood pressure and adult BMIs with the greatest impact in terms of absolute numbers being the burden associated with raised blood pressure. This is consistent with findings of earlier studies which have ranked high blood pressure as the major risk factor for stroke deaths [24, 25]. The high prevalence of uncontrolled hypertension in South Africa could explain the contribution of raised blood pressure on stroke occurrence in the country [26]. These prevalence rates exceed 75 % and were the highest reported rates in the Study on Global Ageing and Adult Health

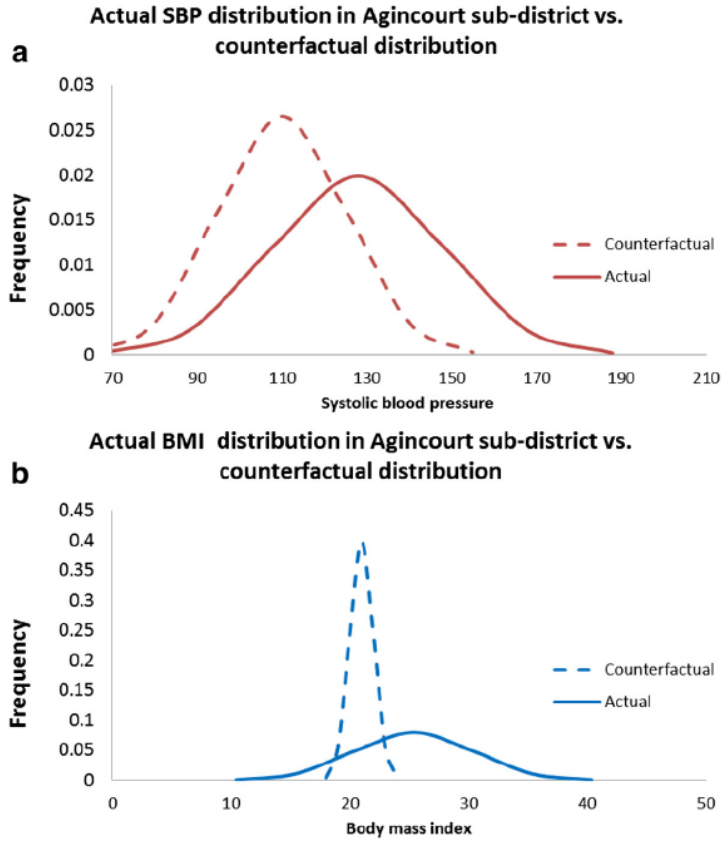

Fig. 2 Graphical representation of comparative risk assessment methodology showing the actual distributions of systolic blood pressure (fig. 2**a**) and body-mass index (fig. 2**b**) in Agincourt sub-district, South Africa, 2010 compared with the targeted "counterfactual" distribution

(SAGE), which surveyed more than 35,000 people older than 50 years in South Africa, China, Ghana, India, Mexico and Russia [26].

Whilst the overall PAF values were lower than national estimates for South Africa produced in 2000 [25], age-specific ratios indicate that the proportion of deaths attributable to high blood pressure is much higher amongst the younger age groups in rural Agincourt. This is likely a ramification of higher prevalence of raised blood pressure within young adults. According to a landmark study by the Prospective Studies Collaboration, the effect of BMI and other vascular risk factors such as high blood

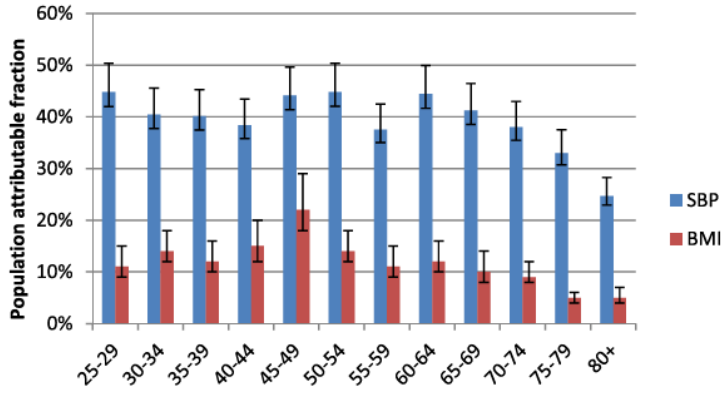

Fig. 3 Distribution of PAFs for stroke due to SBP and BMI in adult males, Agincourt, South Africa, 2010

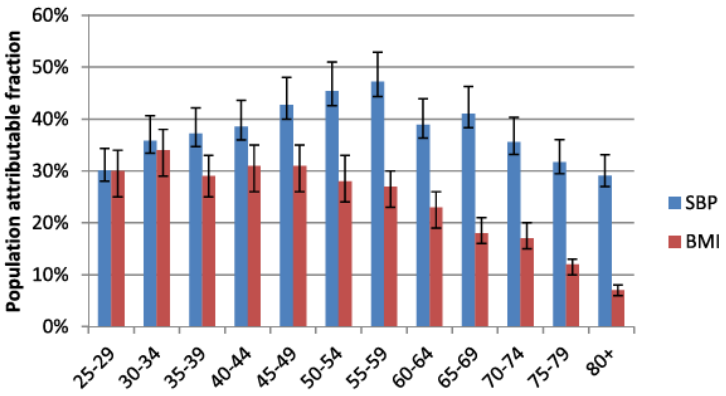

Fig. 4 Distribution of PAFs for stroke due to SBP and BMI in adult females, Agincourt, South Africa, 2010

pressure is far stronger at younger than at older ages [27, 28]. With regard to systolic blood pressure, a 20 mmHg lower SBP was associated with 64 % reduction in the risk of stroke death among individuals aged 40–49 years. In comparison, at ages 70–79 years the corresponding decrease in stroke was 50 % [16]. The mean systolic blood pressure amongst individuals aged 30-44 years was 122 mmHg in males and 116 mmHg in females in the South African National Burden of Disease (SA NBD) study [25]. In comparison, mean SBP was 127 mmHg and 125 mmHg amongst males and females respectively in Agincourt sub-district (author calculations based on data from the Agincourt HDSS).

Table 4 Stroke burden attributable to high blood pressure and body mass index (BMI) in males and females, Agincourt sub-district, South Africa, 2010

	Males		Females		Males		Females	
	SBP				BMI			
Age group	YLL	DALYs	YLL	DALYs	YLL	DALYs	YLL	DALYs
25–29	4.8	6.4	30.3	31.7	1.2	1.6	29.7	31.1
30–34	3.9	5.1	7.3	9.1	1.3	1.8	6.8	8.5
35–39	24.1	25.0	13.7	15.7	7.2	7.4	10.7	12.4
40–44	17.6	18.3	38.0	40.0	6.8	7.1	30.4	32.0
45–49	0.0	1.4	31.1	32.8	0.0	0.7	22.4	23.6
50–54	33.3	35.0	51.6	53.5	10.4	11.0	32.4	33.5
55–59	23.6	24.7	36.0	38.1	7.1	7.4	20.0	21.2
60–64	10.5	11.3	21.1	22.6	2.9	3.1	12.4	13.2
65–69	24.3	24.9	37.6	38.9	5.8	6.0	16.7	17.3
70–74	12.6	13.1	30.3	31.4	3.0	3.1	14.7	15.2
75–79	5.3	5.4	21.6	22.3	0.7	0.7	7.8	8.1
80+	5.6	5.7	36.9	38.1	1.1	1.1	9.1	9.4
25+	165.5	170.7	355.4	225.5	47.5	51.0	213.2	225.5

The table shows the number of years of life and DALY loss due to premature mortality that could have been prevented by shifting the population exposure distributions of systolic blood pressure (SBP) and body-mass index (BMI) from the current distribution observed in Agincourt to distributions that have been shown to be more clinically beneficial (optimal distribution). Those distributions will have means (SD) of 115 (6) mmHg and 23 (1) kg/m^2 for SBP and BMI respectively

Worth noting is that mean blood pressure was high, even when the proportion of the population classified as overweight was low amongst young males, suggesting that other factors contribute to increases in systolic blood pressure. These factors could include low birth weight, which is inversely associated with subsequent blood pressure, and is prevalent within the study population [29]. It has been estimated that a 1 kg higher birther weight is typically associated with a 2–4 mmHg drop in systolic blood pressure in 50-year-olds [30]. Nonetheless, we have no trend data on birth weight to support this explanation but these results warrant further exploration.

With respect to BMI, we show that burden of stroke attributable to this risk factor is concentrated amongst females and predominates in the younger age groups. Studies from elsewhere in the world corroborate this finding [26]. Similar to high blood pressure, the age-related differences in the PAFs can be attributed to the high prevalence of excess weight amongst young females, which increases the risk of cardiovascular disease [28].

Whilst the trend in age- and sex- specific PAFs in our study was similar to other studies [31–33], the absolute PAF values at younger ages were much higher in the current study even when prevalence rates of obesity were similar. A likely explanation is the difference in the "theoretical minimum risk" values applied across studies. In the current study we assumed that the optimal BMI distribution for a population that would confer minimum cardiovascular disease risk would have a mean of 23 kg/m^2. In contrast, a multi-country analysis based on Asian populations used a higher mean of 24–25 kg/m^2[31]. Had the latter study used a lower threshold as used in our study, the estimated PAFs would have been higher.

In light of our findings which indicate that considerable variation in the burden of stroke attributable to

excess weight and raised blood pressure exists across age and sex groups, the anticipated benefits in terms of stroke prevention would differ across population subgroups. We therefore propose that intervening at two levels through population wide policy and targeted health promotion campaigns is the best way forward to effectively reduce the stroke risk in rural South Africa. Evidence suggests that a policy led approach to health promotion in relation to two broad food categories - salt and sugar would be cost-effective levers for a population wide health promotion approach due to the impact on SBP and BMI [34]. For example, for each 100 mmol reduction in sodium intake, an SBP reduction of 5–10 mmHg is expected, with variation according to age [35]. Further, the downstream impacts on stroke reduction are well documented, with a recent study based on South African data indicating that legislated sodium reduction could prevent some 2,900 fatal and 4,300 non-fatal strokes in South Africa and save the health system R300 million (US$35 million in 2012) [36]. Based on these and related estimates, the Minister of Health of South Africa, under section 15(1) of the foodstuffs, cosmetics, and disinfectants Act, 1972 (act 54 of 1972), gazetted the regulations relating to the reduction of sodium in certain foodstuffs [37]. The foodstuffs specifically mentioned include bread, butter spread, fat spread, processed meats, raw processed meat sausages and ready to eat savoury snacks. According to these regulations the first total sodium reductions should be effected by 30 June 2016; for bread that means total sodium content of bread should be 400 mg (per 100 g of bread) by that date. A further reduction of 20 mg should be achieved by June 2019. If implemented effectively, such a policy has the potential to reduce cardiovascular disease (CVD) burden in the country.

With regard to obesity, legislative options on sugar content which do not rely on individual behaviour change or a well-functioning health service offer an alternative population-wide approach. For example, a 20 % tax in sugar sweetened beverages was predicted to reduce obesity by 3.8 % (95 % CI: 0.6–7.1 %) in men and 2.4 % (95 % CI: 0.4–4.4 %) in women in South Africa [38]. However, the confidence intervals of that study were wide and suggest that the intervention would prevent less than 1 % of the obesity burden. More innovative research is needed in this area to assess interventions that could reduce cardiovascular diseases including stroke by targeting obesity.

In addition to population wide approaches, the implementation of interventions that target specific groups needs to be carefully developed. For example, "anti-obesity" campaigns specifically tailored towards young South African women may reap greater benefits than more generic campaigns aimed at the whole population. Similarly, pharmacological treatment for people whose risk of a cardiovascular event over the next 10 years is above 35 %, offers an alternative individual-based intervention that could reach the older age groups with fairly frequent encounters with the health system. Within the Agincourt sub-district other novel initiatives are being explored and one such example is the Nkateko (Hope) trial [39]. This cluster randomised trial, focused on integrated chronic care will evaluate the impact at community and clinic levels of using a clinic-based lay health worker, supervised by a nurse, in managing hypertension. There are other interventions that could effectively address high blood pressure and excess weight that we have not mentioned but the main message from this work is to use a combination of approaches so as to achieve maximal benefits - interventions tailored by population subgroup and population-wide policies.

Conclusions

High blood pressure and excess weight, which both have effective interventions, are responsible for a significant proportion of the stroke burden in rural South Africa. Unless they are addressed through effective public health measures, the impact on the future stroke burden in rural South Africa will be substantial. When funds are limited, knowing which risk factor to target and whom to target in order to derive maximal benefit, is crucial for any informed decision making process. The current study provides this information within a rural South African context by applying an established comparative risk assessment methodology.

Limitations

While this study provides the first estimates of burden of stroke attributable to key risk factors in rural South Africa, there are a few limitations. We elected not to report on the impact of HIV/AIDS on stroke occurrence in this HIV-prevalent setting due to limited data to support this analysis. The best available data that independently assessed HIV as a risk factor for stroke was based on a study from the Unites States [40]. Different genetic profiles and possibly, risk-factor disease associations between that population and the current study population challenged use of that data. We however show the "results" of that analysis in Additional file 1, and indicate that the uncertainty in the analysis was too high to allow any meaningful conclusions to be drawn. The joint effects of high blood pressure and BMI were not examined even though effects of high body-mass index are partly mediated through blood pressure. We chose not to assess the joint effects as the correlation between these risk factors is unknown and the grouped data could overestimate the burden from combined risk factors. We used BMI as a measure of overweight and obesity. However, other measures such as waist circumference and body fat are

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considered better predictors of CVD risk [19]. Available data was not sufficient to establish risk factor- disease relationships of these indicators and opportunity exists to examine use of such measures in future comparative risk assessment studies. In future, it will be important to assess the full spectrum of risk factors including alcohol, vegetable consumption and physical activity. Nonetheless, the results presented give us a snapshot into the impact of lifestyle risk factors on stroke burden in a rural South African setting undergoing rapid epidemiological transition.

Additional file

Additional file 1: CRA methodology as implemented in Excel for Agincourt sub-district, South Africa. (XLSX 643 kb)

Abbreviations

BMI: Body-mass index; CRA: Comparative Risk Assessment; CVD: Cardiovascular disease; DALYs: Disability adjusted life years; GBD: Global Burden of Disease; HDSS: Health and Demographic Surveillance System Site; NCDs: Non-communicable diseases; PAF: Population attributable fraction; SBP: Systolic Blood Pressure; SD: Standard deviation; SSA: Sub-Saharan Africa; WHO: World Health Organization.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

MM, MYB, XGO and ST contributed towards the conceptualization of the study. MM carried out all the initial analysis and drafted the manuscript. ST assisted with the statistical analysis. ST, MYB and XGO critically appraised the manuscript for intellectual content and assisted with interpretation of data. All authors edited subsequent drafts and approved the final manuscript.

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Economic burden of stroke in a rural South African setting

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Abstract

Background—Stroke is the second leading cause of mortality and leading cause of disability in South Africa yet published data on the economic costs of stroke is lacking particularly in rural settings.

Methods—We estimate the total direct costs of stroke in 2012 from a health system perspective using a prevalence-based, bottom-up costing approach. Direct costs include diagnosis, inpatient and outpatient care. Analysis is based on the Agincourt health and socio-demographic surveillance system, which covers approximately 90,000 people. Published data from the SASPI study, Tintswalo Hospital Stroke register, and national cost databases were used. Sensitivity analysis was carried out to account for the variability in the data used.

Results—The total direct costs of stroke were estimated to be R2.5 - R4.2 million (US$283,500 – US$485,000) in 2012 or 1.6-3% of the sub-district health expenditure. Of this, 80% was attributed to inpatient costs. Total costs were most sensitive to the underlying incidence rates and to assumptions regarding service utilisation.

Conclusions—Our study provides a snapshot of costs incurred on stroke in rural South Africa. We show that stroke is a disease with high economic costs. Further studies that assess the lifetime costs of stroke are needed to better understand savings accrued from intervening at different stages of the disease.

Keywords

stroke; direct costs; Agincourt HDSS; cost-of-illness; rural; South Africa

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Competing Interests
The authors declare that they have no competing interests.

Author contributions
MM and LC contributed towards the conceptualization of the study. MM carried out all the initial analysis and drafted the manuscript. LC critically appraised the manuscript for intellectual content and assisted with interpretation of data. Both authors edited subsequent drafts and approved the final manuscript.

1. Introduction

Stroke is the second most common cause of death in South Africa, after HIV/AIDS and the leading cause of disability (Pillay-van Wyk et al. 2013). Recent estimates suggest that at least 30,000 strokes occur yearly in rural South Africa (Maredza, Bertram & Tollman 2015). Globally, approximately 3% of total health care system resources are devoted to stroke indicating that stroke imposes a significant economic burden on countries (Evers et al. 2004). Studies looking at the economic consequences of stroke in South Africa are few and somewhat dated. According to one such study, cardiovascular disease (CVD) including stroke consumed 4·1 billion to 5·0 billion South African Rands (R) in 1991, excluding costs of rehabilitation or community care (Pestana et al. 1996). Adjusting the costs to 2014 values using the consumer price index, the current cost of CVD would be R19–24 billion annually. Other stroke related studies focussed on cost of medication for stroke prevention (Bergh et al. 2013), or cost of inpatient care at tertiary facilities but did not estimate total cost of stroke (Viljoen, Dalmeyer & de Villiers 2013). Further, none of the studies considered the cost of stroke within a rural setting.

Economic data can be used to advocate for new interventions or the increased uptake of existing ones. Policy makers in South Africa are becoming increasingly aware of the need to justify health decisions on the basis of both effectiveness and costs; this is echoed strongly in the Department of Health's National Strategic Plan on non-communicable diseases (National Department of Health, 2013). Previous analyses on the economic implications of high sodium intake in South Africa led to a draft policy on salt reduction (Department of Health 2013) (Bertram, Steyn, Wentze-Viljoen, Tollman, & Hofman, 2012). As such, documenting the economic implications of stroke could promote evidence based decision making, assist in priority setting and influence adequate budgeting and planning for the prevention and treatment of stroke.

The present study is designed to meet the need for up-to-date information on the cost of stroke by (i) estimating the cost of stroke care in rural South Africa for prevalent cases in 2012 based on the standard of care (treatment protocols, coverage of interventions) and (ii) estimating the costs of stroke cases in the same population when coverage of all essential treatment or service utilisation is scaled up to 90%.

We utilise a variety of data sources namely: published data on stroke from the Agincourt Health and Demographic Surveillance Site, clinic-linked data for the Agincourt population on health care utilization patterns and the Tintswalo Hospital Stroke Register (THSR) – a rural hospital-based stroke register. The results of this study could help to understand the resource implications of stroke in South Africa and similar settings in sub-Saharan Africa, as well as make a case for intensifying efforts for stroke prevention initiatives in the rural settings of South Africa.

2. Methods

2.1. Setting and Population

This analysis is based on a population of approximately 90,000 people residing in the Agincourt sub-district of Mpumalanga province, north-east of South Africa (Kahn et al. 2012). The area is completely covered by a health and demographic surveillance system (HDSS). Comprehensive data on mortality and causes of death, births, and inward and outward migration have been collected through a yearly census update since 1992 via verbal autopsies (Kahn et al. 2012). Additional data on labour participation and educational status have been collected at different time intervals to complement demographic data and provide contextual information.

Social infrastructure and utilities are quite limited in the Agincourt sub-district. There is no formal sanitation, piped water to communal standpipes is erratic and electricity is affordable to a minority. High unemployment results in temporary labour migration of men and women which was estimated at 50-70% amongst males and 25-35% amongst females in the 20-59 year age group (Collinson et al. 2014). There are two public health centres, one private health centre and seven satellite clinics in the site. The Agincourt community is served by three district hospitals that are approximately 25-60 km away.

The health profile of the Agincourt population is characterized by the persistent burden of TB and HIV/AIDS, high maternal and child morbidity and mortality, and increasing non-communicable diseases. Using 1994-97 as the base year, the probability of dying from non-communicable diseases trebled by 2005 within the sub-district (Houle, Clark, Gómez-Olivé, Kahn, & Tollman, 2014). Though a slower decline was observed from 2006-2009, the mortality rates have plateaued at high levels (Kabudula et al., 2014). Similarly, deaths due to HIV/AIDs initially decreased, then plateaued at high levels (Houle et al., 2014; Kabudula et al., 2014). Stroke, rather than ischaemic heart disease is the dominant manifestation of CVD within this population (Kahn et al. 2006). Between 2007 and 2011, stroke incidence and mortality rates were 244 and 144 per 100,000 person years respectively (Maredza, Bertram & Tollman 2015a, Kahn et al. 2006).

2.2. Cost-of-illness analysis

This study is predominantly a cost of illness (COI) analysis that utilizes a prevalence-based approach. Prevalence-based COI studies estimate the costs of all disease cases (new as well as pre-existing) in a given year (Saha & Gerdtham, 2013). They include all medical care costs and morbidity costs for a disease within the study year and nothing has to be known or assumed about the survival rate or course of the illness (Segel, 2006). Because new disease cases that occur in that given year of analysis must be known, incidence data is required. The name prevalence-based should therefore not be confused to mean the exclusion of epidemiological incidence data..

2.3. Perspective

The perspective of the analysis is the health system, with the government as the payer of public health services. This was the most appropriate perspective to choose as the intent was

to inform evidence-based priority setting within the public health care sector. Because the government perspective was chosen, only direct costs related to provision of health care were assessed. These costs included hospital inpatient stay, diagnostic costs, outpatient costs and secondary prevention costs. Direct costs of patient transport were not included. Productivity losses as a result of time off work due to illness or due to caring for a stroke patient were also not included as these are indirect costs and not borne by the government. All costs were adjusted to 2012 using the consumer price index and reported in local currency, South African Rand (R) and United States dollar ($).We used an exchange rate of 1US$ = R8.70 for the year 2012 based on the South African reserve bank historical exchange rates (South African Reserve Bank, 2015)

2.4. Costing approach

There are 2 main approaches to resource costing: top-down and bottom-up) (Mogyorosy & Smith, 2005) . Top-down approach involves estimation of resource utilisation and costs by assigning a (national) average figure on non-patient specific bases such as using Diagnostic Related Groups (DRGs), or Healthcare Resource Groups (HRGs) (Mogyorosy & Smith, 2005). DRGs are 'diagnosis-related' groups of patients that have similar resource consumption patterns (Fetter, 1991). It is not possible to use this method in South Africa where DRGs or similar classifications are not used in the public sector. The second approach, which is used in this study, is the bottom-up approach. This approach requires understanding the service delivery process for a patient (treatment pathway) and estimating relevant resource items and assigning costs to these items. Each of these processes requires detailed data and inventories. We use the Tintswalo hospital stroke register to understand the type of treatment a patient with stroke receives at a hospital in rural South Africa and the probability of receiving that treatment. The stroke register was established in 2001 to ascertain and assess rural stroke patients over 20 months (Connor 2007). We use the treatment pathway (Figure 1) as a guide. We focus on the inpatient treatment pathway in the figure as the 'treatment' of stroke in the outpatient setting usually involves controlling risk factors, high blood pressure in particular and rehabilitation; the latter being largely unavailable in rural settings of South Africa. We do however calculate the outpatient costs. Clinic data linked to the Agincourt demographic surveillance system is used to determine health facility utilization patterns by patients with stroke as well as the type of medication that stroke or hypertensive patients are on. We also use available data from published studies to estimate treatment coverage and adherence rates. Unit costs were abstracted from several national sources: (i) South African district health barometer for inpatient and outpatient care, (i) South African medicines price registry for cost of medicines, and (iii) NHLS for costs of laboratory investigations.

2.5. Estimating prevalence and incidence of stroke in rural Agincourt sub-district

The Southern African Stroke Prevention Initiative (SASPI) study conducted in 2001 within the Agincourt population determined stroke prevalence through verbal autopsy with subsequent assessment of suspected stroke victims by a neurologist (Connor et al. 2004). That study is the only "community-based" prevalence study of stroke in rural South Africa with a well-defined denominator. Trained fieldworkers used a previously validated questionnaire to interview each household informant. The key questions were: "Has (person)

ever had weakness down one side of the body?" and "Has (person) ever had a stroke?" Clinical assessment of possible stroke victims was lowest amongst migrant males 25–44 years. To account for this noncontact, the investigators adjusted the stroke rates in each 10-year age stratum and assumed the same proportion of stroke survivors in employed men as among predominantly unemployed men. Thus the local population denominator included men who temporarily reside outside the sub-district as they consider the sub-district home and return to seek health care when too ill to work (Connor et al. 2004). Based on this study, 103 cases of stroke were identified amongst 724 individuals visited, giving an adjusted stroke prevalence rate, adjusted for non-response of 290 per 100,000 person years.

To the best of our knowledge there is currently no other information on incidence of stroke from community-based studies in South Africa. A hospital based study conducted in 1986 estimated a crude stroke incidence of 101 per 100,000 per year in a population ≥20years in suburban areas of Pretoria (Rosman 1986). However, in developing countries, most people who suffer a stroke do not reach hospitals and the data is out-of-date. These figures are therefore likely an underestimate.

In our study, estimates of stroke incidence were derived from a study that combined primary data from Agincourt HDSS with modelling techniques (Maredza, Bertram & Tollman 2015a). In the study by Maredza et al (2015), the incidence of stroke was estimated to be 244 per 100,000 persons. However, the stroke types (ischaemic and haemorrhagic) were not differentiated, but were all commonly categorised as 'stroke'. However, the treatment plan for ischaemic and haemorrhagic strokes is different, thus in our study, we estimate the proportion of ischaemic and haemorrhagic strokes in Agincourt sub-district using data from a previously published study. The study indicated that 71% and 23% of stroke were ischaemic stroke and cerebral haemorrhages whilst 6% of strokes were undefined respectively (Connor 2007). We conduct a sensitivity analysis around the incidence estimates using rates obtained from a prospective based study in a rural Tanzanian HDSS and also vary the baseline input parameters by ±20%.

2.6. Estimating direct costs

These included diagnostic costs, inpatient stay costs, outpatient visit costs and outpatient drug costs which were separately calculated to give total direct costs of care (Table 1). The inpatient care and diagnostic costs were calculated by multiplying the incidence of stroke by the related unit costs (Massyn, Day & Barron 2013). In the SASPI study, 80% of stroke patients indicated that they had sought care at a hospital/clinic following a stroke. We estimate that 50% of new stroke cases seek hospital inpatient care (are admitted) though the actual figure is likely to be much lower. Because of the uncertainty surrounding this figure we conduct sensitivity analysis around the point estimate, varying our baseline figure by ±20%.

2.7. Diagnostic costs

Stroke diagnosis is based on signs and symptoms, a physical exam and test results and Figure 1 shows the generic treatment pathway. We use this pathway and the THSR to estimate the proportion of stroke patients undergoing the various diagnostic tests. We

assume that all patients undergo blood tests to check glucose and cholesterol, as well as routine tests for blood pressure and heart rate measurements. Computerized Tomography (CT) scans are conducted to determine the cause, part of the brain affected and severity of the stroke and because of the cost are only ever conducted in a certain proportion of patients. For this analysis, we assume that 7% of the stroke patients had a CT scan. This is based on the SASPI rural stroke register which showed that amongst all patients who were admitted to the Tintswalo district hospital, which is one of the district hospitals for the Agincourt community, 7% were referred for CT scans at the provincial capital as no CT scans are available at the district hospital.

2.8. Inpatient care costs

The average length of stay for stroke patients is multiplied by the inpatient day cost to estimate the cost of inpatient care. Average length of stay of 8 days (95% CI, 7 to 9 days) was derived from the Tintswalo hospital stroke register (Connor 2007). We use a cost per patient day equivalent (PDE) as a proxy measure for the cost of an inpatient day at public sector hospitals. The cost per PDE is calculated by dividing the total expenditure of the hospital by the number of patient days. The PDE traditionally combines outpatient visits with inpatient days by assuming that the cost of one outpatient visit equals a third of the cost of an inpatient day. It is calculated by all public sector hospitals in South Africa. The cost per PDE for Tintswalo hospital was R1,772 in 2012/13 (Massyn, Day & Barron 2013. We perform sensitivity analysis around the cost per inpatient day estimate since this figure also partly captures the cost of treating an outpatient.

The cost of thrombolysis was calculated separately. According to data collected through the THSR, 20% of stroke patients that sought hospital care arrived within 3 hours of stroke onset (Connor 2007). Three hours is the time frame for administering thrombolysis. We therefore assume that of the 50% of patients who reach hospitals after a stroke 14.2% get thrombolytic therapy. The 14.2% is based on the assumption that 71% of those arriving within 3 hours have ischemic strokes and are eligible to receive thrombolytic therapy. Unit cost of alteplase was taken from the South African medicine price registry (South African Medicines Price Registry 2015), along with all other medication costs.

2.9. Outpatient costs

In line with assumptions of other studies, we assumed that stroke victims who survive past 30-days visit the hospital at least once a year (Saka, McGuire & Wolfe 2005). Whilst this may result in an under-estimate of costs, this is offset by the fact that patients with moderate to no-disability will rarely visit a specialist after the first year of stroke. Stroke prevalence estimates and cost of outpatient days were used to derive the estimate of total outpatient costs (Massyn, Day & Barron 2013; Connor et al. 2004). We conservatively assumed that the cost per outpatient day is one-third the cost an inpatient day. Outpatient care for stroke predominantly involves reducing risk factors for stroke namely hypertension and secondary prevention with drugs. We assume that all patients with ischaemic stroke (71%) were on secondary prevention (aspirin) therapy a month after the stroke. From month 2 onwards we assume that only 1% of the patients continue with the aspirin therapy and no patient is on warfarin (Connor et al. 2004). Hypertension is the most common risk factor in stroke

survivors therefore we assume that 70% of stroke survivors are prescribed hypertensive medication following the stroke. 70% was the prevalence of hypertension in the SASPI study. After month 2, we assume that only 7% continued with medication. Unit costs of drugs were obtained from the Medicines Pricing list of South Africa (South African Medicines Price Registry 2015). Since different hypertension drugs clusters (Beta Blockers, ACE inhibitors etc.) include various drugs (generics and brands) with different costs, the clinic data that is linked to the Agincourt health and demographic surveillance system was used to identify the most commonly prescribed drug in each drug cluster. There were no patients prescribed cholesterol lowering drug in the SASPI register, thus this was not included in the cost estimates.

2.10. Primary health care costs

We assumed that 90% of patients will utilise the public sector (based on the proportion of patients with medical insurance in the HDSS). The cost per PHC visit (Massyn, Day & Barron 2007) was used as the proxy measure for the cost of a clinic visit. We assumed that 7% of all stroke patients will visit the clinic once a month. This assumption was based on the SASPI study finding that 7% of stroke patients were on hypertensive medication (Connor et al. 2004).

3. Results

The total direct costs of stroke were R2.5 million (US$284,000) in 2012, with inpatient costs comprising 80% of the total costs (Table 2).

3.1. Costs when different incidence or prevalence rates were used

Using alternative incidence estimates from a rural HDSS in Tanzania, Hai district (108 per 100,000), which were collected prospectively over a 3 year period, had a significant impact on the total costs. The incidence rates in that study were half the incidence estimates used in our analysis. Total annual direct costs change by 50% when these incidence estimates are used (Table 3).

Varying prevalence estimates by up to 50% had a lower effect on the total direct costs; increasing (or decreasing) the total direct costs by 5% of the baseline value.

3.2. Sensitivity analysis

A sensitivity analysis was conducted by simultaneously increasing or decreasing the unit costs by 20% from their current value. The result was total direct costs ranging between R2 million and R3 million. Varying the unit costs individually showed that inpatient day costs had the greatest effect on total costs, changing the baseline total costs by 16% (Table 4).

3.3. Total direct costs from base-case to best-case scenario

When the percentage use of all service items were increased simultaneously to 90% (i.e. proportion reaching hospitals, acute use of aspirin for secondary prevention in ischaemic strokes, use of blood pressure lowering drugs) then costs of stroke treatment increased by

70%. The total direct costs of care are therefore expected to be approximately R4. 2 million if stroke victims have adequate access to care after stroke.

4. Discussion

The present study gathered information on costs of treating stroke cases (both new and existing) in the year 2012 in Agincourt HDSS, adding valuable knowledge to current information on the known burden of stroke. To the best of our knowledge this is the first study to estimate the costs of stroke in a rural setting of South Africa. The major strength of this study is its use of predominantly local data sources - both epidemiological and cost data. Previous studies on economic costs of stroke in sub-Saharan Africa are difficult to generalize as they vary with regards to cost categories included, number of patients assessed, duration of patient follow-up and unit costs of treatment procedures (table 6) (Viljoen, Dalmeyer & de Villiers 2013, Gnonlonfoun et al. 2013, Gombet et al. 2009, Guinhouya et al. 2010, Kabadi et al. 2013, Toure et al. 2005).

In this present study we found that total direct costs of stroke were between R2.5 million and R4.2 million (US$283,000 – US$485,000) in Agincourt sub-district in 2012. Because total health system costs to a sub-district are not known it is difficult to precisely calculate the proportion of the expenditure that is consumed by stroke. Nonetheless, assuming that the overall sub-district health expenditure is the product of the population size and the health expenditure per capita in the district (R1, 413 in 2012/13) (Massyn, Day & Barron 2007); total sub district health expenditure equals R155 million (US$18 million) in 2012. Total direct costs of stroke therefore account for approximately 1.6-3% of the sub-district health expenditure. Within an international context, Evers et al report that stroke accounts for 2-4% of the health expenditure in developed countries (Evers et al. 2004). Thus our study suggests that stroke has the same relative economic burden in rural South Africa as it does in developed country contexts.

What was clear from our analysis was that the high cost of stroke in Agincourt HDDS is a result of the high incidence of the disease. Intervening to reduce the onset of stroke is therefore a priority. Cost of illness studies that estimate the lifetime costs of the disease are urgently needed to understand the economics of stroke and its changing cost structure over a lifetime. This will allow policy makers to better understand how much resources can be saved by intervening at different stages of the disease cycle. In addition, methodologically rigorous, follow-up studies on stroke incidence are needed within the country to permit such cost of illness analysis to be undertaken.

We have shown the immediate effect of changing the service utilisation of items on total costs and shown that under the best case scenario, the actual total costs of stroke will almost double the figures reported in the baseline analysis. However, one short-coming of the study is that it does not consider the impact of increased access to services (e.g. reduced risk of stroke recurrence and mortality) on future cost-savings. Previous analyses has shown that increasing access to health services can in fact reduce the lifetime costs of stroke even though the first year costs of treatment increase (Saka, McGuire & Wolfe 2005).

Information collected via the THSR was useful in providing basic, yet fundamental information on stroke types and treatment procedures within the rural sub-district population. Equally important was the study on stroke prevalence that was conducted in 2001. The THSR was designed for a specific research purpose, as such current data on strokes is not readily accessible from the hospital. Going forward it would be important to track stroke cases, so as to allow better estimation of current costs of stroke cases and understanding of the drivers of costly expenditures.

4.1. Limitations

This study did not calculate a cost per stroke patient mainly because in the case of stroke there is a wide difference in the average costs of cases. In Tanzania, for example, costs of stroke cases ranged from USD75 to USD150 in rural Hai district, whilst in Dar es Salaam the differences were even larger (USD282 to USD674). Unlike incidence-based COI studies which can estimate the lifetime costs of a disease from its onset to its termination, prevalence-based studies (such as ours) can only provide a snapshot of costs at a particular point in time. We did not consider the impact of differing disabilities on our cost calculations but instead assumed all stoke patients access hospitals only once a year. This assumption could have underestimated the total costs we reported as stroke victims in Africa generally report greater disability and need for care (Connor et al. 2004) than developed country counterparts. There is significant disability associated with stroke which results in loss of income to individuals and families. These productivity losses are highest in developing countries where people delay seeking care and studies from other settings have indicated that productivity losses make up a significant part in total costs of care (Kabadi et al. 2013). This study did not attempt to estimate such costs; as such the findings underestimate the total costs of stroke in 2012.

5. Conclusions

Stroke is a disease with high economic costs and rural settings of South Africa are no exception. It costs health services 2-3% of their expenditure. In light of competing health priorities, reducing this burden is critical in resource constrained settings. Whilst our study provides a snapshot of costs incurred in a particular year, incidence-based studies coupled with modelling techniques are urgently needed to estimate lifetime costs. Such studies will give a more accurate understanding of the lifetime costs of stroke, and the savings accrued from intervening at different stages of disease. Demographic surveillance sites could act as platforms through which such studies are implemented as systems for following up individuals are already in place.

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Highlights

- This paper presents the first estimate of total costs of stroke in a rural setting of South Africa from the health system perspective. The total direct costs are US $283,500 – US$485,000 and represent 1.6-3% of the sub-district health expenditure.
- Cost-of-illness studies for stroke can be conducted using available information sources
- Further research that uses an incidence-based approach to costing is needed to estimate lifetime economic impact of cost-effective solutions for stroke in rural areas.

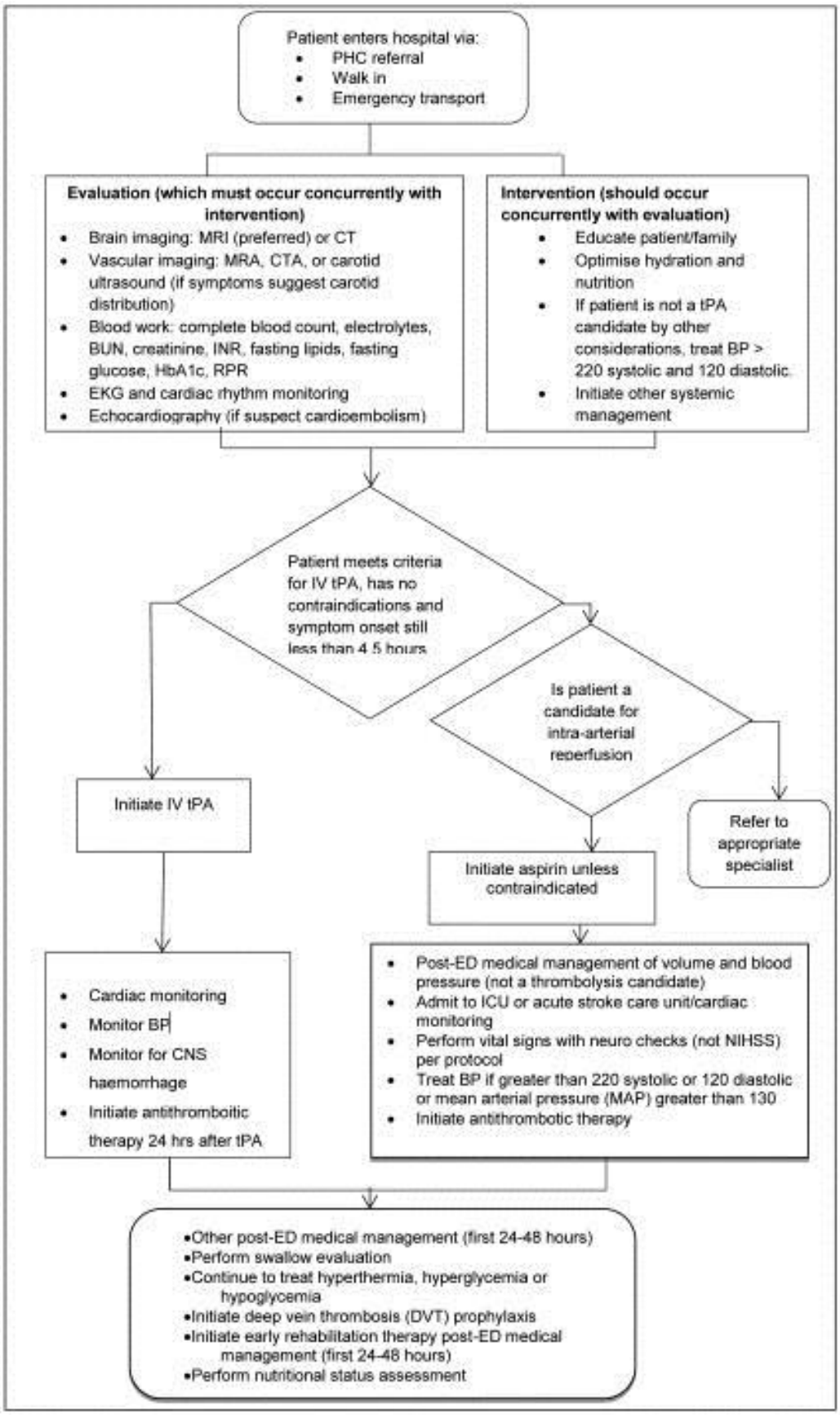

Figure 1.
Stroke treatment algorithm. Adapted from Anderson et al (Anderson et al., 2012)

Table 1

Epidemiological, cost and coverage assumptions used in baseline cost analysis, Agincourt sub-district, South Africa

Parameter	Base estimate used in analysis	Source
Prevalence	290 per 100,000	(Connor et al. 2004)
Incidence	244 per 100,000	(Maredza, Bertram & Tollman 2015a).
Proportion ischaemic strokes	71%	(Connor 2007).
Proportion haemorrhagic strokes	23%	(Connor 2007).
Costs (in Rands)		
Diagnostic costs		
CT Scan	2000	2009 National Health Reference Price List
Cholesterol	50	2009 National Health Laboratory Services pricelist
Blood sugar (glucose testing strip)	50	2009 National Health Laboratory Services pricelist
Full blood count	50	2009 National Health Laboratory Services pricelist
Electrocardiogram	32	
Cost per outpatient visit	584	(Massyn, Day & Barron 2013)
Cost per inpatient day	1770	(Massyn, Day & Barron 2013)
Thrombolysis	6 920	MRP
Outpatient hypertension drug costs/month	75	SA Medicines Price Registry (MPR)
Secondary prevention (aspirin) per month	6.93	SA MPR
Cost per PHC visit (Provincial PHC expenditure per uninsured)	670	(Massyn, Day & Barron 2013)
Coverage and health care utilization assumptions		
Proportion of incident strokes reaching hospital	50%	Conservative assumption
Proportion of stroke cases diagnosed by CT scan	7%	(Connor 2007)
Proportion utilizing public sector	90%	(Massyn, Day & Barron 2013)
Average length of stay in hospital	8 days (7-9)	(Connor 2007)
Proportion receiving thrombolysis	20%	(Connor 2007)
Proportion of patients on warfarin	0%	(Connor et al. 2004)
Proportion on secondary prevention on month 1	100%	(Connor et al. 2004)
Proportion on secondary prevention from month 2	7%	(Connor et al. 2004)

Parameter	Base estimate used in analysis	Source
Proportion on antihypertensive medication	7%	(Connor et al. 2004)

Table 2

Total baseline costs of stroke in Agincourt sub-district, rural South Africa in 2012

Cost items	Cost (Rands)	Cost (US$)
Diagnostic costs	**R 43 212**	**$4967**
CT Scan	R 18 788	$2 160
Cholesterol	R 6 710	$771
Blood sugar (glucose testing strip)	R 6 710	$771
Full blood count	R 6 710	$771
Electrocardiogram	R 4 294	$494
Inpatient care costs	**R 2 164 000**	**$248 736**
Cost per inpatient day	R 1 900 300	$218 425
Thrombolyis	R 263 720	$30 313
Costs of outpatient care	**R 258 947**	**$29 764**
Cost per hospital outpatient visit	R 126 703	$14 564
Cost per PHC visit	R 111 909	$12 863
Outpatient drug costs (11months)	R 12 629	$1 452
Drug costs (1 month after stroke)	R 7 706	$886
Total annual direct care cost	**R 2 466 159**	**$283 465**

Table 3

Variation in inpatient, diagnostic and total costs under different incidence assumptions

Cost Items	Cost (Rands)	Cost (US$)	Difference from baseline estimates
Diagnostic costs	R 19 126	$ 2 198	56%
Inpatient care costs	R 957 831	$ 110 096	56%
Drug costs (1 month after stroke)	R 3 411	$ 392	−56%
Total annual direct care cost	R 1 231 553	$ 141 558	−50%

Table 4

Sensitivity analysis - effect on total direct costs of increasing or decreasing unit costs by 20%

Parameter	Baseline	Total direct costs in South African Rands (−20%;+20%)	Relative change in total costs
Diagnostic costs			
CT Scan	2000	(2466417;2473933)	0.36%
Cholesterol	50	(2468832; 2471517)	0.03%
Blood sugar (glusose testing strip)	50	(2468832; 2471517)	0.05%
Full blood count	50	(2471517; 2468832	0.03%
Electrocardiogram	32	(2469316; 2471034)	0.02%
Cost per outpatient visit	584	(2444834; 2495516)	0.61%
Cost per inpatient day	1770	(2064779; 2875570)	9.80%
Thrombolysis	6920	(2417431; 2522918)	1.27%
Outpatient hypertension drug costs/month	75	(2466260; 2522918)	8.16%
Secondary prevention (aspirin) per month	6.93	(2470022; 2470327)	0.00%
Cost per PHC visit (Provincial PHC expenditure per uninsured)	670	(2447793; 2492557)	0.54%
			100.00%
Total direct cost	**2470175**	**(1955062; 2993661)**	**20.5%**

Table 5

From base case to best case scenario of increasing uptake of services to 90%

Cost items	Cost – Base Case in Rands (US$)	Cost – Best Case in Rands (US$)
Diagnostic costs	R 43 212 ($4 967)	R265 984 ($30 572)
Inpatient care costs	R 2 164 000 ($248 736)	R 3 684 200 ($423 471)
Outpatient care costs	R 126 700 ($14 563)	R 126 700 ($14 563)
PHC costs	R 111 910 ($12 863)	R 111 910 ($12 863)
Outpatient drug costs (11months)	R 12 629 ($1 452)	R 3 026 200 ($347 839)
Drug costs (1 month after stroke)	R 7 706 ($886)	R 13 342 ($1 534)
Total annual direct care cost	**R 2 466 148** ($283 465)	R 4 215 780 ($484 572)

Table 6

Cost of stroke studies from Sub-Saharan Africa

Study (Year)	Setting	No. of stroke patients	Length of follow up	Costs included	Costs per patient	Comment
Gombet et al 2009	Congo	90	6months	Direct costs (dianosis, inpatient care, medication)	158±10 euros	Only 1st day of hospitalization included (article in french)
Guinhouya et al 2010	Togo	412	12 months	Direct costs (diagnosis, inpatient care, medication)	430±190 euros for ischaemic stroke; 940± euros haemorrhagic stroke	article in french
Toure et al 2005	Senegal	383	12 months	Direct costs (diagnosis, inpatient care, medication)	USD160	article in french
Birabi et al 2012	Nigeria	240	Cross-sectional/ folder review	Direct costs (diagnosis, inpatient care, medication)	USD600 in public facility; USD5,000 in private facility	
Kabadi et al 2013	Tanzania	16	6 months	Direct costs (diagnosis, inpatient care, medication), transport, indirect costs (productivity losses),	USD 107 in rural Hai; USD 420 in urbna Dar es Salaam (excluding productivity losses) USD137 in rural Hai vs. USD380 in urban Dar es Salaam (productivity losses)	Included productivity losses Unit costs shown for some cost parameters
Viljoen et al 2014	South Africa	261	12 months (retrospect ive folder review)	Inpatient costs	USD2,240	Only inpatient costs included
Gnonlonfoun et al 2013	Burkina Faso	122	7 months	Direct costs; transport cost to designated hospitals, physiotherapy and out-of-pocket payments to other points of care.	USD145-USD940	

Appendix D: Paper 4

Cost-effectiveness of medical primary prevention strategies to reduce stroke in rural South Africa: a mathematical modelling study.

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Abstract

Background

Cardiovascular disease (CVD), particularly stroke is a growing cause of mortality and morbidity in rural South Africa yet contextualized evidence on cost-effective medical strategies to prevent it is scarce. A cost-effectiveness analysis of medical interventions for primary prevention of CVD was conducted targeting individuals with low, medium and high absolute risk of developing CVD in the next 10 years of : <10%; 10-19%; and ≥20%. . A fourth target group was individuals with untreated stage 2 hypertension.

Methods

An economic model for the cost-effectiveness of CVD prevention interventions was developed, customised for the Agincourt sub-district population. The markov model simulates disease progression in a cohort of people, starting from a healthy (disease-free) state until death or 100 years of age by accounting for changing risk factor profiles in each age-sex cohort. The cost-effectiveness analysis was performed from a provider perspective. Primary provider and patient costs were based on local databases including the Medicine Price Registry of South Africa and District Health Barometers. Efficacy inputs were derived from systematic reviews and meta-analyses. Disability- adjusted life years (DALYs) averted were used as the outcome measure. Sensitivity analyses were conducted to evaluate the robustness of the model results. Budget impact assessment was conducted to assess yearly spending, and consequently, affordability of interventions when scaled to eligible populations in the entire rural South Africa.

Results

Combination drug treatment comprising a diuretic and β-blocker for individuals having ≥20% absolute risk of developing CVD in the next 10 years is the most cost-effective intervention. It costs US$156 per DALY averted. It remains the most cost-effective intervention for medium-risk individuals (ICER = US$173 per DALY averted) and those with stage 2 hypertension (ICER = US$274 per DALY averted). At a willingness to pay threshold of US$7,500 per DALY averted, the polypill (comprising a statin and three antihypertensive agents) is the next most cost-effective intervention. For low-risk groups, thiazide diuretics are the most cost-effective,

followed by combination drug treatments of β-blocker/diuretic, polypill and ACE-inhibitor/diuretic. The ICERs for these interventions are US$228, US$454, US$683 and US$2,752 per DALY averted respectively. Cost-effectiveness ratios were relatively sensitive to discount rates, halving effectiveness estimates and doubling the cost of drugs. Giving the optimal interventions of β-blocker/diuretic and polypill to at least 90% of individuals with high CVD risk in the entire rural South Africa would cost the government per year, approximately US$4.06 million, and US$6.28 million respectively.

Conclusions

The escalating burden of CVD and its risk factors warrants timely action in rural South Africa. This comparative economic assessment has identified that medical preventive cardiology could be cost-effective in rural South Africa especially when targeted at high risk individuals. Cost-effectiveness evidence is not prescriptive; it should be assessed along other factors such as budget impact which indicate the financial impact of a new intervention over the first few years of its implementation.

Keywords: Cost-effectiveness analysis, cardiovascular disease, stroke, prevention, pharmacotherapy, rural, South Africa, Agincourt health and socio-demographic surveillance site

Introduction

There is increasing evidence that an epidemiological transition, characterised by increases in cardiovascular diseases (CVD) is underway in sub-Saharan Africa (SSA) [1]. The Global Burden of Disease (GBD) 2010 study showed that deaths due to CVD increased from 9.2% of total deaths in 1990 to 11% in 2010 [2]. Disability adjusted life years lost (equivalent to number of healthy life years lost) increased by approximately 20% during that period [2]. South Africa, notably, rural South Africa has not been spared from this tide [3, 4]. During the periods 1990 to 2012, NCD mortality steadily increased in all adult age groups (15 years and above), and this was largely driven by increases in cardiovascular conditions namely stroke and acute cardiac disease [3, 4]. It is estimated that at least 33,500 strokes occurred in 2011 across 'predominantly rural'[29] municipalities of South Africa [5]. This figure translates to an age-adjusted incidence rate of 347 per 100,000 person-years and is significantly higher than rates reported in similar rural settings of SSA [[5].

Exposure to risk factors for cardiovascular disease (CVD) such as high blood pressure, diabetes and obesity seem to be driving this trend. In Agincourt sub-district, rural North-Eastern South Africa, the proportion of adults aged 15 years and above with hypertension was estimated to be 50% in 2010 [6, 7]. Similar results have been reported at the Dikgale Health and Demographic Surveillance Site (HDSS) in Limpopo province [8]. Other important risk factors include overweight and obesity, now evident in both older females (30 years and above) and young adolescent females [9, 10].

The escalating burden of CVD is of concern not just from an epidemiological but economic perspective. Total costs attributable to CVD in the World Health Organization (WHO) African regions D and E amounted to US$11.6 billion in 2010; of which 40% were indirect costs due to productivity losses [11]. Whilst similar studies

[29] The definition of "rural" employed in the study is based on the Municipal Infrastructure Investment Framework (MIIF) which divides local and metropolitan municipalities into five groups: metropolitan municipalities/large cities (A); secondary cities (B1); municipalities with a large town as its core (B2); municipalities with small towns (B3); and municipalities that are predominantly rural (B4).

are scarce in many of the individual SSA countries, a study conducted in South Africa estimated the overall cost of stroke and heart diseases at US$1,250 million, which approximated 4-5% of the GDP of the country at the time the study was conducted in 1991 [12]. Economic data from rural settings are extremely scarce. Only a few studies have estimated costs of CVD, particularly stroke in rural areas [13, 14]. In one such study, based on the Agincourt HDSS in South Africa, the direct medical costs of stroke approximated 2-3% of the sub-district expenditure in 2012 [13]. As risk factors continue to grow, it is likely that available resources may not be sufficient to meet population demands. Thus, preventive action is urgently needed to reduce both the incidence of CVD and resulting economic costs of treatment particularly in rural populations that are traditionally medically underserved.

Deciding on the options that are cost-effective for rural settings of SSA remains a challenge. Though a few studies have investigated cost-effectiveness of CVD preventive interventions [15-28], the analyses have been at a regional or national level. Regional level analyses use aggregated data from countries that are markedly diverse with respect to demographic, epidemiologic, socio-economic and policy contexts and findings should be interpreted with caution when informing policy in individual countries [29]. Similarly, country-level analyses that are not disaggregated by rural/urban (despite differences in underlying social determinants), mask heterogeneity in health status within marginalised communities and undermine local and sub-national level decision-making.

This article examines the relative cost-effectiveness of a set of selected pharmaceutical strategies for preventing stroke in a rural setting of South Africa. Medical preventive cardiology has been shown to be very cost-effective for individuals at medium or high risk of developing CVD in Tanzania [29]. The research is premised upon the overarching hypotheses that the epidemiological profile and burden of CVD and associated risk factors seems to be markedly different in rural areas of South Africa compared to the rest of the country, therefore prioritized interventions will differ. Stroke was chosen as the marker condition for analysis as stroke rather than ischaemic heart disease (IHD) is the dominant manifestation of CVD in black South African populations [30]. To our knowledge, there have been no studies reporting on comparative cost-effectiveness of stroke prevention interventions within rural and marginalised communities of South Africa. This

research is timely. South Africa is currently undergoing wide-ranging health system reforms to strengthen primary health care and promote integrated chronic care with the overall aim of reducing the disease burden. This transitional period is a window of opportunity to present scientific evidence on cost-effective approaches to CVD prevention in heterogeneous communities. Furthermore, it is an opportunity to put forward a range of analytical tools that can be adapted to undertake much broader analyses related to non-communicable diseases.

Objectives

By applying a mathematical simulation model developed for this study, and using locally available data, the overall objective of this paper is to inform policy makers about the costs, effects and cost-effectiveness of selected preventive interventions, and how they can be combined efficiently to prevent and reduce stroke burden in rural South Africa.

Methods

Study Population

We model cost-effectiveness of CVD prevention in the 2012 Agincourt sub-district population of approximately 90,000 people, located in Mpumalanga province, rural north-eastern South Africa [31]. The sub-district shares a border with Mozambique and a third of its population comprises former Mozambican refugees. The sub-district typifies many rural communities in South Africa. Table 1 below depicts its key socio-demographic, economic and health indicators.

Agincourt sub-district is completely covered by a health and socio-demographic surveillance system (HDSS) which has been in operation since 1992. Essentially, the HDSS provides data on who has lived in the study site since then, who has moved in (through birth or in-migration) and who has moved out (through death or permanent out-migration). This data is updated annually through a yearly census. The

surveillance thus involves prospective follow-up of the entire population [32]. Verbal autopsies (VA)[30] are conducted on all reported deaths using previously validated questionnaires. InterVA-4 analytic software (version 4.02) is subsequently used to assign probable causes of deaths. Cause of death assignments through this tool have proven to be well-aligned to physician assessments of VA questionnaires. In addition to the annual censuses, Agincourt site's research infrastructure is used as a platform to 'nest' additional specialized studies that generate much-needed data on risk factors within the community. Examples include the SASPI study [33] which estimated prevalence of stroke and its risk factors in 2001 and the more recent HIV/NCD risk factors study which estimated cardiometabolic risk factors for HIV and NCDs within this community [34]. Further detailed descriptions of the HDSS' activities are provided elsewhere [31].

Table 1: Key demographic, socio-economic and health indicators for Agincourt sub-district, South Africa

Parameter	Value	Year analysed	Source
Total population	90,000	2011	[31]
Sex ratio (male: female)	0.92	2011	[31]
Percentage population ≥15years	36.41	2011	[31]
SES quintile			
Low	15	2009	[35]
Middle-low	19		
Middle	21		
Middle-high	21		
High	25		
Vital Statistics			
Life expectancy at birth (males; females)	(55.7; 64.4)	2009	[31]
Adult mortality rate 15-59	505.9; 382.4	2009	[31]

[30] VA involves interviewing the closest caregiver to the deceased about most prominent signs and symptoms occurring prior to death.

Parameter	Value	Year analysed	Source
years (males; females)			
HIV prevalence in individuals >15 years (%)			
Males	10.6	2010	[35]
Females	23.9		
Overall	19.4		
Non-communicable disease mortality as % of total mortality by period (2002-3; 2004-07; 2008-11)			
Age 18-44 years	11; 12 ; 11	2000-11	[3]
Age 45-69 years	32; 31; 30	2000-11	[3]
Age 70+ years	53; 53; 58	2000-11	[3]
Stroke incidence rate/100,000 person-years	244	2007-11	[5]
Stroke mortality rate/100,000 person-years	144	2007-11	[5]

Target Groups

We determined eligibility for preventive drugs using 2 approaches: (i) single-risk factor based approach i.e. high blood pressure and, (ii) absolute risk factor approach. The 2008 Framingham risk prediction equation was used to derive absolute risk of CVD over the next 10 years on the basis of: age, sex, systolic blood pressure, hypertension treatment status, smoking status, presence or absence of diabetes and body-mass index. We calibrated the risk prediction to the Agincourt population by using risk factor data from the 2010 HIV/NCD study which collected data on risk factors for NCD on a sample of 7,662 individuals within the Agincourt HDSS [34]. We evaluate the cost-effectiveness of stroke prevention for 3 levels of risk over the next 10 years: <10%; 10-19%; and ≥20%.

Cost-effectiveness model

We developed a deterministic “population average” Markov model to simulate the lifetime costs and health impacts of the interventions. The model divides the population into cohorts of individuals, stratified by age and sex, and computes average number of events in each cohort, by assuming that all individuals in the

cohort share the same characteristics. The model has four discrete states: “alive and free of stroke”, “non-fatal stroke in first year”, “alive with stroke after first year” and “dead”. Because we are concerned with primary prevention, each 10-year age and sex cohort begins in the “*Alive and free of stroke”* state. The model has a fixed cycle of length of one year. Hence, at the end of each year, a proportion of each cohort moves from one health state to another, or remains in the same state. Movement between these states is determined by transition rates. These rates capture the probabilities of incidence and case-fatality for fatal and non-fatal stroke (table 2). For example, a non-fatal stroke event may move a patient from a disease-free state to the health state ‘non-fatal stroke in first year’ whilst a fatal stroke event may move a patient from the same disease-free state to the dead state. Incidence and case-fatality rates are derived from a previous modelling study by the authors, based on the same population [5]. Each state (excluding death) is a potential point of intervening with appropriate interventions. This simulation is continued annually until every individual in the cohort has died or reached the age of 100. This simulation is done for both the intervention arm and baseline (no intervention) arm for each cardiovascular disease risk category. One assumption underlying this model is that the baseline event rates are best obtained from country specific sources, while the relative changes in those events (i.e. intervention effectiveness) can be based on available meta- analyses of good-quality studies from other countries.

We do not explicitly model ischaemic and haemorrhagic sub-types of stroke as different states. However, differential rates of incidence and case fatality for either type of stroke event that are fatal within the first year, are taken into account in the transition probabilities [36]. Similar to other studies, we account for incidence and case fatality for gastrointestinal bleeds (a side effect of aspirin therapy) amongst those receiving aspirin therapy in any state of the model [36].

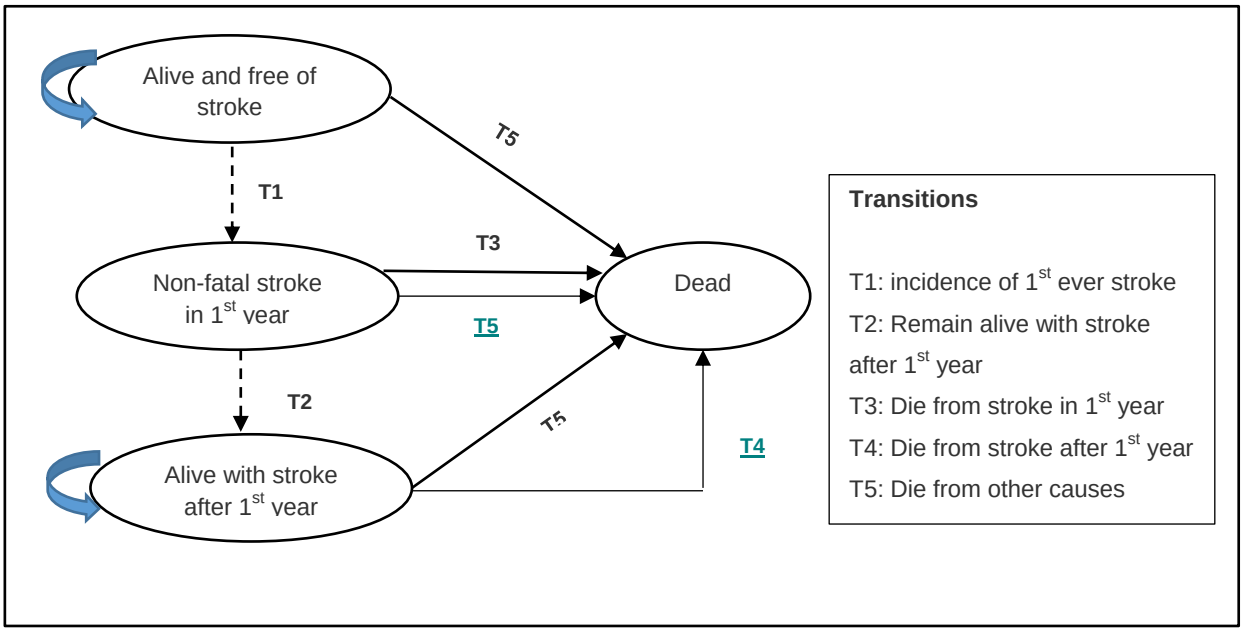

Figure 1: Schematic diagram of markov model depicting the possible movements between health states within a year starting from a disease–free state

The total years of life lived by the population, both with and without intervention, are adjusted for time spent in ill health using disability weights that capture the average 'disability' experienced at each age and sex, with or without stroke or a GI bleed. This allows the calculation of disability adjusted life years (DALYs) lived. Using the model predictions of populations with or without intervention that are in each disease state, the proportions receiving intervention at each yearly cycle, and the years of life lived by each cohort, we simulate costs of treating stroke and GI bleeding. All monetary values are presented in 2012 US dollars (US$)[31] and costs and outcomes are discounted at 3%.

We use the Excel add-in program @Risk (Palisade version 7.5) to conduct multivariate probabilistic sensitivity analysis which enables derivation of uncertainty intervals around costs and health outcomes on the basis of observed uncertainty around input parameters.

General model considerations

[31] An exchange rate of US$1 = R8.70 was used..

Intervention descriptions

We selected blood pressure and cholesterol-lowering drug interventions that have been proven to be effective in preventing stroke in clinical trials [37] and recommended in the WHO's preventive guidelines for CVD [38]. Blood pressure-lowering drugs were classified into five subclasses: thiazide diuretics (Ds), calcium channel blockers (CCBs), beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). These subclasses were selected on the basis that they are prescribed (*albeit* at different frequencies) at clinics within the Agincourt sub-district. Statins were selected because they are the recommended cholesterol-lowering drugs according to the South African treatment guidelines. The analysis was conducted for single drug interventions and combinations of drugs from different classes. Similar to the approach taken in other studies [25, 29], when two or more drugs were used together, their effects, measured as the relative risk (RR) of disease incidence, were combined by using a multiplicative equation (e.g., $RR_1 x RR_2 x RR_3$) [39]. Furthermore, we analysed the effect of the polypill. We assumed, the polypill contains a statin and three antihypertensive agents at half standard doses (diuretic, calcium channel blocker and ACE-Inhibitor) [40]. Since the main strengths of a polypill strategy seem to be the significant beneficial impact on adherence, we derived this data from randomised clinical trials [41-43].

Table 2: Model Parameters and their uncertainty distributions

Parameter	Value Mean (low; high)	Uncertainty distribution	Sources and assumptions
Diuretic			
Relative risk of stroke incidence with diuretic	0.62 (0.53; 0.72)	Triangle	Meta-analyses of primary prevention trials [44]
Annual cost of low-dose diuretic therapy	US$222.70	–	Average annual cost for the standard daily dose* of amiloretic and Ridaq, weighted by proportion on each medication in 2010 in Agincourt HDSS
Beta-blocker			
Relative risk of stroke incidence with beta-blocker -	0.83 (0.709;0.99)	Triangle	Meta-analyses of primary prevention trials [44]
Annual cost of beta-blocker therapy	US$231.84	–	South African Medicine Price Registry (http://www.mpr.gov.za/)
Calcium channel blocker			
Relative risk of stroke incidence with calcium channel blocker	0.66 (0.58;0.75)	Triangle	Meta-analyses of primary prevention trials [44]
Annual cost of calcium channel blocker therapy	US$235.85	–	
ACE inhibitor			
Relative risk of stroke incidence with ACE inhibitor	0.78 (0.66; 0.92)	Normal (lnRR)	Meta-analyses of primary prevention trials [45]
Annual cost of ACE inhibitor therapy	US$320.16	–	Average annual cost for the standard daily dose of enalapril and perindopril, weighted by proportion on each medication in 2010 in Agincourt HDSS
Statin			
Relative risk of stroke incidence with statin	0.78 (0.70; 0.87)	Normal (lnRR)	Meta-analyses of primary prevention trials [46]
Annual cost of statin therapy	US$253.57	–	Average annual cost for the standard daily dose of simvastatin.
Aspirin			
Relative risk of disease incidence with aspirin - Stroke (ischaemic) - Stroke (haemorrhagic) - GI bleed	 0.86 (0.74-1.00) 1.32 (1.00 - 1.75) 1.54 (0.13)	Normal (lnRR)	Meta-analyses of primary prevention trials [47]
Annual cost of aspirin therapy	US$237.85	Uniform	Average annual cost of aspirin

Parameter	Value Mean (low; high)	Uncertainty distribution	Sources and assumptions
			dispensed at primary health care
First year discontinuation with individually-targeted interventions	50% (8%)	Beta	
Polypill	0.25 (0.14 – 0.43)	Normal (ln RR)	Estimate based on multiplicative effects of individual drug components
Treatment costs			
Stroke - First year - Subsequent years	US$3,433.56 US$537.93	Uniform	Estimates derived from author's calculations based on actual resource use for hypertensive patients and stroke patients in Agincourt sub-district
GI bleed - Men - Women	US$530.57 US$432.10	Uniform	Australian study (no data for South Africa) [36]
NB. All costs adjusted to 2012 South Africa Rands using consumer price index and/or purchasing power parities where relevant. *Annual cost of drugs includes costs for primary health care visits since the assumption is that individuals will receive their medication at primary health care centres.			

Treatment assumptions

We assume that CVD risk can be assessed within the primary care setting at regular check-ups based on the risk factors mentioned above. For individuals with high CVD risk (≥20%), we assume that 4 outpatient monitoring visits are necessary. Individuals with lower CVD risk will attend two outpatient follow-up visits for monitoring. Based on current practice in South Africa, we assume that individuals who are currently on treatment for high blood pressure and are controlled receive a 3-month supply of medication. Because default rates are high, we assume that 50% of the patients will default on their treatment within the first year of therapy, based on rates of discontinuation with blood pressure lowering therapies from published meta-analyses [48].

Current practice

The proportion of adults in the Agincourt HDSS currently taking blood pressure and lipid lowering agents 'current practice' is determined from the clinic database that is linked to the HDSS. We exclude those who have already experienced a CVD event as the focus is on primary prevention of CVD.

Calculating costs

Drug costs were calculated based on dosages from standard treatment guidelines of South Africa. We used the South African Pharmaceutical Price Registry to derive unit costs of individual drug treatments [49]. The cost of the combination drug treatments (with exception of polypill) was assumed to be the sum of the individual drug therapies. The average unit costs for two polypills currently marketed for secondary prevention of CVD were used estimate the unit cost for our polypill. The polypills are Fuster-CNIC-Ferrer CV polypill (marketed under the brands of Trinomia® and Sincronium®) and the Indian Polycap (marketed under the tradename (Cadila®) (http://www.who.int/selection_medicines/committees/expert/19/applications/FDCCardio_12_A_Ad.pdf). Costs of primary health care and outpatient visits were based on published estimates for the district in the District Health Barometer[32].

Cost-effectiveness analyses

Cost-effectiveness results are expressed in terms of average cost-effectiveness ratios (ACERs) and incremental cost-effectiveness ratio (ICERs). ACERs are the result of dividing the difference in total costs of an intervention by the difference in DALYs averted when compared to a situation of no intervention. ICERs are reported for successive set of interventions that would be selected at expanding levels of resource availability starting with the intervention with lowest cost per DALY [21]. Interventions were considered cost-effective if the ICERs fell below US$7,550 which was South Africa's GDP per capita in 2012 [50]. This threshold for willingness to pay is based on the commission on macroeconomics and health's GDP-based thresholds which 'suggest' that interventions whose cost-effectiveness falls below the GDP per capita of a country are very cost-effective whilst those that cost less than three times GDP per capita are considered cost-effective [51] . This threshold is a supply side measure of willingness to pay as opposed to a demand side/ payer perspective.

Sensitivity analyses

[32] An initiative of the national NGO, Health Systems Trust (HST) , which works closely with the Department of Health.

Sensitivity analysis was conducted to evaluate the impact of single assumptions about costs and outcomes on model results. Table 2 shows the upper and lower variable ranges used in the sensitivity analyses. These upper and lower figures were derived from reported 95% confidence intervals. Where these were not available for costs we assumed a range of +/− 25% around the base case value. For the multivariate probabilistic uncertainty analysis, we ran a Monte Carlo simulation. The model was run 1000 times, with distributions for each parameter rather than point estimates to determine the probability of optimal intervention being cost-effective against a range of cost-effectiveness thresholds.

Budget Impact Analysis

Cost-effectiveness analysis does not provide the impact of new interventions on the payer's budget. Thus we estimated the budget needed to provide the most cost-effective interventions to all eligible patients in rural South Africa who present with high CVD risk. We make the conservative assumption that the Agincourt sub-district population's risk profile is representative of the entire rural South Africa.

RESULTS

Costs and effects of the interventions

The polypill yields the highest number of healthy life years among all the alternatives and across all absolute CVD-risk groups. It averts a total of 112 DALYs per year in the Agincourt sub-district when targeted at individuals with >20% risk of developing CVD within the next 10 years (high CVD-risk). Total DALYs averted per year due to the polypill for the medium and low absolute CVD-risk groups were 128 and 205 DALYs respectively whilst 89.7 DALYs were prevented when the polypill was given to individuals with blood pressure greater than or equal to 160/90mmHg (stage 2 hypertension) (table 3). Combination therapies of two or more blood pressure lowering agents increased the health benefits, compared to the therapies given individually due to the assumed multiplicative effects of the therapies. For example, a combination of diuretic and β-blocker averted 95.4 DALYs in the high absolute CVD-risk compared to 88.3 DALYs averted by diuretics alone. Aspirin, also effective on average, has a higher probability of causing gastrointestinal bleeding and increases

risk of haemorrhagic strokes; if other more effective therapies are given first, the potential additional health benefits of aspirin are reduced.

Statins, including simvastatin, are still relatively expensive in South Africa and resulted in the highest net cost (cost of interventions less projected savings from reduced treatment costs) among the selected pharmacotherapies. Maintaining status quo (current practice) also resulted in higher net costs compared to the other therapies assessed. The incremental benefits (life years saved and DALYs averted) per person as well as the incremental costs for all strategies are presented non-age weighted and discounted at 3% in table 3.

Cost-effectiveness

Table 3 shows the results of the cost-effectiveness analysis for the 3 CVD-risk groups and for individuals presenting with stage 2 hypertension. We present both the average and incremental cost-effectiveness ratios.
As shown by the diagonal bands in figure 2, average cost-effectiveness ratios fell within the range of US$160 to US$500 per DALY averted for all pharmacotherapies. The diagonal bands 'represent' alternative cost-effectiveness thresholds since there is no set threshold for South Africa. Proposed thresholds in literature range from as low as US$150/DALY averted [52-54]. Using, as an alternative, the GDP per capita figure of US$7,548 (estimated for South Africa in 2012) [50] as the threshold for considering an intervention to be highly cost-effective, we found that all the interventions assessed met this criterion for all the risk groups.

Incremental cost-effectiveness

We determined the optimal "intervention package" for each target group by assessing the incremental cost-effectiveness ratios for the next best intervention(s) to be added onto the package; starting with the most cost-effective intervention first.
<u>Low risk</u>
The results suggest that providing diuretics is the most cost-effective intervention; requiring US$228 to avert a DALY. The favorable price of hydrochlorothiazide is the major reason for this intervention showing such high cost-effectiveness in low-risk groups. Adding β-blocker to the diuretic is the next most cost-effective intervention, with an ICER of US$454 per DALY averted. Whilst combination of ACE-I and diuretic

is cost-effective, it results in the highest ICER of US$2,752 per DALY averted. All the other strategies are dominated either by strong[33] or extended dominance[34].

Medium-risk, high-risk and stage 2 hypertension

The combination of β-blocker and diuretic yielded the lowest ICER of US$173 in the medium-risk group. Providing this intervention averts a total of 109 DALYs per year at an additional cost of US$18,900 within the rural population of Agincourt sub-district. The polypill is the next most cost-effective intervention with an ICER of US$416 per DALY averted. All other strategies were either weakly or strongly dominated. The optimal interventions are similar for the high absolute CVD-risk groups and for the group with stage 2 hypertension. Nonetheless the interventions have better cost-effectiveness in the higher-risk group i.e. those with ≥20% absolute risk of developing CVD in the next 10 years.

Summary for polypill

The polypill improved health for less than the GDP per capita of South Africa in 2012 for all the target groups assessed. It produced much better effects than combination treatment of two blood pressure lowering agents and aspirin due to predominantly increased adherence. In addition, it was much cheaper than the combination therapies. We assumed that the costs for the latter would be the sum of the individual drug components whilst the polypill cost was derived from an average unit cost of currently marketed 'polypills'.

Deterministic sensitivity analysis

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[33] Strong dominance - any of the competing interventions is ruled out if there is another intervention that is both more effective and less costly.

[34] Extended dominance (sometimes called "weak dominance") rules out any intervention that has an ICER that is greater than that of a more effective intervention. The list of interventions, trimmed of strongly dominated alternatives, is ordered by effectiveness first then each intervention is compared to the next most effective alternative by calculating the incremental cost-effectiveness ratio. Extended dominance shows that the decision-maker prefers the more effective intervention with a lower incremental cost-effectiveness ratio (https://www.herc.research.va.gov/include/page.asp?id=cost-effectiveness-analysis).

Table 4 presents the results from the one-way sensitivity analysis for the non-dominated interventions for all target groups. Doubling the price of drugs and primary health care visits, reducing the intervention effectiveness to 50% of the point estimate and not discounting health benefits resulted in a change in ACER of more than 10%. The average cost-effectiveness ratios were most sensitive to unit cost of drugs, with respective ACERs increasing by 50-75%. However, the results were less sensitive to a change in drug effectiveness, to the lower boundary of effectiveness (the upper and lower boundaries are shown on table 2). The probabilistic sensitivity analysis indicates the uncertainty surrounding our results with overlapping uncertainty ranges for cost and effectiveness estimates (figure 2).

Budget impact for CVD prevention in high risk groups

In 2012, there were approximately 4.3 million people over the age of 30 residing in predominantly rural communities of South Africa. Assuming that the same pattern of CVD risk observed in Agincourt sub-district exists throughout the entire rural South Africa, the number of people with low, medium and high absolute CVD risk would be 4.1million, 132,000 and 55,000 respectively. We estimate the budget impact of giving the optimal interventions of diuretic, β-blocker/Diuretic and polypill to at least 90% of individuals with high CVD risk. We find that the government would need approximately US$4.06 million, US$ 6.28 million each year to cover these drug costs for the β-blocker/Diuretic and polypill respectively.

DISCUSSION

Our study suggests that the optimal pharmacotherapies to prevent CVD in rural South Africa included the ‘polypill’ and hydrochlorothiazide alone or as combination therapy with either β-blocker or ACE-I across the three absolute risk-based groups. Cost-effectiveness was greater as absolute risk of CVD increased and this is consistent with published findings from similar studies for the sub-Saharan African region [55]. The modest ‘efficiency loss’ related to lowering the risk thresholds is due to the relatively greater number of individuals eligible for the intervention which significantly increases costs at modest health gains. Thus, for our population, setting the risk threshold at which preventive pharmacotherapy is offered at ≥20% is a worthwhile strategy. Currently, the World Health Organization recommends that very low-income countries may place the threshold for implementing high-risk strategies at

a 10-year risk of CVD of 40% whilst other countries with additional resources may lower this threshold to 30% [56].

Though direct comparison with other studies is challenging due to methodological differences, the effectiveness estimates derived in this study are consistent with published regional analyses for the World Health Organization African E (Afr-E)[35] region. For example, a regional analysis by Ortegón and colleagues found that primary prevention of CVD through multi-drug treatment targeted at individuals with a CVD risk of ≥25% averted 0.004 DALYs per person per year (3689 DALYs per 1 million population) [21]. In comparison, our study showed that the most effective intervention (polypill) averted 0.005 DALYs per person per year whilst the β-blocker diuretic combination averted 0.004 DALYs per person per year in the high risk group. It is noteworthy that our study only included stroke and not ischaemic heart disease; had we included the latter the number of DALYs averted may have been slightly higher. However, IHD was not included in analysis, because at the time this study was conceived, stroke was the dominant manifestation of CVD in black South African populations.

Targeting individuals based on a single risk factor - in our case high blood pressure – proved to be less cost-effective compared to targeting individuals based on absolute risk. This corroborates previous studies which showed that targeting individuals based on absolute risk was more cost-effective than using single risk factor guidelines [57].. This finding is reinforced by the recently-released Joint National Committee (JNC) guidelines which now propose a lower cut-off for blood pressure compared with JNC 7 guidelines [58]. According to the updated guidelines, adults with an average systolic blood pressure of 130 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg are categorized as having stage 1 hypertension; these were previously classified as prehypertension in JNC 7 [58].

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[35] WHO AFr-E region includes the following countries: Botswana, Burundi, Central African Republic Congo, Côte d'Ivoire, Democratic Republic of Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.

To a certain extent, the findings of this study render preventive cardiology more attractive in terms of cost-effectiveness compared to 2 earlier studies conducted in Tanzania [25, 29]. According to one of the studies, preventive drugs are cost-effective when the willingness to pay threshold exceeds $1,397 [29]. This is contrary to our study where incremental cost-effectiveness ratios for a diuretic for the low CVD risk group was $230. Differences in CVD risk cut-off points, cost and clinical evidence and WTP thresholds could partially explain some of these differences.

The polypill has been hailed as a promising concept in CVD prevention; therefore findings related to it deserve particular mention. In line with other studies, we found that the polypill seems potentially a highly effective intervention for primary prevention of stroke [24, 25, 59]. Average cost-effectiveness ratios also indicated that compared to no intervention this could be a highly cost-effective strategy for our setting. When compared with other therapies in an incremental cost-effectiveness analysis, the polypill remained a potentially highly cost-effective option for primary prevention of CVD in rural South Africa. The cost-effectiveness studies on the polypill have reported different findings but direct comparison with our results is challenging due to methodological differences in WTP thresholds, outcomes assessed and unit costs of polypill. For example, Franco et al. reported that, for the polypill to be cost-effective, annual cost of the medication alone needed to be no more than 302 euros for men aged 50 years and above [60]. However they used a much higher WTP threshold of €20,000 per life year saved in contrast to our study where the willingness to pay was $7,550 per DALY averted. Similarly, Ferket et al, in a microsimulation model based on a UK population of 259,146 individuals, compared the cost-effectiveness of a polypill offered at different absolute risk thresholds and alternative starting ages. Using a cost-effectiveness threshold of £30,000 per QALY gained, the authors found that starting the polypill at age 60 was the most cost-effective scenario when annual drug prices were lower than £240 whilst all polypill scenarios would be cost-effective at annual unit cost prices of below £50 [61]. The annual cost of polypill used in that study was £382.64 and was four times as high as unit costs used in similar modelling studies for LMICs [59]. The authors concluded that " a population approach with the polypill is currently too costly to be implemented in the UK but would become cost-effective if drug prices were reduced" [61]. It is important to note that the unit cost of a polypill used in our study was much lower (US$182.5) per year

than estimates in other studies and based on average unit costs of polypills that are currently marketed for secondary prevention of cardiovascular disease. A potential limitation of this and other published studies is that we assumed that the effectiveness of the polypill would be the multiplicative effect of individual drug components. As empirical data from ongoing clinical trials [41] becomes available, it would be critical to re-examine the cost-effectiveness of the polypill.

Determining whether an intervention is cost-effective or not requires some sort of "decision rule," (preferably pre-specified) that defines the circumstances where a new intervention is accepted as cost-effective. However, such ceiling ratios are currently unavailable in South Africa and in many countries throughout the world [62]. The threshold values used are arbitrary and have been met with extreme criticism [63, 64]. For example, we based our decision rule of cost-effectiveness on the GDP based thresholds of the Commission on Macroeconomics in Health. The latter suggest that interventions with ICERs below the GDP per capita of a country are very cost-effective. However, the validity of these thresholds for determining cost-effectiveness at a country level have been questioned because they lack country specificity, tend to make almost all health care interventions and programmes cost-effective and do not reflect the "true" budget impact of interventions. Had we used more stringent threshold of US$150/DALY averted [52-54] as utilised in other studies, the majority of interventions assessed in this study would have been easily ruled out with little justification just as easily as they were ruled in with the GDP-based threshold [63]. As more countries adopt results from cost-effectiveness analysis as one of the measures to inform decisions on allocation of resources, it will be critical that country-specific thresholds be established, that if possible, account for budgetary constraints within a setting.

We conducted a simple budget impact assessment for the optimal intervention strategies for the high risk group which showed that South Africa would need to spend between 4 million and 6.3 million dollars a year on pharmacotherapy as a preventive measure to reduce CVD. This value corresponds to less than 1% of the health care budget (the 2012/13 budget for the country was R121 billion). Whether or not these values indicate that medical interventions are affordable will need to be considered alongside budgetary demands for other health care programmes and interventions.

Strengths and limitations

We used local data on disease epidemiology, demography, intervention use, adherence and costs of interventions in our analysis to ensure more precise cost-effectiveness estimates. Furthermore, we calibrated the Framingham risk equation using local data derived from the Agincourt sub-district, rural North-east of South Africa. Though there have been debates in the past about the validity of using the Framingham equation for a South African population, recent evidence indicates that in terms of assigning CVD risk, there is a high level of correlation between commonly-used laboratory-based risk scores and the Framingham (non-laboratory based) method [57]. We present the budget impact of introducing seemingly cost-effective interventions to high risk individuals; thus giving policy-makers additional evidence upon which to make decisions. Contrary to previous studies, we accounted for non-adherence to drug therapy in our model [29]. Non-adherence to antihypertensive treatment is a global challenge [48] and not including this would have potentially biased results in favour of drug therapy.

The conclusions of our analysis are subject to important limitations reflecting the nature of the model. Most of the treatment effect data was derived from meta-analysis of randomised control trials. Many of these trials are based on populations in developed countries and treatment effect could differ in our population thus affecting cost-effectiveness of interventions as evidenced by the sensitivity analysis. Furthermore, RCTs are conducted in controlled settings and the effectiveness in real life could be lower than assumed in our model. HIVAIDS is highly prevalent in South Africa and there is emerging literature to suggest that HIV/AIDS co-morbidity could affect our approach to CVD prevention. However, we did not attempt to include HIV/AIDS interactions in our model. Adding these would have complicated the model and moreover data needed to populate such a model are not yet available.

Similar to the approach taken in other studies [55], we assumed that intervention effects were uniform across sub-groups with varying absolute risk levels. This may, however, result in underestimation of impact in high-risk individuals and over-estimation in low-risk individuals making it challenging to predict the overall direction of the bias. Another potential limitation is that we adopted a narrow health system perspective in our analysis. Future analysis should adopt a wider societal perspective

that includes transport costs, and productivity losses and loss of earnings due to work absences by patients and caregivers. There is robust evidence that stroke results in significant disability in rural South Africa and in similar settings of sub-Saharan Africa. Such disability results in loss of income to individuals and families and were found, in a pilot study in Tanzania to comprise a significant proportion of total costs of stroke care [14]. Interactions of HIV/AIDS treatment with CVD risk factors and CVD outcomes were not assessed. This is despite the high prevalence of HIV/AIDS in South Africa and the emerging evidence that HIV and highly active antiretroviral therapy could affect CVD outcomes [65, 66]. A more complete single model that is capable of simultaneously dealing with all cardiovascular risk factors and HIV interactions is needed. However, current empirical data on HIV/CVD interactions to support the development of such a model are still scarce and based on small scale studies in high-income countries [67].

CONCLUSIONS

With cardiovascular disease, particularly stroke and its risk factors on the increase in rural South Africa, investing in primary prevention could assist the government to reduce more expensive acute and secondary prevention measures that could be incurred in the longer term. Medical preventive cardiology could be cost-effective in rural South Africa especially when targeted at high risk individuals. However, incremental cost-effectiveness ratios should be interpreted in the context of other local policy and programme options, including funding sources, impact on equity and feasibility. Notwithstanding the limitations, mathematical models customised to a specific population that can be easily re-calibrated can generate much-needed piece of evidence on cost-effectiveness that could be used to inform resource allocation (along other factors). As more up-to-date data on intervention effects (including lifestyle interventions) becomes available, evidence on cost-effectiveness of primary prevention approaches to CVD can be re-examined. There is an urgent need for a new framework for articulating cost–effectiveness in global health policy – specifically focusing on low- and middle-income countries that takes into account the budgetary restrictions in these settings.

Key Messages

What is already known on this topic?

- Cardiovascular disease (CVD), particularly stroke, is escalating in sub-Saharan Africa and rural South Africa is no exception.
- Cardiovascular disease imposes a high epidemiological and economic burden in developing countries.
- A range of effective individual and population-wide strategies are available to counteract CVD, that if implemented could bring considerable health gains.

Evidence Gaps

- Evidence on the cost effectiveness of pharmacotherapy to prevent CVD in resource-limited settings is mixed. Analyses using local data are needed to develop a context-specific policy framework for combating cardiovascular disease.

What this study might add

- Within a rural South African population in which stroke burden and associated risk factors are unacceptably high, pharmacotherapy targeted at individuals with an absolute risk of developing CVD over the next 10 years of ≥20% is potentially a highly cost-effective intervention.
- A lifetime population model customised to a rural South African population could be adapted to undertake much broader analyses related to CVD prevention in this population.

Policy Implications

- The findings from this study are not prescriptive. However, they indicate that primary prevention using pharmacotherapy should not be excluded as an option to prevent strokes in predominantly rural communities of South Africa. The cascade of care, should however work right through to encouraging personal adherence to medication. Moreover, the findings do not preclude lifestyle interventions as critical for prevention of CVD as these are necessary for keeping the number of individuals who are at risk of CVD at a minimum.

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Table 3: Total annual cost, annual health benefits and cost-effectiveness ratio of selected pharmacotherapies for prevention of stroke in Agincourt sub-district, rural South Africa, 2012

Intervention	Life years saved	Years lived with disability averted	DALYs averted	Net costs (US$; 2012)	ACER	ICER
High absolute CVD risk (≥20%)						
Thiazide diuretics	53.8	34.5	88.3	15,500	176	Dominated
Aspirin + Diuretic	51.7	33.1	84.8	14,700	173	Dominated
B-Blocker+ Diuretic	58.1	37.3	95.4	14,900	157	$ 156
B-Blocker+ Diuretic+Statin	60.3	38.6	98.9	16,800	170	Dominated
β-blockers	45.6	29.3	74.9	17,400	232	Dominated
PolyPill	68.3	43.8	112	21,100	189	$ 373
Calcium channel blockers (CCBs)	52.3	33.5	85.8	21,100	246	Dominated
Aspirin + B-Blocker	42.7	27.4	70.1	17,600	251	Dominated
Daily Aspirin	35.5	22.8	58.2	20,500	352	Dominated
ACEi / ARB	47.6	30.5	78.1	21,100	271	Dominated
ACE-I + Thiazide Diuretic	59.3	38	97.3	19,100	196	Dominated
Current Practice	40.2	25.8	65.9	26,800	406	Dominated
40mg/day statin (simvastatin)	43.3	27.8	71	28,200	397	Dominated
Medium absolute CVD risk (10-19%)						
Thiazide diuretics	67.5	33.6	101	19,700	195	Dominated
Aspirin + Diuretic	64.8	32.3	97.1	18,600	202	Dominated
B-Blocker+ Diuretic	72.9	36.3	109	18,900	205	$ 173
B-Blocker+ Diuretic+Statin	75.6	37.6	113	21,300	230	Dominated
β-blockers	57.3	28.5	85.7	22,100	248	Dominated
PolyPill	85.6	42.6	128	26,800	266	$ 416
Calcium channel blockers (CCBs)	65.6	32.6	98.2	26,800	273	Dominated
Aspirin + B-Blocker	53.6	26.7	80.2	22,300	275	Dominated
Daily Aspirin	44.5	22.2	66.7	26,000	279	Dominated
ACEi / ARB	59.7	29.7	89.4	26,900	300	Dominated

Intervention	Life years saved	Years lived with disability averted	DALYs averted	Net costs (US$; 2012)	ACER	ICER
Current Practice	50.4	25.1	75.5	24,100	320	Dominated
ACE-I + Thiazide Diuretic	74.4	37	111	34,000	321	Dominated
40mg/day statin (simvastatin)	54.3	27	81.3	35,600	331	Dominated
Low absolute CVD risk (<10%)						
Thiazide diuretics	133	29	162	36,900	228	$ 228
Aspirin + Diuretic	128	27.8	155	38,200	246	Dominated
B-Blocker+ Diuretic	144	31.3	175	42,800	244	$ 454
B-Blocker+ Diuretic+Statin	149	32.4	181	49,100	271	Dominated
β-blockers	113	24.6	137	41,400	302	Dominated
PolyPill	169	36.8	205	63,300	309	$ 683
Calcium channel blockers (CCBs)	129	28.1	157	50,700	323	Dominated
Aspirin + B-Blocker	106	23	128	42,500	332	Dominated
Daily Aspirin	87.7	19.1	107	36,800	344	Dominated
ACEi / ARB	118	25.6	143	50,700	354	Dominated
ACE-I + Thiazide Diuretic	146	31.9	178	66,200	372	$ 2,752
Current Practice	99.2	21.6	121	46,300	383	Dominated
40mg/day statin (simvastatin)	107	23.3	130	50,900	392	Dominated
Stage 2 Hypertension (BP>160/90mmHg)						
B-Blocker+ Diuretic	45	31	76.3	20,900	274	$ 274
Thiazide diuretics	42	29	70.6	19,800	280	Dominated
B-Blocker+ Diuretic+Statin	47	32	79	27,100	343	Dominated
Aspirin + Diuretic	40	28	67.8	23,300	344	Dominated
PolyPill	53	36	89.7	35,400	395	$ 1,082
β-blockers	36	24	59.9	23,700	395	Dominated
Calcium channel blockers (CCBs)	41	28	68.6	27,200	397	Dominated
Aspirin + B-Blocker	33	23	56	22,900	408	Dominated
Daily Aspirin	28	19	46.6	19,400	417	Dominated

Intervention	Life years saved	Years lived with disability averted	DALYs averted	Net costs (US$; 2012)	ACER	ICER
ACEi / ARB	37	25	62.4	27,200	437	Dominated
Current Practice	31	21	52.8	25,200	477	Dominated
ACE-I + Thiazide Diuretic	46	32	77.8	37,100	477	Dominated
40mg/day statin (simvastatin)	37	21	58.1	27,900	481	Dominated

Values are rounded to 3 significant figures
DALYs – Disability adjusted life years are the sum of years lived with disability and years of life lost due to premature mortality
Net Costs – Intervention costs less projected savings from reduced treatment costs.
ACER - average cost-effectiveness ratio are median values and represent the cost-effectiveness of intervention against the alternative of doing nothing. ICER – incremental cost-effectiveness ratio is the ratio of the incremental costs and incremental effects of moving from one intervention to the next more effective intervention starting from the most cost-effective intervention.
ICER – where ratio is dominated, the intervention costs more and is less effective than an alternative strategy

Table 4: Average cost-effectiveness ratios for stroke prevention interventions under multiple scenarios

Intervention description	Base Case	Undiscounted health benefits	Double Cost [a]	Lower effect* [b]	50% effect [c]
Diu (<10% risk)	228	132.6	396.2	237.7	320.2
B-Blocker +Diu (<10% risk)	244	141.9	424	254.4	342.6
B-Blocker +Diu (10-19% risk)	205	119.8	330.1	213	287.5
B-Blocker +Diu (>20% risk)	157	91.39	241.4	161.7	220.3
B-Blocker +Diu (stage 2 hypertension)	274	159.3	476.1	287.6	386.7
Polypill (<10% risk)	309	179.7	536.9	322.1	433.9
Polypill (10-19% risk)	266	155.5	428.4	276.4	373.1
Polypill (>20% risk)	189	110	290.6	194.6	265.2
Polypill (stage 2 hypertension)	395	229.7	686.3	414.6	557.5
ACE-I + Diu (<10% Risk)	477	277.4	828.8	497.3	669.8

*Change in cost-effectiveness ratio of less than 10%
[a] Double unit costs for drugs and primary health care visits
[b] Lower boundary of effectiveness estimate as derived from meta-analyses of randomised controlled trials
[b] 50% of point estimate of effectiveness

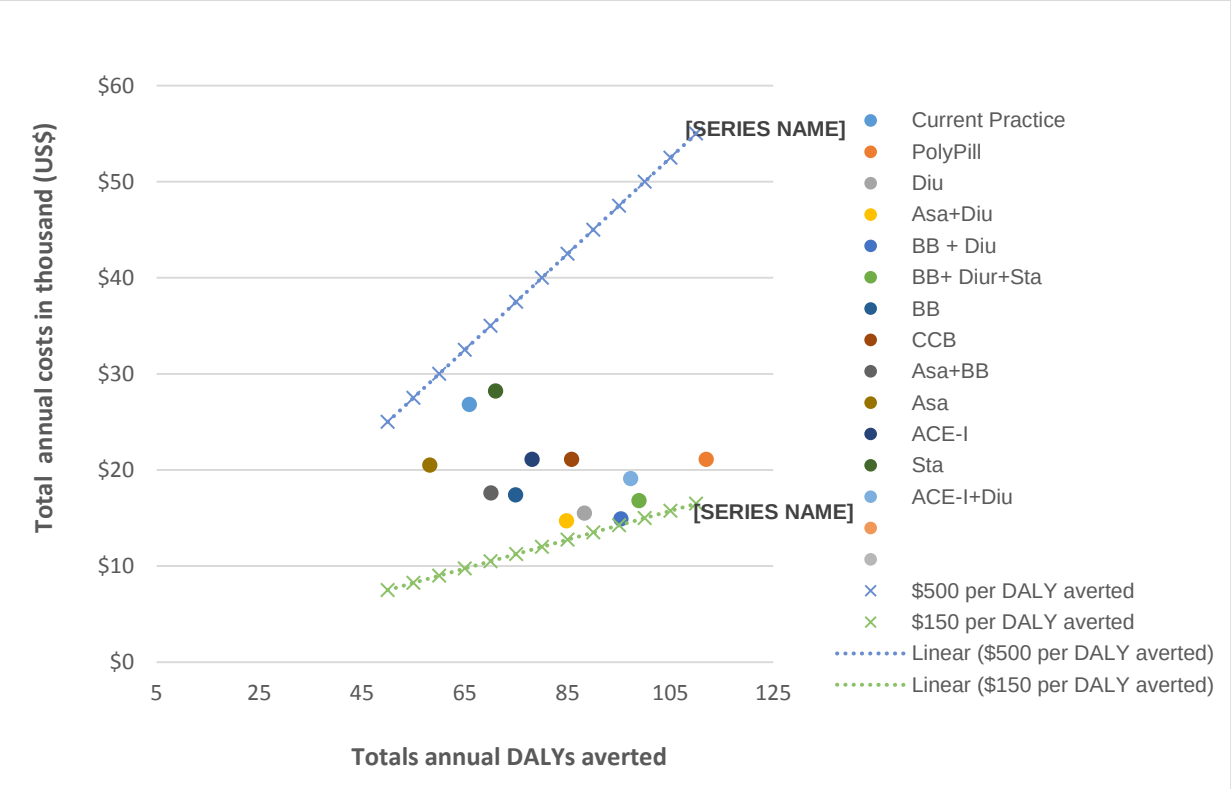

Figure 2: Cost effectiveness of alternative pharmacotherapies for cardiovascular disease prevention in Agincourt sub-district, 2012 targeted at individuals with ≥20% absolute risk of developing CVD within the next 10 years.

*The diagonal bands indicate alternative willingness to pay thresholds. All interventions lie below the '$500 per DALY averted' line indicating that all interventions produce health gains

at a cost of less than US$500 per DALY averted. Asa = aspirin; Diu = Diuretic; BB = B-blocker, ACE-I = ACE-inhibitor; CCB = calcium channel blocker; Sta = statin

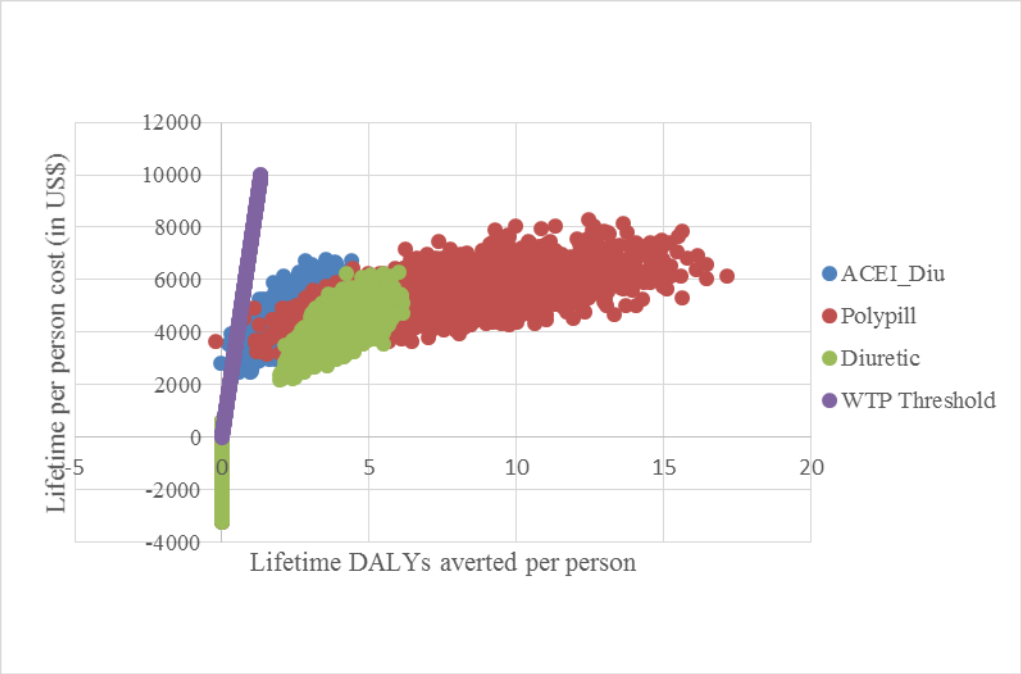

Figure 3: Probabilistic sensitivity analysis of non-dominated CVD interventions for the low-risk group in rural South Africa

Appendix E: Literature review search strategy

Table E 1: Sample literature search strategy in PubMed for cardiovascular disease studies on prevalence, incidence, mortality costs, cost-effectiveness in developing countries/ low and middle-income countries

#1	"Cardiovascular disease" OR "Coronary heart disease" OR "ischaemic heart disease" OR "coronary disease" OR "acute coronary syndrome" OR "heart attack" OR "heart disease" OR "atherosclerosis" OR "myocardial infarction" OR "myocardial ischaemia" OR "stroke" OR "cerebrovascular disease" OR "cerebrovascular accident" OR CVA OR "cardiovascular event"
#2	"prevalence" OR "cases"
#3	"mortality" OR "deaths" OR "survival" OR fatal*
#4	"incidence" OR "cases" OR "new cases"
#5	"Afghanistan" OR "Albania" OR "Algeria" OR "American Samoa" OR "Angola" OR "Armenia" OR "Azerbaijan" OR "Bangladesh" OR "Belarus" OR "Belize" OR "Benin" OR" "Bhutan" OR "Bolivia" OR "Bosnia and Herzegovina" OR "Botswana" OR "Brazil" OR "Bulgaria" OR "Burkina Faso" OR "Burundi" OR "Cabo Verde" OR "Cambodia" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "China" OR "Colombia" OR "Comoros" OR "Democratic Republic of Congo" OR "Congo" OR "Costa Rica" OR "Cote d'Ivoire" OR "Ivory Coast" OR "Cuba" OR "Djibouti" OR "Dominica" OR "Dominican Republic" OR "Ecuador" OR "Egypt" OR "El Savador" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Fiji" OR "Gabon" OR "The Gambia" OR "Georgia" OR "Ghana" OR "Grenada" OR "Guatamela" OR "Guinea" OR "Guinea Bissau" OR "Guyana" OR Haiti" OR "Honduras" OR "India" OR "Indonesia" OR "Iran" OR "Iraq" OR "Jamaica" OR "Jordan" OR "Kazakhastan" OR "Kenya" OR "Kiribati" OR "Democratic People's Republic of Korea" OR "Kosovo" OR "Kyrgyz Republic" OR "Lao DPR" OR "Lebanon" OR "Lesotho" OR "Liberia" OR "Libya" OR" Macedonia" OR "Madagascar" OR "Malawi" OR "Malaysia" OR "Maldives" OR "Mali" OR "Marshall Islands" OR "Mauritania" OR "Mauritius" OR "Mexico" OR "Micronesia" OR "Moldova" OR "Mongolia" OR "Morocco" OR "Mozambique" OR "Myanmar" OR "Namibia" OR "Nepal" OR "Nicaragua" OR "Niger" OR "Nigeria" OR "Pakistan" OR "Palau" OR "Panama" OR "Papua New Guinea" OR "Paraguay" OR "Peru" OR "Philippines" OR "Romania" OR "Russian Federation" OR "Rwanda" OR "Samoa" OR "Sao Tome and Principe" OR "Senegal" OR "Serbia" OR "Sierra "Russian Federation" OR "Rwanda" OR "Samoa" OR "Sao Tome and Principe" OR "Senegal" OR "Serbia" OR "Sierra Leonne" OR "Solomon Islands" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sri Lanka" OR "St Lucia" OR "St Vincent and the Grenadines" OR "Sudan" OR "Suriname" OR "Swaziland" OR "Syrian Arab Republic" OR "Tajikistan" OR "Tanzania" OR "Thailand" OR "Timor-Leste" OR "Togo" OR "Tonga" OR "Tunisia" OR "Turkey" OR "Turkmenistan" OR "Tuvalu" OR "Uganda" OR "Ukraine" OR "Uzbekistan" OR "Vanuatu" OR "Vietnam" OR "West Bank of Gaza" OR "Yemen" OR "Zambia" OR "Zimbabwe" OR Africa OR "sub-Saharan Africa" OR "low and middle income countr*" OR "low income countr*" OR Low OR middle income countr* OR "developing country" OR" "underdeveloped country" OR "resource limited"
#6	"legislation" OR "prevention" OR "control" OR "primary prevention" OR "secondary prevention" OR "cardiovascular risk" OR "risk factor" OR "lifestyle" OR "behaviour" OR "diet" OR "food" OR "hypertension" OR "blood pressure" OR "smoking" OR "tobacco" OR "alcohol" OR "alcohol consumption" OR "physical activity" OR exercise OR salt OR "salt reduction" OR "lipid lowering" OR "cholesterol" OR "fat" OR "intervention" OR "strategies" OR "modification" OR

	improve OR “address*” OR tax OR “taxation” OR “advertising” OR “counselling” OR “diet advice” OR “health education” OR “patient education” OR “media”
#7	“costs and cost analysis” OR “cost allocation” OR “Cost–benefit analysis” OR “Cost of illness” OR “Health care costs” OR “hospital costs” OR “cost-effectiveness” OR “cost-effective” OR “cost-utility” OR “economic evaluation”
#8	#1 AND #2 AND #5
#9	#1 AND #3 AND #5
#10	#1 AND #5 AND #6
#11	#1 AND #5 AND #7

Appendix F: Agincourt data request form

MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt),
School of Public Health,
University of Witwatersrand,
Johannesburg, South Africa

Data Request Form

Project Name:

_____

Author(s):

_____

Purpose (Brief description of the purpose of the study):

_____

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Analytical Plan:

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Data requirements:

_____

Population (study):

_____

Period:

_____

_____

Unit of analysis:

_____

File Structure:

Variables:

Table	Variable	Comments

NB: List the variables that you will be using for your analysis even if they seem not to exist in the list provided in the data dictionary. We shall suggest the proximate ones you that you can use. The data dictionary or code is a useful tool for this

File Format:

Additional Information:

(Provide relevant information that the above fields might have left out that may ease the data extraction process)

Appendix G: Data extraction form for collecting effectiveness estimates

Instructions for filling out the form

1. *Please complete for each study*
2. *Please note you can tick more than one box. E.g. if location is South Africa and in rural area tick both boxes.*
3. *Where a number or text is required – fill in as appropriate.*

Variable	Type of data collected	Response
Reference	First author / Year / Journal citation	
Study type		
	Single-centre randomized controlled trials	☐
	Multi-centre randomized controlled trials	☐
	Meta-analysis	☐
	Prospective community-based study	☐
	Hospital-based registries	☐
	Retrospective community/hospital-based study	☐
	Cross-sectional study	☐
	Other	☐
Location		
	Low and middle-income	☐
	Sub-Saharan Africa	☐
	South Africa	☒
	Rural	☒
	Urban	
Sample Size	Intervention population sample (#)	
	Control population sample (#)	
Population focus	General population	☐
	Specific Population (provide details below)	☒
Interventions assessed:	Intervention A	
	Intervention B	
	Intervention C	
	Intervention D	

Variable	Type of data collected	Response
	Intervention E	
	Intervention F	
	Intervention G	
	Intervention H	
Add lines for other interventions		
Outcomes assessed:		
	1. Mortality	
	2. Systolic blood pressure	
	3. Relative risk of stroke	
	4. Relative risk of IHD	
	5. Other	
Condition targeted (e.g. IHD, stroke)		
	Stroke	
	IHD	
	Other	
Effectiveness estimate:		
	1. Relative Risk	
	2. SBP lowering	
	3. BMI lowering	
	4. Hazard ratio	
	5. Other	
Quality score: **Adjustment for confounding variables?**		
	Yes	☐
	No	☐
Duration of study (in months)		
Notes (and additional bibliography):		

Appendix H: Supplement to Published Paper 1

Disease burden of stroke in rural South Africa: an estimate of incidence, mortality and disability adjusted life years

Supplementary Appendix

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A. Population figures for Agincourt HDSS and 70 ‘mostly rural’ municipalities

Table 1: Total number of deaths and population in Agincourt 2007-2011

	Person-years (over 5 yrs)		**Deaths from any cause**		**Mortality rate**		**Population numbers**		**Deaths due to stroke**	
	Males	**Females**	**Males**	**Females**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
0	2 767	2 751	68	44	0.025	0.016	553	550	0	0
1-4	15 624	15 723	137	104	0.009	0.007	3125	3145	0	0
5-9	18 649	18 840	52	39	0.003	0.002	3730	3768	0	0
10-14	19 021	19 370	72	42	0.004	0.002	3804	3874	0	0
15-19	20 445	20 591	41	95	0.002	0.005	4089	4118	0	2
20-24	20 569	20 301	134	176	0.007	0.009	4114	4060	1	1
25-29	16 417	16 736	276	454	0.017	0.027	3283	3347	1	9
30-34	12 824	13 144	432	446	0.034	0.034	2565	2629	1	2
35-39	9 440	10 479	346	340	0.037	0.032	1888	2096	7	4
40-44	7 509	9 010	492	275	0.066	0.031	1502	1802	6	12
45-49	5 770	7 332	308	252	0.053	0.034	1154	1466	0	10
50-54	4 329	5 724	309	233	0.071	0.041	866	1145	13	18
55-59	3 626	4 548	238	201	0.066	0.044	725	910	13	14
60-64	2 526	3 365	231	205	0.091	0.061	505	673	6	12
65-69	1 751	2 984	235	204	0.134	0.068	350	597	19	25
70-74	1 637	2 593	200	205	0.122	0.079	327	519	14	30
75-79	795	2 325	151	213	0.190	0.092	159	465	9	32
80-84	713	2 189	174	295	0.244	0.135	143	438	7	58
85-89	725	1 573	221	281	0.305	0.179	145	315	20	48
Total	165 137	179 578	4 117	4 104	0.025	0.023	33 027	35 916	117	277

Table 2: Total population figures by age and sex in 70 “mostly rural” municipalities of South Africa (Statistics South Africa, 2011)

Age Group	**Male**	**Female**	**Total**
0 - 4	861 642	850 647	1 712 289
5 - 9	781 287	771 497	1 552 784
10 - 14	788 169	743 658	1 531 827
15 - 19	814 390	792 860	1 607 250
20 - 24	593 558	630 462	1 224 020
25 - 29	424 774	515 353	940 127
30 - 34	312 116	401 640	713 756
35 - 39	262 005	360 947	622 952
40 - 44	215 597	323 176	538 773
45 - 49	199 145	316 641	515 786
50 - 54	176 989	274 667	451 656
55 - 59	156 852	233 453	390 305
60 - 64	134 876	200 053	334 929
65 - 69	92 362	153 551	245 913
70 - 74	77 401	138 986	216 387
75 - 79	41 936	104 697	146 633
80 - 84	29 739	83 493	113 232
85+	23 306	66 402	89 708
Total	5 986 137	6 962 183	12 948 320

Table 3: Classification of municipalities in South Africa (National Treasury, 2011)

Class	Characteristics	Municipalities country-wide (N)
Metros	Category A municipalities	6
Secondary Cities	All local municipalities referred to as secondary cities	21
Large Towns	All local municipalities with an urban core. There is huge variation in population sizes amongst these municipalities and they do have large urban dwelling population.	29
Small Towns	They are characterised by no large town as a core urban settlement. Typically, these municipalities have a relatively small population, a significant proportion of which is urban and based in one or more small towns. Rural areas in this category are characterised by the presence of commercial farms, as these local economies are largely agriculturally based. The existence of such important rural areas and agriculture sector explains their inclusion in the analysis of rural municipalities.	111
Mostly Rural	These are characterised by the presence of at most one or two small towns in their areas, communal land tenure and villages or scattered groups of dwellings and typically located in former homelands	70
Districts	District municipalities that are not water services providers.	25
Districts	District municipalities that are water service providers	21

B. Computation of DALYs

DALYs were calculated by predominantly applying the methodological principles employed in the Global Burden of Disease Studies. DALYs are the sum of years of life lost due to premature mortality (YLL) plus years of life lost due to time lived in states of less than optimal health, loosely referred to as "disability" (YLD) (equation 1)[36]. YLL due to stroke among all persons that die of stroke is the sum of years that victims would have lived if they had completed the life expectancy attributed to their age (as assessed by a standard population) at the time of their death. YLLs measure the fatal burden of disease. The YLD figure expresses the consequences of living with less than perfect health conditions. It is an estimate based on the length of time that a condition persisted along with any accompanying disability and thus is an indicator of the non-fatal burden of disease. One DALY can be thought of as one lost year of 'healthy' life whilst the measured disease burden is the gap between a population's health status and that of a normative reference population [37].

Thus,

$$DALY_i = YLL_i + YLD_i$$

Estimating fatal burden of disease

The basic formula for calculating YLL for a particular cause, age or sex is

[36] Mathers CD, Vos T, Lopez A, Salomon J, Ezzati M. National burden of disease studies: a practical guide. 2001.

[37] World Health Organization. WHO methods and data sources for global burden of disease estimates 2000-2011. 2013 Global Health Estimates Technical Paper WHO/HIS/HSI/GHE/2013.4 Contract No.: GHE/2013.4. 253.

YLL = N × L,

where N is the number of deaths and L is the standard life expectancy (in years) at the age of death. The standard reference life-table is intended to represent the potential maximum life span of an individual in good health at a given age. We chose the reference life tables used in GBD 1990 study which was based on the highest life expectancy at the time, Japanese females with a life expectancy at birth of 82.5 years, to ensure comparability with previous burden of disease studies. However, YLLs based on the GBD 2010 study reference life table were also calculated to allow comparison with the GBD 2010 study. The life table for GBD 2010 study was based on the lowest observed death rate for each age group in countries with populations of more than 5 million, and the new life expectancy at birth was set at 86 years.

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Estimating non-fatal burden of disease

The basic formula for calculating YLD for a particular disability event is

YLD = I × DW × L,

where:

I is the number of incident cases in period; DW is the disability weight and reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead); L is the average duration of disease (in years).

The recent GBD 2010 study based the YLD calculation on prevalence rather than incidence:

$$YLD = P\ x\ DW$$

where:

P = number of prevalent cases

DW = disability weight

To ensure consistency with the YLL calculation, which takes an inherently incidence perspective, and for comparison with earlier GBD studies, we compute incidence YLDs. Prevalence-based YLDs were calculated mainly for comparison with the GBD 2010 study.. To be consistent with GBD 2010, we did not discount or apply age weighting in computing prevalence- based DALYs but apply discounting when YLDs are calculated using incidence.. The latter allows comparison with earlier studies that discounted DALYs. Comparative analysis of the incident and prevalence YLDs is warranted as the two are not directly comparable. The incidence approach does not reflect the current prevalent burden of disabling sequelae for a condition for which incidence might have been substantially reduced. Secondly, in an incidence perspective, all YLDs for a condition are assigned to the age-groups at which the condition is incident, whereas in many cases for health policy-making, the ages at which the loss of health is experienced are of most interest

C. Computation of YLLs due to stroke

Table 4: YLLs due to stroke calculated based on reference population

	Standard population					Derived life expectancy at Agincourt (undiscounted)		Discounted life expectancy			YLL Undiscounted		YLL discounted	
Age	Males	Females		Age group	Age at death In Agincourt	Males	Females	Males	Females		Males	Females	Males	Females
A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
0	80.00	82.50		0	0.05	79.97	82.47	30.31	30.53		0.00	0.00	0.00	0.00
1	79.36	81.84		1-4	1.65	78.72	81.21	30.19	30.42		0.00	0.00	0.00	0.00
2	78.36	80.87	5.00	5-9	7.50	72.89	75.47	29.59	29.87		0.00	0.00	0.00	0.00
3	77.37	79.90	10.00	10-14	12.50	67.91	70.51	28.99	29.31		0.00	0.00	0.00	0.00
4	76.38	78.92	15.00	15-19	17.50	62.93	65.55	28.29	28.67		0.00	131.10	0.00	57.34
5	75.38	77.95	20.00	20-24	22.50	57.95	60.63	27.47	27.93		57.95	60.63	27.47	27.93
6	74.39	76.96	25.00	25-29	27.50	52.99	55.72	26.53	27.07		52.99	501.48	26.53	243.62
7	73.39	75.97	30.00	30-34	32.50	48.04	50.83	25.44	26.08		48.04	101.65	25.44	52.15
8	72.39	74.97	35.00	35-39	37.50	43.10	45.96	24.19	24.94		301.72	183.82	169.30	99.74
9	71.40	73.98	40.00	40-44	42.50	38.20	41.13	22.74	23.63		229.22	493.50	136.43	283.52

Table 5: Calculations for YLLs as they relate to table above

	Standard population					Derived life expectancy at Agincourt (undiscounted)		Discounted life expectancy			YLL Undiscounted		YLL discounted	
Age	Males	Females		Age group	Average at death in Agincourt	Males	Females	Males	Females		Males	Females	Males	Females
A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
0	80	82.5		0	0.045	=B8+F8*(B9-B8)	=C8+F8*(C9-C8)	=(1-EXP(-discount rate*G8))/ discount rate	=(1-EXP(-discount rate*H8))/discount rate		=G8*# of stroke deaths at this age	=H8*# of stroke deaths at this age	=I8*# of stroke deaths at this age	=J8**# of stroke deaths at this age
1	79.358	81.84		1-4	1.645	=B10+($F9-$A10)*(B11-B10)	=C10+($F9-$A10)*(C11-C10)	=(1-EXP(-discount rate *G9))/ discount rate	=(1-EXP(-discount rate*H9))/discount rate		=G9*# of stroke deaths at this age	=H9*# of stroke deaths at this age	=I9*# stroke deaths at this age	=J9*# stroke deaths this age

Table 6: Age and sex specific cause death rate at 28days post-stroke (Walker et al 2011)

	Cases identified by TSIP		Cases identified by VA	
	Males	Females	Males	Females
Age*	No of deaths/total cases (%)	No of deaths (%)	No of deaths (%)	No of deaths (%)
0–44 years	0/3 (0%)	1/6 (16.7%)	2/4 (50.0%)	3/13 (23.1%)
45–54 years	2/6 (33.3%)	0/5 (0%)	2/8 (25.5%)	4/11 (36.4%)
55–64 years	4/10 (40.0%)	3/11 (27.3%)	2/14 (14.3%)	2/11 (18.2%)
65–74 years	3/22 (13.6%)	5/18 (27.8%)	5/35 (14.3%)	8/24 (33.3%)
75–84 years	5/21 (23.8%)	3/8 (37.5%)	15/42 (35.7%)	9/32 (28.1%)
≥85 years	1/7 (14.3%)	4/13 (30.8%)	5/11 (45.5%)	7/18 (38.9%)
Overall	15/69 (21.7%)	16/61 (26.2%)	31/114 (27.2%)	33/109 (30.3%)
Mean age (years) at stroke of those dead	70.5 (95% CI 65.8 to 75.2)		71.3 (95% CI 67.0 to 75.6)	
Mean age (years) at stroke of those alive	68.2 (95% CI 65.1 to 71.2)		69.7 (95% CI 67.5 to 72.0)	

- * Ages given are at time of stroke.

Table 7: Age and sex-specific cause death rates at 3years post stroke (Walker et al 2011)

	Cases identified by TSIP		Cases identified by VA	
	Males	Females	Males	Females
Age	No of deaths/total cases (%)	No of deaths (%)	No of deaths (%)	No of deaths (%)
0–44 years	1/3 (33.3%)	2/6 (33.3%)	4/4 (100.0%)	8/13 (61.5%)
45–54 years	4/6 (66.7%)	2/5 (40.0%)	6/8 (75.5%)	7/11 (63.6%)
55–64 years	5/10 (50.0%)	6/11 (54.5%)	11/14 (78.6%)	8/11 (72.7%)
65–74 years	10/22 (45.5%)	12/18 (66.7%)	29/35 (82.9%)	20/24 (83.3%)
75–84 years	16/21 (76.2%)	5/8 (62.5%)	40/42 (95.2%)	30/32 (93.8%)
≥85 years	6/7 (85.7%)	9/13 (69.2%)	9/11 (81.8%)	16/18 (88.9%)
Overall	42/69 (60.9%)	36/61 (26.2%)	99/114 (86.8%)	89/109 (81.7%)
Mean age (years) at stroke of those dead	71.2 (95% CI 68.0 to 74.3)		71.6 (95% CI 69.5 to 73.7)	
Mean age (years) at stroke of those alive	65.0 (95% CI 60.7 to 69.4)		62.5 (95% CI 57.1 to 67.9)	

Table 8: Sensitivity analysis of changes in DALYs due to change in case fatality and disability weight input parameters

			Incidence-based DALY		**Prevalence-based DALY**
Parameter	**Value**	**Source**	**Incidence/100,000**	**DALY/100,000**	**DALY/100,000**
28-day CFR	0.238	Walker et al 2011	244	1552	N/A
	0.33		277*	1571.4	N/A
Disability weight	0.18	Calculated in this study	244	1552	2156
	0.25	Bertram et al	244	1605	2196
Combined DW + CFR	0.238; 0.18		244	1552	2156
	0.33; 0.25		277	1631	2196

*There is than a 10% difference in incidence when 28day CFR is changed from 0.238 to 0.33. However, changes in CFR or DW do not significantly affect DALY results.

Table 9: Dismod output for males in rural South Africa

DisMod II input and output, database Example											
Males, Disease: Stroke (Rates * 100,000), sex: Males											
Written 2015/01/22, 12:00:02 PM											
Age	Prevalence (rates * 100000)	Remission (rates * 100000)	Case fatality (rates * 100000)	Incidence (rates * 100000)	Prevalence (rates * 100000)	Remission (rates * 100000)	Case fatality (rates * 100000)	Duration (years)	Mortality (rates * 100000)	RR mortality (number)	Age of onset (years)
0-4	0	0	33333.33	0	0	0	33333.33	0	0	0	2.3888
5-9	0	0	33333.33	0	0	0	33333.33	0	0	97.9448	8.5115
15-29	200.2512	0	33333.33	70.0654	118.7767	0.4684	32216.16	2.8943	38.5412	23.714	26.3361
30-44	714.6205	0	33333.33	253.6468	707.3427	0.6142	33145.36	2.6683	234.6233	9.2776	37.121
45-59	2469	0	25555.56	588.8698	1986.206	0.6142	23832.01	3.5375	474.3607	5.2936	51.3497
60-69	2619.795	0	20909.09	492.0761	2598.319	0.6142	17488.74	2.8047	454.5316	2.6782	65.6919
70-79	2840	0	42099.57	1067.789	2853.771	0.6142	37390.71	1.7955	1067.03	3.5411	74.5778
80+	2840	0	65476.19	1716.161	2839.655	0.6142	60420.15	1.1446	1715.69	3.3258	87.1851
All ages	556.6484	NA	NA	162.5183	487.2139	0.6033	28430.3	2.7373	138.7172	6.9397	53.1563

Incidence, and duration of disability calculated in Dismod are used for YLD calculations. However, incidence calculated in Dismod reflects those who survive the high mortality period (28days post stroke). To show incidence of all cases (those who die within 28days plus those who survive past 28days), we use equation 1 to make an adjustment. As such the figures shown in this table, will differ from what is indicated in table 4 (main manuscript)

Equation 1:

$$Incidence\ of\ stroke\ amongst\ those\ who\ survive\ the\ first\ 28days\ (calculated\ in\ Dismod) = All\ incident\ cases * (1 - 28\ day\ case\ fatality\ rate)$$

Table 10: Dismod output for all females, rural South Africa (2011)

DisMod II input and output, database Example											
Females, Disease: Stroke (Rates * 100,000), sex: Females											
Written 2015/01/22, 11:58:53 AM											
Age	Prevalence (rates * 100000)	Remission (rates * 100000)	Case fatality (rates * 100000)	Incidence (rates * 100000)	Prevalence (rates * 100000)	Remission (rates * 100000)	Case fatality (rates * 100000)	Duration (years)	Mortality (rates * 100000)	RR mortality (number)	Age of onset (years)
0-4	0	0	16666.67	0	0	0	0	0	0	0	2.5
5-9	0	0	16666.67	9.6158	16.5658	0.3574	16495.77	5.7878	2.7483	74.2581	12.7161
15-29	378.3188	0	16666.67	92.651	303.9778	0.6106	16664.85	5.1995	50.7549	15.3184	24.015
30-44	1052.262	0	16666.67	211.8057	1000.436	0.6142	17547.49	4.3222	175.6392	6.4945	37.9858
45-59	1549.475	0	35757.58	526.5974	1499.517	0.6142	30779.99	2.8313	462.1387	8.7696	53.4427
60-69	2721.188	0	33080.81	918.1675	2641.668	0.6142	31819.04	2.5635	841.2487	5.9659	65.1759
70-79	3210	0	31944.44	1021.857	3230.551	0.6142	31294.86	2.5985	1011.129	4.8251	74.2858
80+	3210	0	34254.81	1005.893	3208.253	0.6142	31275.37	2.0428	1003.4	3.0002	87.9055
All ages	772.6741	NA	NA	227.3615	738.2209	0.6125	26609.21	3.1772	196.5887	7.1692	56.5695

Table 11: Results of uncertainty analysis for incidence

DisMod II input and output, database Example											
Uncertainty results, Stroke Incidence (Rates * 100,000), sex: Males											
Written 2015/01/25, 01:25:46 PM											
Age	Central value (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)
0-4	0	0	0	0	0	0	0	0	0	Lower 95%	Upper 95%
5-14	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005
15-29	82.7721	80.9025	84.65	80.3099	85.7169	79.6331	86.0738	78.9537	86.5566	77.6854	87.1297
30-44	362.7304	343.9262	381.7513	339.3563	386.4783	334.7465	393.5493	326.0037	400.8414	314.8333	402.0014
45-59	996.259	952.2208	1044.394	942.7682	1054.61	931.4384	1067.277	917.761	1082.992	895.63	1088.152
60-69	992.9667	942.0334	1049.509	930.5803	1065.351	920.2192	1076.063	899.0685	1084.685	874.0841	1088.748
70-79	854.7003	813.8763	899.4919	803.0066	915.6193	791.7156	935.7374	776.2358	935.7374	749.7328	937.5481
80+	815.4258	755.0467	879.5458	744.0346	895.2449	728.3506	907.0968	713.4334	924.0331	680.9618	934.5198
All ages	222.3856	212.2388	233.151	209.8706	236.0078	207.2913	239.1363	203.4364	242.2961	197.8219	243.3567

Table 12: Uncertainty analysis around incidence rates in Agincourt sub-district

DisMod II input and output, database Example											
Uncertainty results, Stroke Incidence (Rates * 100,000), sex: Females											
Written 2015/01/25, 01:27:31 PM											
Age	Central value (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)	Lower (rates * 100000)	Upper (rates * 100000)
0-4	0	0	0	0	0	0	0	0	0	0	0
5-14	8.334	8.1473	8.5341	8.0858	8.5661	8.0235	8.6547	7.9241	8.6997	7.8535	8.7391
15-29	218.1548	209.1043	227.7929	207.3535	231.1318	204.9564	233.5182	200.4196	237.8484	194.553	246.5341
30-44	716.5761	675.6113	762.1474	667.8358	774.0021	661.1696	781.5302	651.468	790.9189	630.158	794.3594
45-59	565.8346	540.713	593.5385	536.8873	601.7795	531.1185	606.0975	522.5315	620.5967	508.7643	628.3351
60-69	916.5916	870.3266	963.1494	860.5355	986.6467	848.1217	1008.164	835.4017	1023.493	814.3992	1024.339
70-79	936.0564	885.3828	1002.942	869.6958	1011.425	852.2927	1013.336	836.3574	1017.084	808.0737	1020.354
80+	933.6584	879.0555	996.8913	865.8952	1001.573	849.5166	1007.214	828.0996	1014.235	786.2658	1018.862
All ages	335.0924	318.0726	354.0293	314.6578	359.231	310.8394	362.7384	305.4223	368.0569	295.9081	372.4527

Appendix I: Ethics clearance certificate

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M131050

NAME: (Principal Investigator)	Ms Mandy Maredza
DEPARTMENT:	School of Public Health Medical School
PROJECT TITLE:	Preventing Cardiovascular Disease in Rural South Africa
DATE CONSIDERED:	25/10/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Melanie Bertram
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 25/10/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**

Principal Investigator Signature M131050Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES