# Non-communicable diseases in public sector primary care clinics in South Africa: multimorbidity, control, treatment, socioeconomic associations, and evaluation of educational outreach with a clinical management tool

Naomi Folb

MBChB, MRCGP (UK)



Thesis presented for the degree of Doctor of Philosophy in the Department of Medicine, Faculty of Health Sciences, University of Cape Town

March 2017

Supervisors: Associate Professor Lara Fairall and Professor Max Bachmann

# Abstract

This thesis uses experience gained from a large implementation trial in two rural districts of the Western Cape, South Africa, to address the needs of patients with non-communicable diseases (NCDs) and depression, and to identify solutions to those needs.

The Primary Care 101 intervention supports and expands nurses' role in integrated care, in particular for NCDs. It comprises a comprehensive clinical management tool implemented in primary care services using educational outreach training. It was evaluated using a pragmatic cluster randomised controlled trial: 38 clinics in the Eden and Overberg districts of the Western Cape were randomised to receive the intervention or to continue with usual care. 4393 Patients were enrolled and four cohorts identified: hypertension, diabetes, chronic respiratory disease and depression. Patients were re-interviewed once, 14 months later. Primary outcomes for the trial were treatment intensification for the hypertension, diabetes and chronic respiratory disease cohorts, and case detection for the depression cohort. Multimorbidity, NCD care and their socioeconomic associations were assessed on the whole trial cohort (combining intervention and control arms) at baseline and follow-up.

The results are presented in published papers. Baseline data revealed considerable multimorbidity and unmet treatment needs (Paper 1). Socioeconomic indicators such as education, and modifiable clinic-level factors such as adequate staffing and community-based chronic medication collection services were associated with blood pressure control (Paper 2) and depression management (Paper 3). The intervention was shown to be feasible and safe but none of the four primary outcomes showed significant improvement (Paper 4).

The thesis addresses the public health challenge of providing integrated chronic disease primary care in South Africa by:

- Providing original evidence for high levels of NCD multimorbidity and unmet treatment needs.
- Identifying modifiable factors that could improve care for these diseases.
- Providing new evidence from South Africa to support the bidirectional relationship between poverty and depression.
- Reporting evidence of the effectiveness of a novel intervention aimed at improving NCD care.

The findings point to the need for improved strategies for NCD care, including equipping primary health care providers to manage the complexities of multimorbidity.

# Thesis overview

## Background

Non-communicable diseases (NCDs) are the leading causes of death globally. The burden of NCDs in South Africa has been estimated to be two to three times higher than that in developed countries. This thesis uses experience gained from a large (38 clinics; 4393 patients) implementation trial in two rural districts of the Western Cape during 2011 -2013 to address the needs and potential solutions to the needs of patients with NCDs, including depression, attending primary care services. It examines multimorbidity, control and treatment of NCDs and depression; socioeconomic predictors of hypertension control and treatment; socioeconomic predictors of depression symptoms and treatment; and the effectiveness of educational outreach in the use of a clinical management tool (Primary Care 101) in improving NCD care.

## Methods

The thesis is based on experimental evidence from the randomised trial and observational evidence from the trial cohort. The Primary Care 101 (PC101) programme was evaluated using a pragmatic cluster randomised controlled trial (RCT). Thirty-eight clinics in the Eden and Overberg districts of the Western Cape were randomised to receive the PC101 programme, which provides an integrated platform for NCD management, or to continue with usual care for these diseases. 4393 Patients were enrolled between March 2011 and November 2011, and four cohorts of patients identified: hypertension, diabetes, chronic respiratory disease and depression. Patients were interviewed once more, 14 months after

enrolment. Primary outcomes for the RCT were treatment intensification for the hypertension, diabetes, and chronic respiratory disease cohorts, and case detection for the depression cohort.

Multimorbidity, control and treatment of NCDs; socioeconomic associations with hypertension control and treatment; and socioeconomic associations with depression symptoms and treatment were assessed on the whole trial cohort at baseline and follow-up, combining the intervention and control arms of the trial. Multiple regression models were used to avoid confounding and to estimate independent effects of socioeconomic factors and clinic characteristics.

## Findings

**The first paper describes the baseline data and demonstrates considerable multimorbidity and unmet treatment needs.** Among participants with hypertension, diabetes, respiratory disease and depression, 80%, 92%, 88% and 80% respectively, had at least one of the other three conditions. The data confirmed poor levels of disease control and unmet treatment needs. Fifty-nine percent of participants with hypertension had a blood pressure ≥140/90 mmHg. Among participants with diabetes, the mean haemoglobin A1c (HbA1c) value was 9%, 2% above target. Only 12% of participants with symptoms of depression had been prescribed an antidepressant at a therapeutic dose. Fewer than a half of participants with chronic respiratory disease (asthma or chronic obstructive pulmonary disease) had received a beta2-agonist and only 34% an inhaled corticosteroid. These findings of poor control and low treatment levels for NCDs are similar to those of previous studies in South Africa and

suggest little, if any, change in recent years. The high levels of multimorbidity indicate the need for primary health care services to provide better integrated NCD care.

**The second paper examines socioeconomic and modifiable predictors of blood pressure control and treatment intensification in patients with hypertension.** The study confirms both patient and clinic-related factors that are associated, first, with the likelihood of blood pressure control (patient factors), and second, with treatment intensification during the study period (patient and clinic-related factors). Blood pressure control at baseline was more likely in patients with more education (p=0.001) and in English compared with Afrikaans speaking participants (p=0.033). Treatment intensification was more likely in participants with higher blood pressure at baseline (P<0.001), concurrent diabetes (p=0.013), more education (p=0.020), and who attended clinics offering community-based chronic medication collection services (community-based medication supply) (p=0.009), with a doctor every day (p=0.004), or with more nurses (p<0.001). Health services need to be sensitive to the impact of socioeconomic factors, in particular, lower levels of education. The study points to clinic factors that may be addressed to improve the care of hypertensive patients. Besides attempting to improve staffing of clinics, this includes providing community-based medication supply.

**The third paper examines socioeconomic predictors and consequences of depression and its treatment.** Socioeconomic disadvantage was shown to be both a cause and consequence of depression, and may also be a barrier to treatment. Symptoms of depression (higher Center for Epidemiologic Studies Depression Scale (CESD-10) scores) at baseline were associated with less formal education (p=0.004) and lower personal income (p=0.003).

Higher CESD-10 scores at follow-up were associated with less education (p=0.010) or receipt of welfare grants (p=0.007). In addition, participants with CESD-10 scores of ≥10 at baseline had 25 % higher odds of being unemployed at follow-up (p=0.016). Prescription of antidepressant medication for participants with a CESD-10 score of ≥10 at baseline was significantly higher in participants with more education (p=0.002), higher income (p< 0.001), or who were unemployed (p=0.001). Antidepressant medication at follow up was more likely in participants with higher income (p=0.023), and in clinics with better access to pharmacists (p=0.053) and community-based medication supply (p=0.013). Primary care clinics should be adequately staffed and have pharmacists on site but also enable patients to collect their repeat medications at more convenient locations. Evidence in support of the bidirectional relationship between poverty and depression reinforces arguments for the expansion of mental health services and improving the prevention, detection and treatment of depression in primary health care settings, for clinical and economic reasons.

**The fourth paper presents the results of the RCT.** The PC101 intervention was shown to be feasible and safe but none of the four primary outcome measures, treatment intensification for hypertension, diabetes and chronic respiratory diseases, or case detection for depression, showed significant improvement (hypertension: 44% in the intervention group versus 40% in the control group, risk ratio [RR] 1.08 [95% CI 0.94 to 1.24; p = 0.252]; diabetes: 57% versus 50%, RR 1.10 [0.97 to 1.24; p = 0.126]; chronic respiratory disease: 14% versus 12%, RR 1.08 [0.75 to 1.55; p = 0.674]; depression: 18% versus 24%, RR 0.76 [0.53 to 1.10; p = 0.142]). PC101 offers a practical and acceptable tool to help expand the scope of practice of non-physician clinicians to include NCD care. While no primary outcomes showed a significant benefit of the intervention, there was also no evidence of

harm. The study illustrates the limitations of trials designed to study the effects of complex system interventions in real life, where even small changes across many endpoints, as seen in our study, may be useful to decision-makers.

## Conclusion

This thesis provides new and original evidence for high levels of multimorbidity and unmet treatment needs for NCDs in the South African public primary care sector. It confirms associations between socioeconomic and clinic characteristics, and hypertension control and treatment, and depression symptoms and treatment. It identifies potentially modifiable clinic-level factors that could improve care for these diseases. It provides new evidence from South Africa in support of the bidirectional relationship between poverty and depression. Finally, it reports evidence of the effectiveness of a novel programme aimed at improving NCD management by supporting and expanding nurses' role in NCD care.

The work points to the need for improved strategies for diagnosing and managing NCDs and for better integrated NCD care, including equipping primary health care providers to manage NCDs and the complexities of multimorbidity.

Health services need to be sensitive to the impact of socioeconomic factors, in particular lower levels of education. Clinic factors that may be addressed to improve NCD care include adequate staffing of clinics, having pharmacists on site, and provision for community-based collection of chronic medications. The latter is likely to be relevant to the care of all chronic diseases, and points to the need for expansion of convenient medication delivery services in

South Africa. Together, these measures should be viewed as achievable opportunities for improving the management of NCDs in primary care in South Africa.

PC101 offers a practical and acceptable tool to help expand the scope of practice of non-physician clinicians to include NCD care. The programme, with several subsequent adjustments aimed at increasing its impact, has been rolled out nationally in South Africa and is included in the National Department of Health's checklist criteria for the Ideal Clinic and Integrated Clinical Services Management (ICSM) compliant package of clinical guidelines.

PC101 forms the basis for the Practical Approach to Care Kit (PACK) (pack.bmj.com) which now extends to children, adolescents and community health workers. In partnership with the British Medical Journal (BMJ), global templates of the 'PACK Adult' programme have been developed. Localisations of PACK Adult for Brazil and Nigeria have been completed, and a randomised controlled trial is underway to evaluate the programme in the city of Florianópolis, Brazil. Ongoing development and evaluation of these programmes is required to ensure continued improvements in the management of NCDs in primary care.

In summary, this thesis, including the four publications, addresses the public health challenge of providing integrated chronic disease management in South African primary care. It identifies needs and potential solutions to the needs of patients with NCDs in the public primary care setting.

# Acknowledgements

I wish to acknowledge and express my sincere thanks to Lara Fairall and Max Bachmann, my supervisors of this thesis, for their invaluable guidance and mentorship. This work would not have been possible without the dedicated efforts of many, as acknowledged in the thesis and publications. The statistical design and analyses form a special aspect of this work, for which I thank Carl Lombard, Max Bachmann and Lara Fairall for their contribution. Naomi Levitt and Krisela Steyn provided guidance and support throughout the project. The study was funded by the United States National Heart, Lung, and Blood Institute, National Institutes of Health. It was approved and supported by the University of Cape Town Human Research Ethics Committee, the Western Cape Department of Health, and the Eden and Overberg district management. In compiling this thesis I acknowledge with special appreciation my supervisors and Professor Eric Bateman. I dedicate this thesis to my son, Daniel.

# Publications and statement of contributorship

The following four papers are included as part of the thesis:

1. Folb N, Timmerman V, Levitt NS, Steyn K, Bachmann MO, Lund C, et al. Multimorbidity, control and treatment of noncommunicable diseases among primary healthcare attenders in the Western Cape, South Africa. S Afr Med J. 2015;105(8):642-647. DOI:10.7196/SAMJnew.7882

2. Folb N, Bachmann MO, Bateman ED, Steyn K, Levitt NS, Timmerman V, et al. Socioeconomic and modifiable predictors of blood pressure control for hypertension in primary care attenders in the Western Cape, South Africa. S Afr Med J. 2016;106(12):1241-1246. DOI:10.7196/SAMJ.2016.v106i12.12005.

3. Folb N, Lund C, Fairall LR, Timmerman V, Levitt NS, Steyn K, Bachmann MO. Socioeconomic predictors and consequences of depression among primary care attenders with non-communicable diseases in the Western Cape, South Africa: cohort study within a randomised trial. BMC Public Health. 2015;15:1194. DOI 10.1186/s12889-015-2509-4.

4. Fairall LR, Folb N, Timmerman V, Lombard C, Steyn K, Bachmann MO, et al. Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-communicable Chronic Disease Management in Primary Care in South Africa: A Pragmatic Cluster Randomised Controlled Trial. PLoS Med. 2016;13(11): e1002178. doi:10.1371/journal.pmed.1002178.

I contributed to the development and finalisation of the PC101 clinical management tool including the hypertension, cardiovascular diseases, diabetes, and mental health sections, prior to moving into the role of Trial Manager for the PC101 randomised controlled trial.

As Trial Manager I contributed to the design and planning, preparation of materials (for example, the patient questionnaires and training manuals) and clinic sites, and supervised the conduct of the study. I led the training of fieldworkers throughout the study period, and

oversaw supervision of fieldworkers, ensuring the quality of their data collection in the study sites. I monitored the data to identify unusual values or trends, cleaned the data, ensuring it was accurate, and prepared the datasets for analysis. I personally reviewed all prescription charts and recorded prescriptions of chronic medication for each patient at the time of their baseline and follow-up interviews. I performed the statistical analyses, supported by Professor Max Bachmann, for papers 2 and 3. I collaborated with the trial statistician (Professor Carl Lombard) and principal investigator Associate Professor Lara Fairall in the statistical design and analyses for the randomised controlled trial (paper 4). I prepared reports for the institutional ethics review board and funders throughout and at the completion of the study.

I confirm that the thesis constitutes original research, and that I served as the lead and corresponding author for the first three submitted papers, and co-lead author for the fourth paper, sharing lead authorship with principal investigator and my supervisor Associate Professor Lara Fairall. All co-authors contributed to the preparation of the manuscripts and approved the final submissions. Specific contributions are reported in the introduction to each paper in Chapter 3. I alone prepared this thesis.

## Plagarism declaration

I confirm that this thesis is my own work, is not copied from any other person's work (published or unpublished), and has not previously been submitted for assessment either at the University of Cape Town or elsewhere.

# List of abbreviations

ART: antiretroviral treatment

BMJ: British Medical Journal

CCW: Community Care Worker

CESD-10: Center for Epidemiologic Studies Depression Scale

CHCs: community health centres

COPD: chronic obstructive pulmonary disease

CVD: cardiovascular disease

DALYs: disability adjusted life years

DHS: Demographic and Health Survey

HbA1c: haemoglobin A1c

HCTZ: hydrochlorothiazide

ICSM: Integrated Clinical Services Management

IHD: ischaemic heart disease

LMICs: low- and middle-income countries

NCDs: non-communicable diseases

NIDS: National Income Dynamics Study

NIMART: nurse initiated and managed antiretroviral treatment

PACK: Practical Approach to Care Kit

PAL: Practical Approach to Lung Health

PALSA: Practical Approach to Lung Health in South Africa

PC101: Primary Care 101

PEN: Package of Essential Noncommunicable

PRIME: Programme for Improving Mental Health Care

RCT: randomised controlled trial

SASH: South African Stress and Health study

TB: tuberculosis

WHO: World Health Organization

YLD: years lived with disability

# Contents

# Chapter 1: Introduction and Literature Review

## 1.1 Introduction

Non-communicable diseases (NCDs) are the leading causes of death globally. They are projected to overtake communicable, maternal, perinatal, and nutritional diseases as the most common cause of death in Africa by 2030 (WHO 2011a). The burden of NCDs in South Africa has been estimated to be two to three times higher than that in developed countries (Mayosi et al. 2009). Further, multimorbidity is becoming the norm rather than the exception, with most people with chronic conditions having more than one (Mercer et al. 2012) (Barnett et al. 2012).

Despite this burden, chronic diseases and risk factors are often undiagnosed and inadequately treated in South Africa, resulting in high levels of uncontrolled hypertension, diabetes and chronic respiratory diseases (Mayosi et al. 2009) (Steyn K, Fourie J, and Temple N 2006) (Steyn et al. 2008) (Rayner 2010).

Primary Care 101 (PC101) expands on PALSA PLUS, a clinical management tool which focussed on HIV and respiratory diseases, to include NCDs and mental health. PC101 is designed to strengthen health services by supporting and expanding nurses' role in NCD care, alongside the demands of communicable and acute disease management. It addresses the need for improved diagnosis and management of NCDs with an integrated approach to primary health care. The programme comprises a clinical management tool, enhanced prescribing provisions for nurses, and educational outreach.

This thesis uses experience gained from a study in two districts of the Western Cape to address the needs and potential solutions to the needs of patients with NCDs attending primary care services. It examines multimorbidity, control and treatment of NCDs; socioeconomic and modifiable predictors of hypertension and depression control; and effectiveness of the PC101 programme in improving NCD care.

## 1.2 Literature review

This literature review provides the background to the problem of NCDs and multimorbidity globally and in South Africa, socioeconomic associations with hypertension and depression control, nurse-led primary care and task-sharing, and clinical tools including the PC101 programme, necessary to understanding the motivation for the current studies. Additional background is provided in each of the four papers.

### 1.2.1 The Burden of NCDs in South Africa and globally

NCDs are the leading causes of death globally, killing more people each year than all other causes combined (WHO 2011a). In 2015, NCDs caused 71% of deaths globally (GBD 2015 Mortality and Causes of Death Collaborators 2016). NCD deaths are projected to continue to rise worldwide, and the greatest increase is expected to be seen in low- and middle-income (LMIC) regions (WHO 2011a). In addition, NCDs are the leading cause of global disability-adjusted life-years (DALYs) (GBD 2015 DALYs and HALE Collaborators 2016).

The increasing significance of NCDs is the result of several factors, including population growth, the increasing average age of the world's population, and decreasing death rates from communicable, maternal, neonatal, and nutritional causes (Lozano et al. 2012)

(Jamison et al. 2013). In African nations, NCDs are projected to exceed communicable, maternal, perinatal, and nutritional diseases as the most common causes of death by 2030 (WHO 2011a).

South Africa is experiencing a simultaneous burden of communicable and non-communicable diseases (Mayosi et al. 2009). The burden of HIV and tuberculosis (TB), in particular, is high. In 2015, an estimated 7 million people in South Africa were living with HIV, and there were 180 000 deaths due to AIDS in that year (UNAIDS 2015). The World Health Organization (WHO) reported 454 000 cases of TB and 98 000 deaths from the disease in 2015 (WHO 2015).

In parallel with these deaths from TB and HIV infection is a rise in NCDs in South Africa (Kasprowicz, Achkar, and Wilson 2011) (UNAIDS 2015). WHO estimates place the burden from NCDs in South Africa to be two to three times higher than in developed countries (Mayosi et al. 2009). Heart disease, diabetes and stroke together constitute the second most important cause of death in adult South Africans (Mayosi et al. 2009) and NCDs accounted for 39% of deaths and for considerable premature mortality in South Africa in 2010 (Nojilana et al. 2016).

### *Hypertension*

In 2010, high blood pressure was the leading risk factor for global disease burden, contributing to 7% of (DALYs) (Lim et al. 2012), and was estimated to be responsible for 7.5 million deaths, about 12.8% of the total annual deaths worldwide (WHO 2011a). It is the leading cause of cardiovascular disease (CVD) including heart attacks, heart failure, stroke

and kidney failure. It is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke (WHO 2013a). The prevalence of high blood pressure globally in adults aged 25 and over was around 40% in 2008 (WHO 2011a), and raised blood pressure has a notably higher prevalence in LMICs (WHO 2011a). A recent survey in four provinces in South Africa found that hypertension was the commonest diagnosis and reason for attendance in public sector clinics (Mash et al. 2012).

### *Diabetes*

In 2010, diabetes was the sixth leading cause of mortality and the eighth leading cause of DALYs worldwide (Murray and Lopez 2013). The Global Burden of Disease Study 2015 ranked diabetes the sixth leading cause of global years lived with disability (YLDs) (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016). Diabetes increases the risk of developing CVD, and is also a significant cause of blindness in adults, non-traumatic lower limb amputations, and end-stage renal disease requiring transplantation and dialysis (Tracey et al. 2016). The International Diabetes Federation estimates that 415 million people have diabetes worldwide and this is predicted to rise to 642 million by 2040 (IDF 2015). More than 80% of people with diabetes live in LMICs (Chan et al. 2016), and the number of people in South Africa with diabetes is estimated to be 2.3 million (IDF 2015).

### *Chronic respiratory disease*

Chronic respiratory diseases are the third leading cause of NCD deaths (GBD 2015 Mortality and Causes of Death Collaborators 2016), with chronic obstructive pulmonary disease (COPD) and asthma the most common respiratory NCDs (Beran et al. 2015).

As many as 334 million people have asthma worldwide. Most people affected are in LMICs, where its prevalence is estimated to be increasing fastest (Global Asthma Network 2014). In addition, more than 80% of asthma related deaths worldwide occur in LMICs. This high and increasing burden is probably related to both increasing prevalence and poor control (Beran et al. 2015). Disease severity among asthmatics has been found to be greater in lower socioeconomic groups in Cape Town, South Africa, and a strong positive association was found between social deprivation and admissions to intensive care units for asthma and (all-age) mortality from asthma (Poyser et al. 2002).

COPD mortality is also most common in low-resource regions (Beran et al. 2015). A community-based study of COPD in Cape Town found the prevalence of COPD (Stage 2 and above) to be 19% in persons aged 40 years and older, the highest of the 12 centres from different continents sampled (Buist et al. 2007).

*Depression*

There were an estimated 298 million cases of major depressive disorder worldwide in 2010 (Ferrari et al. 2013) and this disorder was ranked the second leading cause of YLDs (Ferrari et al. 2013) (Vos et al. 2012). The Global Burden of Disease Study 2013 found that mental and substance abuse disorders accounted for 21% of YLDs, with major depressive disorder a crucial contributor in both developed and developing countries: it was the leading cause of YLDs in 56 countries, the second leading cause in 56 countries, and the third in 34 countries (Global Burden of Disease Study 2013 Collaborators 2015). In 2015, mental and substance use disorders were a leading cause of NCD burden (GBD 2015 DALYs and HALE Collaborators

2016) and depressive disorders were ranked the third leading cause of global YLDs (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016).

The South African Stress and Health (SASH) study indicated a lifetime prevalence of major depression of 9.7% and a 12 month prevalence of 4.9 % (Tomlinson et al. 2009). The relationships between mental disorders and other NCDs are complex and bidirectional (Patel and Chatterji 2015). Mental disorders increase risk for communicable and NCDs. Conversely, many health conditions increase the risk for mental disorder (Prince et al. 2007).

### 1.2.2 Multimorbidity

Worldwide, with ageing populations in almost all countries, most people with a chronic condition have more than one (Mercer et al. 2012) (Barnett et al. 2012). Multimorbidity is more common and occurs at an earlier age in patients of lower socioeconomic position (SEP) (Moffat and Mercer 2015) (Barnett et al. 2012).

Some conditions may affect the risks of adverse outcomes associated with other conditions. For example, diabetes triples the risk of tuberculosis (Lönnroth, Roglic, and Harries 2014); people with COPD have a 2.5 times increased risk of cardiovascular disease (Chen et al. 2015); and depression has been found to be an important risk factor for the development of ischaemic stroke (Rahman et al. 2013).

Mental health problems such as depression are known to be common in patients with multimorbidity. The prevalence of mental health problems increases with increasing numbers of physical conditions within individuals (Moffat and Mercer 2015) (Gunn et al.

2012) (Barnett et al. 2012) and negatively influences outcomes for chronic conditions, including acute admissions (Morrison et al. 2016) (Payne et al. 2013). In addition, mental combined with physical multimorbidity is 2–3 times more common in patients living in deprived areas compared with those in affluent areas (Moffat and Mercer 2015).

Studies in South Africa have demonstrated high levels of comorbidity with hypertension and diabetes (Peer et al. 2013) (Steyn et al. 2008) (Lalkhen and Mash 2015), and psychological distress in women with physical disease (Mendenhall et al. 2013).

Despite such evidence of multimorbidity, traditionally NCDs are managed separately, without adequate consideration of comorbidity in individual patients. There is an urgent need to integrate chronic disease care, including mental health (Patel and Chatterji 2015), and to equip primary health care providers to manage NCDs and the complexities of multimorbidity.

### 1.2.3 Management of NCDs in the public sector in South Africa

Chronic diseases and risk factors are often undiagnosed and inadequately treated in South Africa, resulting in high levels of uncontrolled hypertension, diabetes and chronic respiratory diseases (Mayosi et al. 2009) (Steyn K, Fourie J, and Temple N 2006) (Steyn et al. 2008) (Rayner 2010).

A survey in 18 community health centres in the Cape Peninsula, South Africa, carried out in 1999 found that 67 % of hypertensive patients had uncontrolled blood pressure (> 140/90 mmHg) and that the mean HbA1c among diabetic patients was 8.8% (Steyn et al. 2008). A

study of goldminers in Gauteng province, South Africa, in 2009/2010 found that only 42% of patients diagnosed with hypertension received antihypertensive medication, while 69% of patients on antihypertensive medication were poorly controlled (Maepe and Outhoff 2012). Notably, poor levels of hypertension control have also been associated with high levels of target organ damage (Peer et al. 2008).

In the Global Initiative for Asthma report in 2004, South Africa ranked fourth of almost 70 countries for asthma case fatality rates (Masoli et al. 2004), indicating inadequate management. The results of the South African Stress and Health (SASH) study indicated a high unmet need for treatment of mental health disorders with only 28% of those with severe and moderately severe mental disorders receiving treatment (Williams et al. 2008).

### 1.2.4 Inequalities in South Africa and socioeconomic associations with hypertension and depression control

South Africa is one of the most unequal countries in the world (Tregenna and Tsela 2012), with wide disparities in wealth and health (Benatar 2013). The Gini coefficient, a number between 0 and 1, where 0 indicates total equality and 1 indicates total inequality, was calculated to be approximately 0.65 based on expenditure data (per capita excluding taxes) and 0.69 based on income data (per capita including salaries, wages and social grants) in 2011. These levels of inequality are amongst the highest in the world (Statistics South Africa 2014). Consistent with global patterns, the burden of ill-health in South Africa has been demonstrated to be greater among lower socio-economic groups (Ataguba, Akazili, and McIntyre 2011).

The majority of the population of South Africa is dependent upon the public sector health services for their medical needs (van Rensburg 2014). Primary care in the public sector is nurse-led with support from doctors, with nurses seeing over 85% of all patients (Mash et al. 2012).

Studies have found associations between low socioeconomic position and increased risk of hypertension (Leng et al. 2015) (Kautzky-Willer et al. 2012) (Fan et al. 2015) (Grotto, Huerta, and Sharabi 2008) (Gorman and Sivaganesan 2007). In South African women, more education has been found to predict lower values of both diastolic and systolic blood pressure, while higher income predicted lower systolic blood pressure. This did not hold true for men (Cois and Ehrlich 2014).

A number of studies in LMICs have shown an association between indicators of poverty and mental disorders (Lund et al. 2010) (Patel and Kleinman 2003). A systematic review found a consistent and strong association between common mental disorders and education, food insecurity, housing, social class, socio-economic status and financial stress; whereas income, employment and consumption (defined as household per capita expenditure) were found to be less consistently or strongly associated with mental disorders (Lund et al. 2010). Another systematic review in developing countries found most studies showed an association between risk of common mental disorders and low levels of education, and many studies also showed a relationship with other indicators of poverty such as poor housing or low income (Patel and Kleinman 2003).

### 1.2.5 Policy responses to NCDs

*Global policy response to NCDs*

The United Nations (UN) held a summit on NCDs in 2011 calling for a 'whole-of-government' and 'whole-of-society' approach for the prevention and management of NCDs (Beran 2015) (UNGA 2011). Following the United Nations summit, the World Health Organization developed the Global Action Plan, including a Global Monitoring Framework for the implementation of measures to prevent and control NCDs (WHO 2013b). This framework includes nine general NCD targets, with the overall goal of a 25% relative reduction in premature mortality from NCDs by 2025 (Beran 2015) (WHO 2013b).

In order to achieve this, health systems will play an essential role and will need to be reoriented to meet the challenge (Beran 2015) (Reddy 2002). To aid priority setting and encourage immediate action for addressing NCDs, the WHO Global Status Report puts forward a series of highly cost effective 'best buys' – population-wide and individual healthcare interventions known to be effective, feasible, and affordable in any resource setting. Best buys include counselling and multi-drug therapy for people with a high risk of developing heart attacks and strokes (including those with established CVD), and preventive management of heart attacks with aspirin. Primary health care has been clearly identified by WHO as the best framework for implementing such interventions on an adequate scale to have an impact on morbidity and mortality (WHO 2011a) (WHO 2011b).

*South African policy response to NCDs*

In 2013, following on from the UN summit, the South African National Department of Health released its Strategic Plan for the Prevention and Control of Non-communicable Diseases 2013-17. This document establishes the framework for reducing morbidity and mortality from NCDs in the context of broad health reform in South Africa, such as the re-engineering of primary health care and planned introduction of a National Health Insurance. (Department of Health 2013a) (Department of Health 2015) (Public Health Association of South Africa 2011).

The strategy has three major components: 1) to prevent NCDs and promote health and wellness at population, community and individual levels; 2) to improve control of NCDs through health systems strengthening and reform; and 3) to monitor NCDs and their main risk factors and conduct innovative research (Department of Health 2013a). Further, the plan commits to a set of 10 goals to be achieved by 2020 and 2030 (Table 1) (Department of Health 2013a).

| Table 1. Strategic Plan for the Prevention and Control of Non-communicable Diseases 2013-17: 2020 goals and targets (Department of Health 2013a) |
|---|
| 1. Reduce by at least 25% the relative premature mortality (under 60 years of age) from Non-communicable Diseases by 2020 |
| 2. Reduce by 20% tobacco use by 2020 |
| 3. Reduce by 20% the per capita consumption of alcohol by 2020 |
| 4. Reduce mean population intake of salt to <5 grams per day by 2020 |
| 5. Reduce by 10% the percentage of people who are obese and/or overweight by 2020 |
| 6. Reduce the prevalence of people with raised blood pressure by 20% by 2020 (through lifestyle and medication) |
| 7. Increase the prevalence of physical activity (defined as 150 minutes of moderate-intensity physical activity per week, or equivalent) by 10% |
| 8. Every woman with sexually transmitted diseases to be screened for cervical cancer every 5 years, otherwise every woman to have 3 screens in a lifetime (and as per policy for women who are HIV/AIDS positive) |
| 9. Increase the percentage of people controlled for hypertension, diabetes and asthma by 30% by 2020 in sentinel sites |
| 10. Increase the number of people screened and treated for mental disorder by 30% by 2030 |

Since 2013 the National Department of Health has prioritised the Re-Engineering of Primary Care as part of efforts to work towards a National Health Insurance system (Department of Health 2015). This included initiatives to integrate care of communicable and NCDs at clinic level through a model initially known as Integrated Clinical Disease Management, based on the WHO's Chronic Conditions Framework and incorporating PC101. This has evolved to the Integrated Clinical Services Management (Mahomed, Asmall, and Freeman 2014) (Mahomed and Asmall 2015) which now falls under the Ideal Clinic initiative which has established a list of core standards and indicators for primary care clinics (Department of Health 2016). PC101 forms the key clinical training component alongside the Integrated Management of Childhood Illness.

In addition to these clinical services initiatives, legislation has been introduced in an attempt to control NCDs and their risk factors, in particular smoking and dietary salt intake. South Africa became a Party to the WHO Framework Convention on Tobacco Control in 2005, and has a number of laws to restrict public smoking, regulate advertising, and ensure tobacco products carry health warnings (Campaign for Tobacco-Free Kids 2016). In 2013, legislation was passed to ensure a reduction in the salt content of certain foods, including bread, breakfast cereals, processed meat and stocks (Department of Health 2013b). A tax on sugar-sweetened beverages based on sugar content is likely to be implemented in 2017 (National Treasury 2016).

Despite this welcome policy and focus on NCD prevention and care, the scale of the HIV epidemic has been such that NCDs have had to take a back-seat to initiatives to combat HIV and TB and which have dominated the agenda of funding agencies, donor aid and public health programmes in South Africa.

### 1.2.6 Nurse-led care and task-sharing

Nurse substitution and supplementation in NCD care in high income settings are well recognised strategies (Laurant et al. 2009) (Horrocks, Anderson, and Salisbury 2002). A systematic review (Laurant et al. 2009) on the impact of non-physician clinicians identified 18 reviews and studies focussing on nurse substitution and/or supplementation from developed countries, or where the geographic scope was not reported. The review concluded that role revision between physicians and non-physician clinicians does not jeopardise patient care and may sometimes improve its quality. Patients were significantly more satisfied with nurse-led care than physician-led care, and the process of care was

often improved by nurse–physician substitution. The evidence that role revision increases workforce efficiency or lowers costs is, however, weak and contradictory.

A second systematic review (Horrocks, Anderson, and Salisbury 2002) of whether nurse practitioners working in primary care can provide equivalent care to doctors in developed countries, concluded that patients are at least as satisfied with care at the point of first contact with nurse practitioners as they are with first contact care from doctors. The quality of care and short term health outcomes seem to be equivalent to that of doctors.

Evidence for nurse substitution and supplementation in NCD care in LMICs is sparse and limited to a few non-randomised studies (Labhardt et al. 2010) (Kengne et al. 2009) (Coleman, Gill, and Wilkinson 1998) (Gill et al. 2008). A study in rural districts of Cameroon concluded that the integration of hypertension and diabetes into primary health care at non-physician clinician facilities was feasible, accessible and showed promising blood pressure and blood glucose trends. However, low case-detection rates and a very high attrition among patients enrolled into care, limited the effectiveness of the programme (Labhardt et al. 2010). In another study in Cameroon, involving five clinics, nurse-led protocol-driven hypertension care achieved significant blood pressure reduction in patients with hypertension (Kengne et al. 2009). An old study in rural South Africa demonstrated that appropriate management of patients with NCDs can be achieved in a resource-poor situation by optimising existing primary care services. Using practical stepwise diagnostic and treatment protocols, nursing staff managed to control most patients with hypertension, diabetes and asthma (Coleman, Gill, and Wilkinson 1998). A more recent study from rural South Africa devolving care to primary health clinics delivered by two nurses, concluded that

a diabetes care system based on a simple protocol and education could be successfully introduced and run by nurses in rural Africa (Gill et al. 2008).

Antiretroviral treatment (ART) has transformed HIV/AIDs from an acute to a chronic condition. The scale-up of ART in South Africa, which began in 2004, had the favourable effect of prompting much-needed and urgent reforms to primary care services, to accommodate the extra clinical burden on these facilities. A major development was approval for nurses to play a greater role. In the context of HIV this initially comprised screening, staging and palliative care, but moved to nurse-initiated and managed ART (NIMART). An RCT evaluating nurse-monitored (but not initiated) ART in two South African primary care clinics, found that nurses were non-inferior to doctors in monitoring first-line ART (Sanne et al. 2010). A pragmatic RCT conducted by the University of Cape Town Lung Institute showed NIMART to be at least as effective, and for certain outcomes such as TB case detection, superior to doctor-led care (Fairall et al. 2012).

Large-scale health system reforms such as NIMART can provide a platform for development of NCD programmes (Jamison et al. 2013) (Rabkin and El-Sadr 2011). PC101 aimed to leverage the health system reforms that accompanied the scale-up of ART to improve the quality of primary care for NCDs and mental health.

### 1.2.7 Integrated care and clinical tools

The WHO provides the following working definition of integrated service delivery: “The management and delivery of health services so that clients receive a continuum of

preventive and curative services, according to their needs over time and across different levels of the health system." (WHO 2008a)

Integrating service delivery to prevent inefficiencies and duplication that drive up costs and reduce health effects is particularly crucial for NCDs, which have clinical features that often need a comprehensive diagnostic and treatment approach. Further, most services can be delivered through primary care clinics, supported by community health workers and hospitals (Jamison et al. 2013).

Clinical guidelines are widely used globally and the development of global guidelines ensuring the appropriate use of evidence represents one of the core functions of the World Health Organization (WHO 2017). Guidelines, however, are largely created for individual diseases and rarely account for multimorbidity (Barnett et al. 2012) (Moffat and Mercer 2015) (Barnett et al. 2012).

In 2008, the WHO developed the Package of Essential Noncommunicable (PEN) disease interventions for primary health care in low-resource settings (WHO 2010). The goal of PEN is to close the gap between what is needed and what is currently available to reduce the burden and health-care costs due to NCDs (WHO 2013c). The interventions include protocols for the management of hypertension, diabetes, cardiovascular risk, asthma and chronic obstructive pulmonary disease (WHO 2013c).

The PC101 programme is an approach to managing multimorbidity, and to contributing to improved NCD care in the primary care setting. It provides a single, systematic approach to

the most common symptoms and chronic diseases seen in the management of adults in primary care. It assists clinicians with providing integrated NCD care, by better enabling them to manage all the patient's health needs at the same consultation, prompting targeted screening for NCDs among patients presenting with symptoms suggestive of a diagnosis (e.g. facial weakness or chest pain), and promoting identification and management of important co-morbidities (e.g. cardiovascular risk assessment among patients presenting for COPD follow-up).

### 1.2.8 The PC101 programme

*Background*

In 1998 The World Health Organization initiated the Practical Approach to Lung Health (PAL), a syndromic approach to the management of patients who attend primary health care services for respiratory symptoms (WHO 2008b) (WHO 2005). PAL is aimed at improving the management of all respiratory disorders, and in the process enhances the identification of patients with TB (Murray, Pio, and Ottmani 2006).

PALSA (PAL in South Africa) was developed to address the high incidence and delay in diagnosis of TB in South Africa. The programme was evaluated in a cluster randomised trial and showed modest improvements in quality of care across communicable (TB) and NCDs (asthma), and substantial improvements in detection of TB cases (Fairall et al. 2005) (Bachmann et al. 2010).

PALSA PLUS was developed in response to South Africa's decision to implement a public sector ART programme. It extended the training of clinic nurses to include HIV/AIDS screening, and referral to physicians for diagnosis and initial prescribing of ART, with patients returning to nurses for monitoring. A cluster randomised trial of this programme confirmed modest improvements in the quality of care, and a substantial impact on TB case detection (Zwarenstein et al. 2011).

The scope of PALSA PLUS was subsequently expanded to support Nurse Initiated and Managed ART (NIMART). A third cluster randomised trial found that NIMART resulted in patients being managed as effectively as in physician-led programmes, and showed modest improvements in quality of care and outcomes for patients as well as further improvements in TB case detection (Fairall et al. 2012).

PC101 is an expansion of PALSA PLUS to include NCDs, mental illness and women's health, and is designed to support and expand nurses' roles to cover the full gamut of priority conditions presenting to primary care and NCDs in particular.

PALSA PLUS, the NIMART programme and PC101 have been scaled-up across South Africa, reaching more than 20 000 nurses in 3 500 clinics (Fairall et al. 2015). A summary of the programmes and their evaluation is provided in Table 2.

| Table 2: Development and evaluation of the PALSA and PC101 programmes | | |
|---|---|---|
| **Trial design** | **Main outcome findings** | **Interpretation of findings** |
| **PALSA: adaptation for South Africa of WHO's Practical Approach to Lung Health (PAL)** | | |
| Pragmatic RCT in the Free State province from 2003 (Fairall et al. 2005) (Fairall et al. 2010) (Bachmann et al. 2010) | • Case detection of tuberculosis was higher in the intervention group (6.4% v 3.8%; odds ratio (OR) 1.72, 95% confidence interval (CI) 1.04 to 2.85)<br>• Sputum testing for tuberculosis was similar between groups (22.6% in outreach group v 19.3% in control group; OR 1.22, CI 0.83 to 1.80)<br>• More prescriptions for inhaled corticosteroids in the intervention group (13.7% v 7.7%; OR 1.90, CI 1.14 to 3.18)<br>• The number of antibiotic prescriptions was similar between groups (39.7% v 39.4%; OR 1.01, CI 0.74 to 1.38)<br>• The intervention was more costly than usual training in improving tuberculosis, asthma and urgent respiratory care but was also associated with fewer and shorter hospital admissions.<br>• The syndromic approach increased cost-effectiveness by improving care of other conditions. | • Educational outreach training in syndromic approaches to respiratory symptoms confirmed WHO's original hypothesis that such approaches can strengthen passive case finding for tuberculosis.<br>• It also showed simultaneous improvement in the care for communicable (TB) and non-communicable conditions (asthma).<br>• The intervention was sustainable, and implemented with limited interruption of clinical services and no additional trainers required.<br>• PALSA provided the basis for PALSA PLUS to support nurses' expanding role for HIV care. |
| **PALSA PLUS: PALSA expanded to include HIV/AIDS** | | |
| Pragmatic RCT in the Free State province from 2004-2006 (Zwarenstein et al. 2011) | • Cotrimoxazole prophylaxis was more likely to be prescribed in the intervention group (OR 1.95, CI 1.11 to 3.40)<br>• Tuberculosis was more likely to be diagnosed among patients attending intervention group clinics (OR 1.25, CI 1.01 to 1.55)<br>• No evidence that the intervention was effective in increasing recruitment into the HIV/AIDS/ART programme (OR 1.19, CI 0.51 to 2.77) | • Educational outreach was effective in improving the comprehensiveness of care of patients with HIV/AIDS/ART, although no significant improvement was seen in detection of HIV in patients attending primary care clinics.<br>• The effect on TB case detection was reproduced. |

| **STRETCH (Streamlining Tasks and Roles to Expand Treatment and Care for HIV): nurse initiated and managed ART (NIMART)** | | |
|---|---|---|
| Pragmatic RCT in the Free State province from 2007-2010 (Fairall et al. 2012) | • Adults with CD4 counts of ≤ 350 cells perμL who were not receiving ART (Cohort 1):<br>  ○ Time to death did not differ<br>  ○ In a pre-planned subgroup analysis of patients with baseline CD4 counts of 201–350 cells per μL, mortality was slightly lower in the intervention group than in the control group (hazard ratio 0.73, CI 0.54-1.00; p=0.052)<br>• Adults who had already received ART for at least 6 months and were being treated at enrolment (Cohort 2):<br>  ○ Viral load suppression 12 months after enrolment was equivalent in intervention (2156 [71%] of 3029 patients) and control groups (2230 [70%] of 3202; risk difference 1.1%, CI –2.4 to 4.6).<br>• Secondary outcome measures:<br>  ○ Detection of tuberculosis, programme retention, and CD4 cell count at the end of follow-up were higher in the intervention group than in the control group.<br>  ○ In the intervention group, 965 (26%) of 3712 ART initiations were by a nurse; in the control group, none were. | • Expansion of primary-care nurses' roles to include ART initiation and represcription can be done safely, and improve health outcomes and quality of care.<br>• The effect of the intervention on TB case detection was shown for a third time despite the control clinics all receiving the PALSA PLUS intervention. |

| **PC101: PALSA PLUS expanded to include non-communicable diseases, mental health and women's health** | | |
|---|---|---|
| Pragmatic RCT in the Eden and Overberg districts of the Western Cape from 2011-2013<br>(Fairall et al. 2016) | • Treatment intensification rates in intervention clinics were not superior to those in the control clinics for hypertension, diabetes and chronic respiratory disease; nor was case detection of depression.<br>• Pre-specified subgroup analyses showed that the intervention was associated with treatment intensification among diabetic patients with an HbA1c of 7% to 10% at baseline.<br>• After disaggregation of the disease groups, other significant findings were:<br>  ○ higher rates of aspirin initiation among patients with hypertension and diabetes<br>  ○ higher use of angiotensin-converting enzyme inhibitors in patients with known cardiovascular disease<br>  ○ more prescriptions of sulphonylureas in patients with diabetes and a high body mass index.<br>• No adverse effects of the nurses' expanded scope of practice were observed. | • Educational outreach to primary care nurses to train them in the use of a management tool involving an expanded role in managing NCDs was feasible and safe but was not associated with treatment intensification or improved case detection for index diseases.<br>• This notwithstanding, the intervention, with adjustments to improve its effectiveness, has been adopted for implementation in primary care clinics throughout South Africa. |

*The PC101 programme*

PC101 comprises a clinical management tool, education outreach training, and enhanced prescribing provisions for nurses. The programme is described in detail in Paper 4 and summarised below.

The clinical management tool is a 101-page evidence- and policy-informed clinical decision aid. The first half of PC101 covers 40 of the most common symptoms in adults attending primary care and prompts screening for the 20 chronic conditions included in the second half of the tool. Promotion of comprehensive and integrated care is a key objective of the tool. Clinic staff are trained to use the clinical management tool by trained nurse trainers, who deliver short, on-site, facilitated and case-based sessions. Nurses who completed this educational outreach training were authorised to prescribe an additional seven medications for NCDs previously restricted to doctors: enalapril and amlodipine for hypertension, glibenclamide and glicazide for diabetes, simvastatin for increased cardiovascular risk, inhaled budesonide for asthma and short courses of oral prednisone for exacerbations of COPD.

### 1.2.9 Summary

This literature review identifies NCDs and multimorbidity as important contributors of disease burden and raises important questions regarding NCD care in the public sector primary care setting. Despite the rise in NCDs, these diseases remain under-diagnosed and under-treated in South Africa, resulting in poor disease control. Further, associations have been found between socioeconomic disadvantage and poor disease control, an important consideration in South Africa where the majority of the population is dependent upon public sector health services (van Rensburg 2014). The rising NCD burden necessitates an integrated approach to chronic disease care, including equipping primary health care providers, in South Africa's case nurses, to manage NCDs and the complexities of multimorbidity. This thesis examines levels of multimorbidity and disease control, associations between socioeconomic disadvantage and the management of hypertension

and depression, and the effectiveness of a programme to assist nurses with an integrated approach to the management of NCDs in primary care.

## 1.3 Hypotheses and aims

This thesis addresses the following hypotheses:

I. NCDs in South Africa are associated with high levels of multimorbidity.

II. The burden of NCDs in the resource-restricted South African public sector remains characterised by suboptimal management of NCDs resulting in high levels of undertreated and uncontrolled disease.

III. Associations exist between socioeconomic disadvantage and poor disease control and treatment.

IV. A clinical management tool (PC101) aimed at addressing NCDs and multimorbidity with a systematic and integrated approach, assists nurses in the primary care management of adults, and improves NCD outcomes in primary care attenders.

Our approach to addressing these hypotheses was to study a cohort of adult patients attending public sector primary care clinics in two districts of the Western Cape, with conditions representing the highest burden of disease, in order to understand the extent of multimorbidity, levels of control and treatment, socioeconomic predictors and, finally, in a pragmatic randomised trial, the effectiveness of the PC101 programme.

The aims of this thesis are:

1. To assess current levels of multimorbidity, control and treatment of NCDs in patients attending public sector primary care clinics in the Eden and Overberg districts of the Western Cape, South Africa.
2. To investigate socioeconomic and modifiable predictors of hypertension control, and of treatment intensification in patients with uncontrolled blood pressure.
3. To investigate socioeconomic and modifiable predictors of depression symptoms and treatment.
4. To evaluate the effectiveness of the PC101 programme in improving NCD care.

# Chapter 2: Overview Of Methods

Methods are outlined in detail in each of the four papers and an overview provided in this chapter. Experimental and observational evidence for this thesis was obtained from the randomised trial cohort.

## 2.1 RCT methods (Papers 1 and 4)

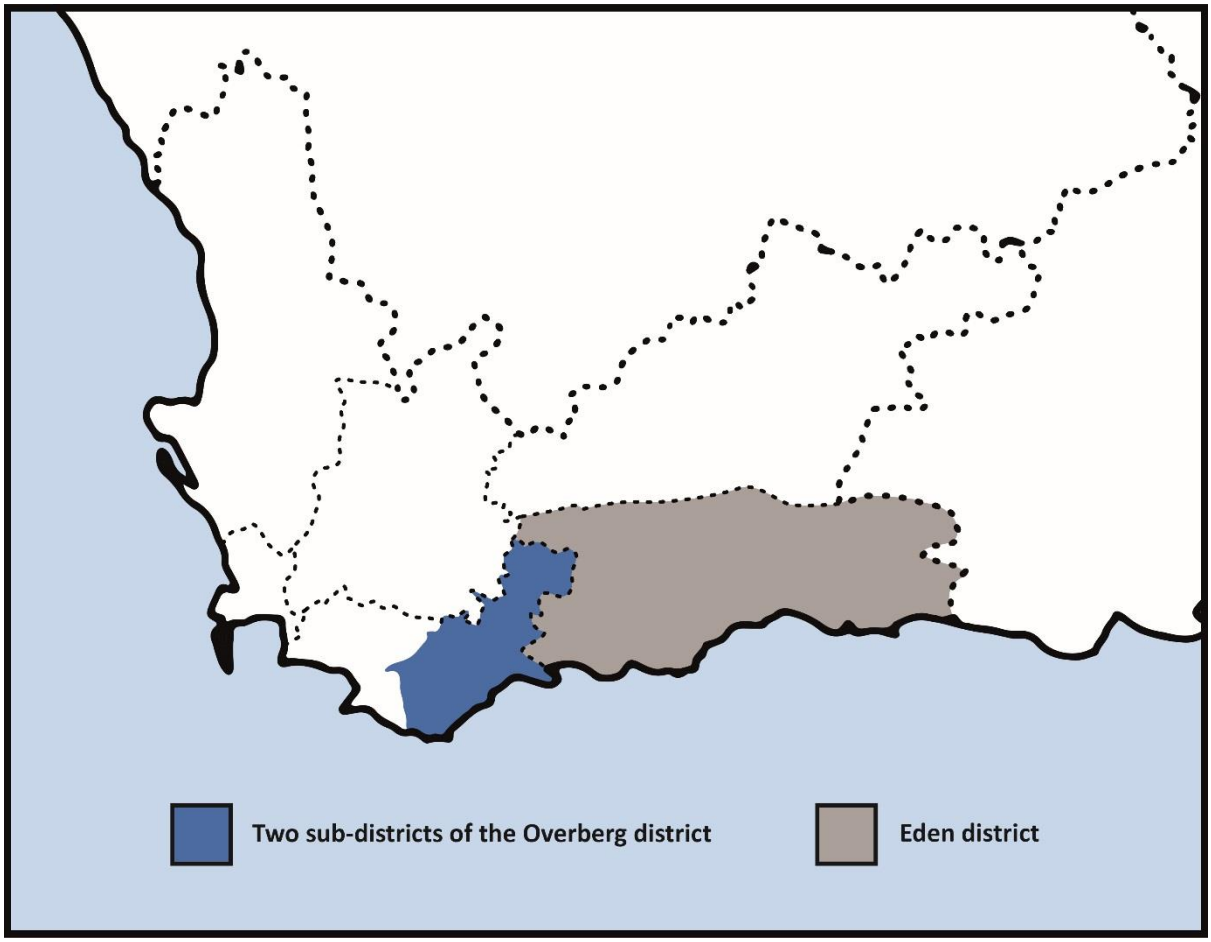
The pragmatic RCT involved clusters of public sector primary health care clinics within six sub-district strata. Outcomes were measured at individual patient level.

The cluster randomised design was appropriate for an intervention directed at groups of nurses working in clinics, reducing the risk of contamination of the intervention between arms. The pragmatic design allowed the intervention to be evaluated in 'real-world' circumstances with minimal research-related distortions of care delivery. Such a design is valuable for policy decision makers who want to know if an intervention will work when scaled-up in a health system and implemented under routine circumstances (Sackett 2011) (Thorpe et al. 2009).

Thirty-eight clinics in the Eden and Overberg districts of the Western Cape (Figure 1) were randomised to receive the PC101 programme or to continue with usual care for NCDs. This region is typical of many low resource settings in South Africa, in which the public sector primary health care clinics are nurse-led with limited doctor support. The clinics are the

main providers of primary health care for local populations with high levels of unemployment and socioeconomic deprivation.

**Figure 1: Eden and Overberg districts of the Western Cape, South AFrica**




We recruited primary healthcare clinic attendees 18 years and older, planning to reside in the area for the next year so that they would be available for follow-up interviews, and capable of actively engaging in an interviewer-administered questionnaire at the time of recruitment.

Among patients who met these criteria, four cohorts representing patients with hypertension, diabetes, chronic respiratory disease and depression were identified. Patients were eligible for the hypertension and diabetes cohorts if they reported being on medication for hypertension or diabetes respectively. They were eligible for the respiratory cohort if they reported being on medication for chronic respiratory disease, or had symptoms of chronic respiratory disease and were not on current treatment for tuberculosis. Patients were eligible for the depression cohort if they scored ten or more on the 10-item Centre for Epidemiologic Studies Depression Scale (CESD-10) (Andresen et al. 1994). Patients may have fulfilled inclusion criteria for more than one disease cohort.

Participants were sampled consecutively within each clinic and invited to participate in the study, until the sample size required for each clinic was obtained. They were screened for eligibility with a questionnaire and, if they met the eligibility criteria, were then asked to provide informed consent to participate.

At baseline trained fieldworkers administered the electronic questionnaire and took clinical measurements. Prescription charts were photocopied and reviewed, and chronic medication prescribed at the time of each participant's interview for depression, hypertension, diabetes and respiratory disease was recorded.

At follow-up the questionnaire, clinical measurements and prescription data were collected and recorded as for the baseline data. Baseline data collection began in March 2011 and ended in November 2011. Enrolment of patients was completed in intervention clinics

before educational outreach sessions to nurses began. Follow-up data collection started in May 2012 and ended in December 2012.

The RCT primary outcome for the hypertension, diabetes and chronic respiratory disease cohorts was treatment intensification, indicated by an increase in dose or number of medications, or change in medication class. This was chosen after considering research identifying clinician inertia as a key reason for failure to control these conditions (van Bruggen et al. 2009) (Schmittdiel et al. 2008); because it is associated with improved control (Berlowitz et al. 1998) (Berlowitz et al. 2005) (Carter et al. 2008); was likely appropriate for the study population where under-treatment was highly prevalent (Mayosi et al. 2009) (Steyn et al. 2008) (Williams et al. 2008); fitted well with the focus of the intervention on the clinical practice of nurses and the expansion of their prescribing with training; and could be applied across three of the four chronic conditions of interest. The primary outcome for the depression cohort was case detection, as this condition is recognised to be severely under-diagnosed and under-treated in primary care (Williams et al. 2008).

Intervention effects in the RCT were estimated using binomial regression models with treatment as the main effect, adjusted for stratification by sub-district and intraclass correlation of outcomes by clinic, and are reported with 95% confidence intervals.

## 2.2 Observational methods (Papers 2 and 3)

While the RCT evaluated the PC101 programme, socioeconomic and potentially modifiable associations with hypertension control and treatment intensification, and with depression

symptoms and treatment were assessed on the whole trial cohort at baseline and follow-up, combining the intervention and control arms of the trial. These observational analyses included cross-sectional baseline data and longitudinal cohort data, allowing analyses on changes from baseline to follow up and inference of causal relations. Multiple regression methods investigated independent effects of both patient and health service characteristics on control and treatment of hypertension and depression. In all analyses the study's cluster sampling design was accounted for in regression models, and intervention or control arm of the RCT was accounted for in all longitudinal analyses.

## 2.3 Ethical considerations

The trial is registered with Current Controlled Trials (ISRCTN20283604). Ethical approval for the trial was obtained from the University of Cape Town Human Research Ethics Committee (reference number 119/2010) and the Western Cape Provincial Department of Health. A randomised controlled trial was important in order to provide evidence for the effectiveness of the PC101 programme, but also to ensure that the programme does not cause harm, an assumption that could not be made. The probability of the intervention being harmful was considered to be low, and the potential for harm was offset by the value of the evidence needed to inform public health policies. Patients provided written consent for data collection after randomisation of clinics and prior to data collection. Participation in the study did not influence patients' care, and patients were free to withdraw from the study at any time. Fieldworkers and members of the research team signed a confidentiality agreement. While no primary outcomes showed a significant benefit of the intervention, there was also no evidence that the intervention caused harm.

# Chapter 3: Results In The Form of Published Papers

## 3.1 Multimorbidity, control and treatment of noncommunicable diseases among primary healthcare attenders in the Western Cape, South Africa

### Paper overview

This paper describes the characteristics of the study population at enrolment. It reports high levels of multimorbidity, poor control and unmet treatment needs for NCDs. It stresses the need for primary health care services to provide better integrated NCD care.

### Contribution to the thesis and novelty

This paper, describing the characteristics of the patient cohort at baseline, provides background context for the thesis and subsequent papers, and addresses the first aim of the thesis. There are few recent studies addressing multimorbidity, control and treatment of NCDs in public sector primary health care clinics in South Africa. The findings confirm previous reports of poor control and treatment of NCDs, and demonstrate little improvement in NCD control since these earlier studies were conducted.

### Role of the candidate

I oversaw data collection for the study and was responsible for data management, including cleaning the data and preparing it for analysis. I drafted the manuscript, incorporated input from co-authors and was responsible for finalising and submitting the final version of the manuscript for publication.

## Role of the co-authors

LF, MB, NL, and KS conceptualised the paper with NF and assisted with the original draft. VT was the data architect. All authors reviewed the manuscript and approved it for submission.

## Publication status

Published in the South African Medical Journal 2015.

*Folb N, Timmerman V, Levitt NS, Steyn K, Bachmann MO, Lund C, et al. Multimorbidity, control and treatment of noncommunicable diseases among primary healthcare attenders in the Western Cape, South Africa. S Afr Med J. 2015;105(8):642-647.*

*DOI:10.7196/SAMJnew.7882*

# Multimorbidity, control and treatment of non-communicable diseases among primary healthcare attenders in the Western Cape, South Africa

**N Folb**,[1,2,3] MB ChB, MRCGP (UK); **V Timmerman**,[1] PhD; **N S Levitt**,[2,3] MB ChB, MD, FCP (SA); **K Steyn**,[2,3] MSc, NED, MD; **M O Bachmann**,[4] MB ChB, PhD, FFPH (UK); **C Lund**,[5] MA, MSocSci, PhD; **E D Bateman**,[1,2,3] MB ChB, MD, FRCP (UK); **C Lombard**,[3,6,7] MSc, PhD; **T A Gaziano**,[3,8] MD, MSc; **M Zwarenstein**,[9] MB ChB, MSc, PhD; **L R Fairall**,[1,2,3] MB ChB, PhD

[1] *University of Cape Town Lung Institute, Cape Town, South Africa*
[2] *Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[3] *Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[4] *Norwich Medical School, University of East Anglia, Norwich, UK*
[5] *Alan J Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, Faculty of Health Sciences, University of Cape Town, South Africa*
[6] *Biostatistics Unit, Medical Research Council, Cape Town, South Africa*
[7] *School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[8] *Cardiovascular Medicine, Brigham & Women's Hospital, Boston, MA, USA*
[9] *Centre for Studies in Family Medicine, Department of Family Medicine, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada*

***Corresponding author:*** *N Folb (naomi.folb@uct.ac.za)*

**Background.** South Africa (SA) is facing a heavy burden of non-communicable diseases (NCDs). Few studies address multimorbidity, control and treatment of NCDs in patients attending primary healthcare (PHC) clinics.
**Objectives.** To describe multimorbidity, related risk factors, disease severity and treatment status of patients with four important NCDs attending public sector PHC clinics in two districts in SA.
**Methods.** A cross-sectional sample of patients completed baseline data collection for a randomised controlled trial of a health systems intervention. The study population comprised adults attending PHC clinics in the Eden and Overberg districts of the Western Cape in 2011. Four subgroups of patients were identified: hypertension, diabetes, chronic respiratory disease and depression. A total of 4 393 participants enrolled from 38 clinics completed a baseline structured questionnaire and had measurements taken. Prescription data were recorded.
**Results.** Of participants with hypertension, diabetes, respiratory disease and depression, 80%, 92%, 88% and 80%, respectively, had at least one of the other three conditions. There were low levels of control and treatment: 59% of participants with hypertension had a blood pressure ≥140/90 mmHg, the mean haemoglobin A1c (HbA1c) value in participants with diabetes was 9%, 12% of participants in the depression group were prescribed an antidepressant at a therapeutic dose, and 48% of respiratory participants were prescribed a $\beta_2$-agonist and 34% an inhaled corticosteroid.
**Conclusion.** Considerable multimorbidity and unmet treatment needs exist among patients with NCDs attending public sector PHC clinics. Improved strategies are required for diagnosing and managing NCDs in this sector.

*S Afr Med J* 2015;105(8):642-647. DOI:10.7196/SAMJnew.7882

South Africa (SA) faces a rise in non-communicable diseases (NCDs) in both rural and urban populations, driven by an increase in risk factors such as tobacco use, physical inactivity and unhealthy diets.[1] These place a heavy burden on public sector primary healthcare (PHC) services. A recent cross-sectional survey of reasons for consultations in PHC in four SA provinces confirmed that management of hypertension was the most common reason for attendance, with NCDs accounting for 14% of visits.[2,3]

PHC in the public sector is nurse-led with support from doctors, with nurses seeing over 85% of all patients.[2] However, at present nurses working at PHC clinics often do not have the necessary skills or capacity to deal adequately with NCDs.[1] Chronic diseases and risk factors are often undiagnosed and inadequately treated, resulting in high levels of poor control and morbidity.[1,4-6]

There is renewed focus on NCD care in SA. However, despite the magnitude of the NCD burden, there are few recent studies addressing multimorbidity, control and treatment of NCDs in this country. In particular, little is known about the multimorbidity of depression with other NCDs.

We present an analysis of the clinical characteristics, level of disease control, presence of multimorbidity and treatment of patients with hypertension, diabetes, chronic respiratory disease and symptoms of depression, identified in PHC clinics in the Eden and Overberg districts of the Western Cape Province, SA, as part of the Primary Care 101 trial described below.

## Methods

This study describes the characteristics of patients participating in the Primary Care 101 trial at enrolment. The Primary Care 101 programme comprised a customised clinical practice guideline and training programme aimed at assisting healthcare providers, largely nurses, with the primary care management of adults. The pragmatic cluster randomised controlled trial evaluated the effects of the

programme on the quality and outcomes of care for hypertension, diabetes, chronic respiratory disease and depression. Clinics were randomised either to receive the intervention or not. The main results of the trial will be published elsewhere.

The 33 largest clinics in the Eden district that provided NCD care, and a convenience sample of five clinics in the neighbouring Overberg district, were included in the study. Each clinic had at least 10 000 attendances per year and was staffed by nurse practitioners, doctors, and community health workers who manage clinic patients in the communities. These clinics are the main providers of PHC for local populations with high levels of unemployment and socioeconomic deprivation.

Eligible participants were clinic attenders aged 18 years or older, likely to reside in the area for the next year, and able to engage in an interviewer-administered questionnaire. Patients attending each clinic were interviewed to assess their eligibility for inclusion in the hypertension, diabetes, chronic respiratory and/or depression groups, until the sample size required for each group was reached. For the hypertension and diabetes groups, a self-reported history of medication use for these conditions was required. For the respiratory group, a self-report of prescription of medications for chronic respiratory disease or symptoms of chronic respiratory disease (cough or difficult breathing for >2 weeks),[7] and no current or recent treatment for tuberculosis, was required. The depression group comprised participants with a score of ≥10 on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10).[8] Individuals could be included in more than one group. In this article 'comorbidity' refers to two coexisting conditions and 'multimorbidity' to three or more coexisting conditions.

For trial purposes the sample sizes for each disease group were calculated separately, and were 27 participants per clinic for the chronic respiratory disease group and 60 per clinic for each of the other three groups. These target sample sizes were attained or exceeded for all disease groups except the diabetes group, which reached 48 participants per clinic.

Fieldworkers invited patients attending the trial clinics to be screened for inclusion in the study using a structured questionnaire. Eligible patients who provided informed consent were enrolled and completed another, baseline, questionnaire. Between March and October 2011, 4 904 patients were screened, of whom 4 393 were enrolled. The questionnaire was available in Afrikaans, isiXhosa and English. It included questions relating to demographic characteristics, socioeconomic factors, medical history and smoking status. Three blood pressure (BP) readings were taken at least 2 minutes apart with an Omron automatic monitor. The first reading was excluded and the values from the second and third readings were averaged.[9] Height, weight and waist circumference were measured using standardised techniques. Height and weight were measured with participants barefoot and wearing light clothing. A flexible tape was used to measure waist circumference, 2.5 cm above the umbilicus. Haemoglobin A1c (HbA1c) was measured only in 20 randomly selected clinics because of cost and logistical constraints. Diabetic participants in the 20 clinics were referred to a clinic nurse at the end of the interview for an HbA1c test, which was processed by the National Health Laboratory Service.

The severity of respiratory disease was assessed with the Symptom and Activity domains of the St Georges Respiratory Questionnaire (SGRQ)[10] in participants enrolled in the respiratory disease group. Scores are expressed as percentages, with 100% representing worst and 0% best possible health status. The presence of symptoms of depression was assessed with the CESD-10 scale, which was administered to all participants enrolled in the study.[8] The items were scored from 0 (rarely or none of the time) to 3 (most of the time).

Treatment for depression was defined as having received counselling or been referred to psychiatric services within the past year, or currently receiving an antidepressant. Counselling was defined as a consultation that intended to seek solutions to problems or provide emotional support, and not simply give advice on medication use. Participants who reported receiving counselling from a mental health nurse, clinic counsellor, social worker, psychiatrist or psychologist were considered to have received counselling, and those who reported receiving counselling from a mental health nurse, psychiatrist or psychologist were considered to have been referred to psychiatric services.

Chronic medication prescribed to participants at the time of their interview for depression, hypertension, diabetes and respiratory disease was recorded. Fieldworkers photocopied all available prescription charts for the year preceding the interview. The trial manager (NF) examined the prescription charts of each participant to identify medications prescribed at the time of their interview. A data capturer entered the prescription data (drug names, doses and frequencies) into an access database, and a total daily dose for each drug was calculated. Prescription charts were available for 99.3% of participants.

Quality control measures included supervision of fieldworkers, electronic alert messages for fieldworkers who entered unusually high or low values, and regular monitoring of the data to identify unusual values or trends. Quality control checks performed on the capturing of prescription data included double entry and checking all unusually high or low doses and frequencies.

The trial was registered with Current Controlled Trials (ISRCTN20283604) and the Office for Human Research Protections Database. Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee and the Western Cape Provincial Department of Health. Participants provided written informed consent for their interview and prescription data to be collected and analysed. All data were anonymised for analysis, and participant identities were revealed only to the fieldworker and a limited number of researchers who received and prepared the data for analysis.

## Results

Thirty-eight clinics were included in the study. The median number of nurses per clinic was four. Forty per cent of clinics had daily doctor support, the remainder had sessional support from doctors, and 42% of clinics had an on-site pharmacy.

A total of 4 393 participants were enrolled into the study, of whom 73% were women. The median age was 52 years, and 73% had hypertension, 42% diabetes, 26% chronic respiratory disease and 56% a CESD-10 score of ≥10 and so could be considered to be at risk of depression.

The majority of the participants (84%) were Afrikaans speaking, 75% were unemployed, 7% had never attended school, and 42% had achieved high-school education. Fifty-eight per cent reported receiving a social welfare grant, including 44% of participants under the age of 60 years. The median income in the month prior to the interview date was ZAR1 140, including personal non-grant income plus any household grant that benefited the participant, such as a disability or child grant.

Although 31% of participants were current smokers, their median pack-year history was only 7.5. Twenty-five per cent of participants provided a history of cardiovascular disease (heart attack, angina or stroke), 11% had a history of tuberculosis (TB), 2% reported

being on medication for TB at the time of the interview, and 2% reported being on antiretroviral drugs.

The NCD-related health characteristics of participants in each of the four disease groups are presented in Table 1.

In the hypertension group (3 227 participants), 59% had a BP ≥140/90 mmHg and 10% had a BP ≥180/110 mmHg, indicating poor control. Their mean body mass index (BMI, kg/m$^2$) was 31, 27% were current smokers, and 26% reported a history of cardiovascular disease. Of the 1 166 participants not in the hypertension group, 25% had a BP ≥140/90 mmHg and were not on medication for hypertension.

The diabetes group comprised 1 842 participants, of whom 704 had their HbA1c measured. The mean HbA1c value was 9.1% and 77% had an HbA1c above the target of 7%, indicating poor glycaemic control. The mean BMI for all participants with diabetes was 32, 23% were current smokers, and 23% reported a history of cardiovascular disease. An elevated BP (≥140/80 mmHg)[11] was present in 77%, and 8% had a BP ≥180/110 mmHg.

The chronic respiratory disease group comprised 1 157 participants, of whom 50% reported being on medication for respiratory disease and 50% were identified by symptoms alone. Eighteen per cent had a previous history of TB and 39% were current smokers. Their median pack-year history was 7.5. The median symptom and activity domain scores of the SGRQ were 60 and 74, respectively.

The depression group comprised a total of 2 466 participants. Their median CESD-10 score was 14 (interquartile range (IQR) 12 - 18).

Of participants with hypertension, diabetes, respiratory disease and depression, 80%, 92%, 88% and 80%, respectively, had at least one of the other three conditions, and 34%, 45%, 53% and 42% had at least two other conditions (Fig. 1). Hypertension was the commonest comorbidity in participants with other categories of chronic disease, followed by depression, diabetes and chronic respiratory disease. Forty-seven per cent of participants in the hypertension group also had diabetes, 84% of participants with diabetes also had hypertension, 22% of participants with hypertension or diabetes also had chronic respiratory disease, and 51% of participants with hypertension, diabetes or respiratory disease had a CESD-10 score of ≥10.

Treatment received by participants in the hypertension group at the time of their interview is presented in Table 2. Four per cent of participants in the hypertension group had no evidence of having received antihypertensive medication, 14% were on one antihypertensive agent, and 15% were on three or more antihypertensive drugs at optimal dosages. Fifty-five per cent of participants with hypertension were prescribed aspirin and 34% a statin.

**Table 1. Characteristics of study participants**

| **Hypertension group** | **All participants (*N*=3 227)** |
|---|---|
| Systolic BP (mmHg), mean (SD) (*n*=3 220) | 139 (23.6) |
| Diastolic BP (mmHg), mean (SD) (*n*=3 220) | 90 (13.2) |
| BP ≥140/90 mmHg, *n* (%) | 1 917 (59.4) |
| BP ≥180/110 mmHg, *n* (%) | 334 (10.4) |
| BMI (kg/m$^2$), mean (SD) (*n*=3 066) | 31.1 (7.5) |
| BMI, proportion obese (BMI ≥30), *n* (%) | 1 628 (50.5) |
| Waist circumference (cm), mean (SD) (*n*=3 194) | 100.5 (15.6) |
| Waist circumference (cm), proportion greater than ideal,* *n* (%) | 2 293 (71.1) |
| Current smokers, *n* (%) | 885 (27.4) |
| Pack-year history for current smokers, median (IQR) (*n*=756) | 8 (4.8 - 13.8) |
| Cardiovascular disease,† *n* (%) | 849 (26.3) |
| **Diabetes group** | **All participants (*N*=1 842)** |
| HbA1c (%),‡ mean (SD) (*n*=704) | 9.1 (2.5) |
| Proportion HbA1c ≥7%, *n* (%) | 544/704 (77.3) |
| SBP (mmHg), mean (SD) (*n*=1 840) | 137 (23.2) |
| DBP (mmHg), mean (SD) (*n*=1 840) | 88 (12.4) |
| BP ≥140/80 mmHg, *n* (%) | 1 414 (76.8) |
| BP ≥180/110 mmHg, *n* (%) | 139 (7.5) |
| BMI, mean (SD) (*n*=1 742) | 32.0 (7.3) |
| BMI, proportion obese (BMI ≥30), *n* (%) | 1 011 (54.9) |
| Waist circumference, mean (SD) (*n*=1 822) | 103.6 (14.8) |
| Waist circumference, proportion greater than ideal,* *n* (%) | 1 436/1 842 (78.0) |
| Current smokers, *n* (%) | 415 (22.5) |
| Pack-year history for current smokers, median (IQR) (*n*=353) | 8.25 (4.8 - 16.0) |
| Cardiovascular disease,† *n* (%) | 423 (23.0) |
| **Chronic respiratory disease group** | **All participants (*N*=1 157)** |
| Self-reported CRD on respiratory medication, *n* (%) | 699 (60.4) |
| Self-reported CRD symptoms and not on respiratory medication, *n* (%) | 458 (39.6) |
| SGRQ symptom domain (% maximum weight), median (IQR) (*n*=833) | 59.50 (36.4 - 74.8) |
| SGRQ activity domain (% maximum weight), median (IQR) (*n*=1 054) | 73.71 (53.6 - 92.5) |
| Current smokers, *n* (%) | 454 (39.2) |
| Pack-year history for current smokers, median (IQR) | 7.8 (4.4 - 13.5) |
| Previous tuberculosis, *n* (%) | 211 (18.2) |
| **Depression group** | **All participants (*N*=2 466)** |
| CESD-10 score, mean (SD); median (IQR) | 15.3 (4.3); 14 (12 - 18) |
| Current smokers, *n* (%) | 860 (34.9) |
| Pack-year history for current smokers, median (IQR) (*n*=754) | 7.2 (3.9 - 13.5) |

SD = standard deviation.
*≥88 cm for women, ≥102 cm for men.
†History of heart attack, angina or stroke.
‡HbA1c measured in a preplanned subgroup of 20 randomly selected clinics.

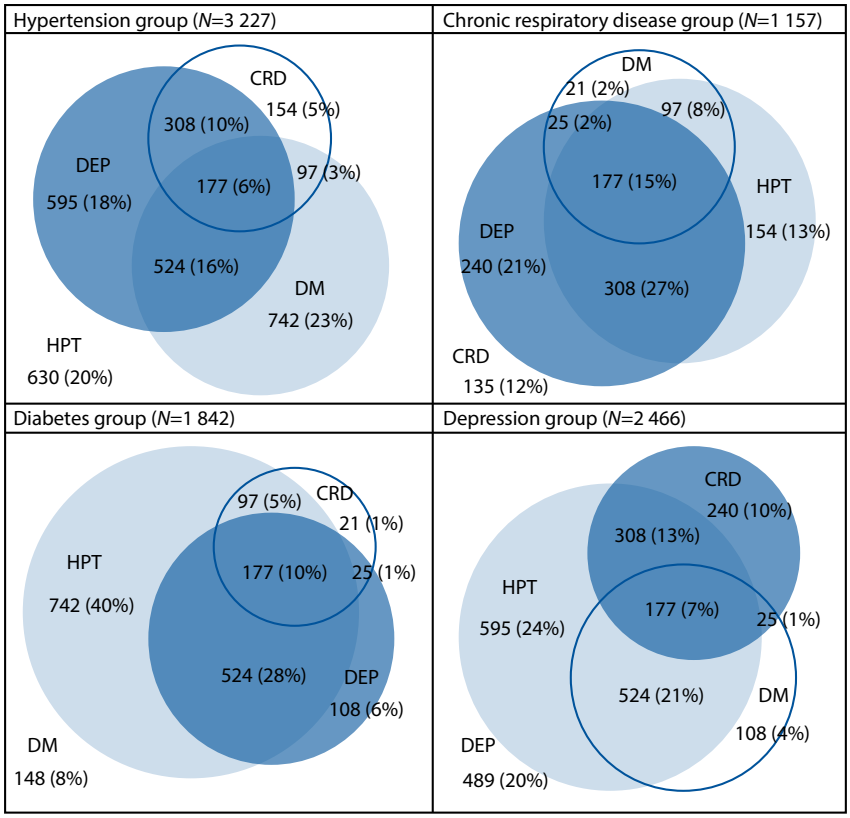



*Fig. 1. Venn diagram of multimorbidity associated with hypertension, diabetes, chronic respiratory disease and depression. (HPT = hypertension; DM = diabetes; CRD = chronic respiratory disease; DEP = depression.)*

**Table 2. Treatment, hypertension group**

| Medications prescribed | All participants (*N*=3 227) *n* (%) | Controlled BP*† (*N*=1 303) *n* (%) | Uncontrolled BP‡† (*N*=1 917) *n* (%) |
|---|---|---|---|
| Hypertension medications | | | |
| No hypertension medication | 129 (4.0) | 80 (62.0) | 47 (36.4) |
| 1 hypertension medication | 436 (13.5) | 207 (47.5) | 229 (52.5) |
| ≥2 hypertension medications | 2 638 (81.7) | 1 003 (38.0) | 1 631 (61.8) |
| ≥3 antihypertensive medications at optimal dosage | 482 (14.9) | 140 (29.0) | 341 (70.8) |
| Missing information | 24 (0.7) | | |
| Aspirin | 1 760 (54.5) | 711 (40.4) | 1 047 (59.5) |
| Statin | 1 093 (33.9) | 445 (40.7) | 647 (59.2) |

*BP <140/90 mmHg.
†Frequencies and row percentages exclude 7 participants with missing BP readings.
‡BP ≥140/90 mmHg.

Treatment received by participants in the diabetes group is presented in Table 3. Sixty-one per cent of participants with diabetes had been prescribed an oral hypoglycaemic agent (without insulin) and 32% were prescribed insulin (with or without oral hypoglycaemic agents). Aspirin had been prescribed for 63% in the diabetes group, and statins for 51%. Seven per cent of participants with diabetes had had no hypoglycaemic agents prescribed. In both the hypertension and diabetes groups, we observed higher medication use in participants with poorer control.

In the respiratory group, 48% of participants had been prescribed a $\beta_2$-agonist metered dose inhaler (MDI) or nebuliser, 34% an inhaled corticosteroid (any dose), 8% an ipratropium bromide MDI or nebuliser, and 11% slow-release theophylline as maintenance treatment (Table 4).

In the depression group, 12% of participants had been prescribed a therapeutic dose of antidepressant and 10% a subtherapeutic dose (<50 mg/d) of amitriptyline or imipramine (Table 5). Twenty-five per cent were receiving treatment for depression, defined as receiving counselling, referral to psychiatric services or being on an antidepressant at a therapeutic dose. Forty-five per cent were not receiving treatment, and it could not be established whether the remaining 30% were receiving treatment for depression, either because prescription charts were not available (14 participants) or because the participant failed to answer the question regarding counselling and psychiatric referral (729 participants).

## Discussion

This study described the clinical profile, disease control, multimorbidity and treatment received by patients with the target conditions attending PHC clinics in two districts in SA. The results indicated poor disease control, high levels of multimorbidity and unmet treatment needs in the public sector in these districts.

These findings confirm previous reports of poor control and treatment of NCDs, and demonstrate little improvement in NCD control since these earlier studies were conducted. A study of 1 089 patients in 18 community health centres in 1999 demonstrated poor levels of control of hypertension and diabetes in community health centres in the Cape Peninsula, with 67% of hypertensive patients recording a BP ≥140/90 mmHg and a mean HbA1c of 8.8% in diabetic patients.[4] A study of goldminers in Gauteng Province, SA, in 2009/2010 found that only 42% of patients diagnosed with hypertension received antihypertensive medication, while 69% of patients on antihypertensive medication were poorly controlled.[12] The South African Stress and Health Study, a community survey of 4 351 adult South Africans between 2002 and 2004, found that only one-quarter of patients with depression, anxiety and substance use disorders received treatment.[6] Comorbidity of hypertension and diabetes was found to be high in a cross-sectional study in Cape Town townships in 2008/2009, with 21% of participants with hypertension also having diabetes, compared with 7% of non-hypertensive patients having diabetes.[9] The cross-sectional study in the Cape Peninsula in 1999 found 31% of participants with hypertension to have diabetes and 64% of participants with diabetes to have hypertension.[4] A more recent survey of SA PHC found that 18% of patients with

**Table 3. Treatment, diabetes group**

| Medications prescribed | All participants (*N*=1 842) *n* (%) | Subgroup with HbA1c test (*N*=704) *n* (%) | Controlled* (*N*=160) *n* (%) | Uncontrolled† (*N*=544) *n* (%) |
|---|---|---|---|---|
| Hypoglycaemic medications | | | | |
| No diabetes medications | 119 (6.5) | 33 (4.7) | 23 (69.7) | 10 (30.3) |
| Metformin and/or sulfonylurea (but not insulin) | 1 126 (61.1) | 438 (62.2) | 112 (25.6) | 326 (74.4) |
| Insulin (with/without oral agents) | 588 (31.9) | 230 (32.7) | 25 (10.9) | 205 (89.1) |
| Missing information | 9 (0.5) | | | |
| Aspirin | 1 155 (62.7) | 477 (67.8) | 101 (21.2) | 376 (78.8) |
| Statin | 931 (50.5) | 407 (57.8) | 82 (20.1) | 325 (79.9) |
| ACE inhibitor | 1 215 (66.0) | 475 (67.5) | 108 (22.7) | 367 (77.3) |

ACE = angiotensin-converting enzyme.
*HbA1c <7%.
†HbA1c ≥7%.

**Table 4. Treatment, chronic respiratory disease group**

| Medications prescribed | All participants (*N*=1 157) *n* (%) | SGRQ symptom domain score Median (IQR) | SGRQ activity domain score Median (IQR) |
|---|---|---|---|
| No chronic respiratory disease medications | 567 (49.0) | 52.6 (29.8 - 68.5) | 67.2 (47.7 - 85.8) |
| Selective $\beta_2$-agonist | 558 (48.2) | 64.6 (44.9 - 78.9) | 79.8 (59.5 - 92.5) |
| Inhaled corticosteroids (any dose) | 388 (33.5) | 64.6 (42.8 - 79.3) | 80.3 (60.3 - 92.5) |
| Inhaled corticosteroid (≥800 µg/d) | 346 (29.9) | 64.9 (41.8 - 80.2) | 80.4 (60.3 - 92.5) |
| Theophylline | 121 (10.5) | 70.4 (51.8 - 83.0) | 79.8 (60.4 - 92.5) |
| Ipratropium bromide | 91 (7.9) | 69.7 (52.2 - 81.6) | 85.8 (60.4 - 93.2) |

**Table 5. Treatment, depression group**

| Medications prescribed or other management | All participants (*N*=2 466) *n* (%) | CESD-10 score Median (IQR) |
|---|---|---|
| Antidepressant medications | | |
| No antidepressant medications | 1 902 (77.1) | 14 (12 - 17) |
| Antidepressant at therapeutic dose | 294 (11.9) | 19 (14 - 22) |
| Antidepressant at subtherapeutic dose | 250 (10.1) | 15 (12 - 19) |
| Missing information | 20 (0.8) | |
| Received counselling in past year | 402 (16.3) | 15 (12 - 20) |
| Psychiatric referral in past year | 175 (7.1) | 17 (13 - 21) |
| Antidepressant at therapeutic dose or counselling in past year or psychiatric referral in past year | 614 (24.9) | 16 (12 - 20) |

hypertension also had diabetes, and 63% of patients with diabetes also had hypertension.[3] Our study demonstrated higher levels of comorbidity than these studies, with 47% of participants with hypertension also having diabetes, and 84% of participants with diabetes also having hypertension. A study of urban SA women demonstrated high rates of comorbid psychological distress with physical disease,[13] consistent with our finding of 51% of participants with hypertension, diabetes or chronic respiratory disease also having symptoms of depression. However, the high rates of multimorbidity in our study, particularly in the reporting of diabetes in the hypertension group, may partly be due to the sampling strategy, as explained in 'Study limitations' below.

## Study limitations and strengths

This study had several limitations. It did not consider other potential comorbid conditions such as osteoarthritis which are likely in such patient populations, so multimorbidity and comorbidity were probably underestimated. The study was not intended to provide estimates of the prevalence of NCDs or depression symptoms, but its inclusion criteria may have influenced the interpretation of results. Because the inclusion criteria for each condition involved self-reporting, there was misclassification; some participants' reported diseases were not confirmed, while others were found to be receiving medications for a disease that they had not reported. For example, of 1 166 participants not enrolled in the hypertension group (denying receiving medication for this diagnosis), 13% had received a prescription for antihypertensive medication and 30% had a BP ≥140/90 mmHg. Further, of 3 227 participants who reported being on medication for hypertension, 5% had no evidence of a prescription for hypertension. The inclusion criterion for the diabetes group was self-reported diabetes medication. Patients with diabetes on dietary control alone were therefore not included in the study. The study's chronic respiratory disease definition was probably more inclusive than usual clinical practice and so may have overestimated disease prevalence. Spirometry was not used to diagnose respiratory disease. We did not distinguish between asthma, chronic obstructive pulmonary disease or other symptomatic chronic lung diseases, and severity was not assessed by lung function tests. For these reasons, the appropriateness of treatments prescribed could not be assessed for individual participants. The study's definition of possible depression indicates, but does not confirm, clinical depression. In addition, the percentage receiving counselling or referral is an

underestimate owing to an error resulting in this question not being administered to all participants. Finally, the sampling strategy may have led to over-representation of reported comorbidities. For the randomised controlled trial we estimated that 60 patients were needed per clinic for each disease group except for the respiratory group, which required 27 patients per clinic. Owing to the high prevalence of hypertension in this clinic population, targets were easily met for the hypertension group, although it was more difficult to do the same for the diabetes group. Fieldworkers were asked to continue recruitment until targets were met for all four groups, with the result that targets were exceeded for all groups except diabetes, where recruitment fell short (81% of target). Since the majority of patients with diabetes also had hypertension, extended recruitment of this group may have led to an over-representation of the proportion of those with hypertension who also had diabetes.

The study had a number of strengths. The sample size was large, data were collected for four disease groups, and prescription data were collected for 99% of participants. There are few other recent studies addressing multimorbidity, control and treatment of NCDs in public sector PHC clinics in SA.

## Conclusion

The rising prevalence of NCDs is a major challenge facing healthcare systems worldwide, with multimorbidity becoming the norm for people with chronic diseases. Despite this, health systems tend to be configured for individual diseases.[14] The high levels of multimorbidity demonstrated in this study stress the need for PHC services to provide better-integrated NCD care. Clinicians need to consider potential coexistence of, and interactions between, diseases. Training of clinicians to manage multimorbidity is essential, and should address both appropriateness of prescribing and adherence to medication. Management of NCDs and multimorbidity need to be addressed at a health systems level and factored into clinical training. The Integrated Chronic Disease Management[15] and Primary Care 101[16] programmes are important current initiatives aimed at integrating chronic disease care and addressing multimorbidity. After a decade of focusing on scaling up antiretroviral therapy programmes, management of NCDs in PHC needs to be prioritised and requires similar investment in order to improve outcomes and limit the impact on morbidity and mortality. With limited time and resources in the PHC setting, careful consideration of how to prioritise care is required.

Understanding the causes of poor NCD control will assist in prioritising care and resources. Further research is required into the development and evaluation of interventions to address the burden and unmet treatment needs of NCDs, including mental health.

**Funding.** This project has been funded in part with Federal funds by the United States National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN268200900030C. Funding was also received from United Health, USA; the Department of Health of the Provincial Government of the Western Cape; the Department of Medicine, University of Cape Town; the UK Department for International Development; and the University of Cape Town Lung Institute. The study sponsors did not contribute to the design of the study, to the collection, analysis and interpretation of data, or to the writing of this article or the decision to submit it for publication. The researchers were independent from funders and sponsors, and researchers involved in the collection, analysis and interpretation of the data had access to all the data.

**Acknowledgements.** The authors thank all clinic nurses, doctors, managers, pharmacists and pharmacy assistants at participating study facilities; the Department of Health of the Provincial Government of the Western Cape; the Eden and Overberg district management; Primary Care 101 trainers and fieldworkers; and the National Health Laboratory Service.

**References**

1. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet 2009;374(9693):934-947. [http://dx.doi.org/10.1016/S0140-6736(09)61087-4]
2. Mash B, Fairall L, Adejayan O, et al. A morbidity survey of South African primary care. PLoS One 2012;7(3):e32358. [http://dx.doi.org/10.1371/journal.pone.0032358]
3. Lalkhen H, Mash R. Comorbidity and multimorbidity in non-communicable diseases in South African primary healthcare. S Afr Med J 2015;105(2):134-138. [http://dx.doi.org/10.7196/SAMJ.8696]
4. Steyn K, Levitt NS, Patel M, et al. Hypertension and diabetes: Poor care for patients at community health centres. S Afr Med J 2008;98(8):618-622.
5. Poyser MA, Nelson H, Ehrlich RI, et al. Socioeconomic deprivation and asthma prevalence and severity in young adolescents. Eur Respir J 2002;19(5):892-898. [http://dx.doi.org/10.1183/09031936.02.00238402]
6. Williams DR, Herman A, Stein DJ, et al. Twelve-month mental disorders in South Africa: Prevalence, service use and demographic correlates in the population-based South African Stress and Health Study. Psychol Med 2008;38(2):211-220. [http://dx.doi.org/10.1017/S0033291707001420]
7. English RG, Bateman ED, Zwarenstein MF, et al. Development of a South African Integrated Syndromic Respiratory Disease Guideline for Primary Care. Prim Care Respir J 2008;17(3):156-163. [http://dx.doi.org/10.3132/pcrj.2008.00044]
8. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med 1994;10(2):77-84.
9. Peer N, Steyn K, Lombard C, Gwebushe N, Levitt N. A high burden of hypertension in the urban black population of Cape Town: The Cardiovascular Risk in Black South Africans (CRIBSA) Study. PLoS One 2013;8(11):e78567 [http://dx.doi.org/10.1371/journal.pone.0078567]
10. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991;85(Suppl B):25-31. [http://dx.doi.org/10.1016/S0954-6111(06)80166-6]
11. Executive Summary: Standards of Medical Care in Diabetes – 2013. Diabetes Care 2013;36(Suppl 1):S4-S10. [http://dx.doi.org/10.2337/dc13-S004]
12. Maepe LM, Outhoff K. Hypertension in goldminers. S Afr Med J 2012;102(1):30-33.
13. Mendenhall E, Richter LM, Stein A, Norris SA. Psychological and physical co-morbidity among urban South African women. PLoS One 2013;8(10):e78803. [http://dx.doi.org/10.1371/journal.pone.0078803]
14. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. Lancet 2012;380(9836):37-43. [http://dx.doi.org/10.1016/S0140-6736(12)60240-2]
15. Department of Health, Republic of South Africa. Department of Health Annual Report 2011/2012. http://www.health.gov.za/ (accessed 27 June 2014).
16. Department of Health, Republic of South Africa. Primary Care 101. http://www.health.gov.za/docs/Policies/2013/Low_res_PC_101_Guideline_v2.pdf (accessed 4 November 2014).

*Accepted 15 June 2015.*

## 3.2 Socioeconomic and modifiable predictors of blood pressure control for hypertension in primary care attenders in the Western Cape, South Africa

### Paper overview

The aim of this study was to investigate the extent to which indicators of socioeconomic position, and characteristics of primary health care facilities, predict blood pressure control at baseline and follow-up, and treatment intensification at follow-up in patients with uncontrolled blood pressure at baseline.

Blood pressure control at baseline was more likely in participants with more education and who chose to complete the interview in English compared to Afrikaans. Treatment intensification was more likely in participants with higher blood pressure at baseline, concurrent diabetes, more education, and in participants who attended more resourced clinics offering community-based medication supply, with a doctor every day, or with more nurses.

### Contribution to the thesis and novelty

This study addresses the second aim of the thesis. The majority of studies in the field of hypertension in South Africa are community-based surveys (e.g. the first Demographic and Health Survey (DHS) from 1998 and the first wave of the National Income Dynamics Study (NIDS) from 2008) (Steyn et al. 2001) (Cois and Ehrlich 2014) and/or prevalence studies (Steyn et al. 2001) (Maepe and Outhoff 2012).

Few studies address determinants of hypertension control and treatment in patients attending primary care services, and modifiable factors associated with improved control, as we have done. One study that examined quality of care for patients attending primary care clinics was performed 12 years earlier than ours (in 1999). Steyn et al investigated health care provider-related determinants of diabetes and hypertension management in patients attending community health centres (CHCs) in the Cape Peninsula (Steyn et al. 2008). They reported that poor blood pressure control was associated with older age, male gender and higher blood pressure at a previous visit. Further, they reported that patients receiving a disability grant had better blood pressure control than those who were employed. The authors concluded that primary care for patients with hypertension and diabetes at public sector CHCs was suboptimal, and stressed the need to improve health care for patients with these conditions. This data is now outdated for informing current policies, and did not address clinic factors associated with blood pressure control or predictors of treatment for hypertension.

Paper 2 provides important and useful new insights into the care of patients with hypertension in primary care facilities in South Africa, and potentially modifiable factors that could improve the situation. It suggests that even seemingly small changes in health facilities, for example, the number of nurses per clinic, the extent of doctor support, and availability of community-based medication supply could improve the hypertension control.

## Role of the candidate

I oversaw data collection for the study and was responsible for data management, including cleaning the data and preparing it for analysis. I carried out the analyses, supported by Professor Max Bachmann. I drafted the manuscript, incorporating input from co-authors and was responsible for finalising and submitting the final version of the manuscript for publication.

## Role of the co-authors

LF, MB, EB, KS and NL conceptualised the paper with NF and assisted with the original draft. MB and CLom provided support with the analyses. VT was the data architect. All authors reviewed the manuscript and approved it for submission.

## Publication status

Published in the South African Medical Journal 2016.

*Folb N, Bachmann MO, Bateman ED, Steyn K, Levitt NS, Timmerman V, et al. Socioeconomic and modifiable predictors of blood pressure control for hypertension in primary care attenders in the Western Cape, South Africa. S Afr Med J. 2016;106(12):1241-1246.DOI:10.7196/SAMJ.2016.v106i12.12005.*

# Socioeconomic and modifiable predictors of blood pressure control for hypertension in primary care attenders in the Western Cape, South Africa

**N Folb**,[1,2,3] MB ChB, MRCGP (UK); **M O Bachmann**,[4] MB ChB, PhD, FFPH (UK); **E D Bateman**,[1,2,3] MB ChB, MD, FRCP (UK); **K Steyn**,[2,3] MSc, NED, MD; **N S Levitt**,[2,3] MB ChB, MD, FCP (SA); **V Timmerman**,[1] PhD; **C Lombard**,[5] MSc, PhD; **T A Gaziano**,[3,6] MD, MSc; **L R Fairall**,[1,2,3] MB ChB, PhD

[1] *University of Cape Town Lung Institute, Groote Schuur Hospital, Cape Town, South Africa*
[2] *Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[3] *Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[4] *Department of Population Health and Primary Care, Norwich Medical School, Faculty of Medicine and Health, University of East Anglia, UK*
[5] *Biostatistics Unit, South African Medical Research Council, Cape Town, and School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[6] *Division of Cardiovascular Medicine, Brigham & Women's Hospital, Boston, Mass., USA*

***Corresponding author:*** *N Folb (naomi.folb@uct.ac.za)*

**Background.** Low socioeconomic status is associated with the risk of hypertension. There are few reports of the effect of socioeconomic and potentially modifiable factors on the control of hypertension in South Africa (SA).
**Objectives.** To investigate associations between patients' socioeconomic status and characteristics of primary healthcare facilities, and control and treatment of blood pressure in hypertensive patients.
**Methods.** We enrolled hypertensive patients attending 38 public sector primary care clinics in the Western Cape, SA, in 2011, and followed them up 14 months later as part of a randomised controlled trial. Blood pressure was measured and prescriptions for antihypertension medications were recorded at baseline and follow-up. Logistic regression models assessed associations between patients' socioeconomic status, characteristics of primary healthcare facilities, and control and treatment of blood pressure.
**Results.** Blood pressure was uncontrolled in 60% (1 917/3 220) of patients at baseline, which was less likely in patients with a higher level of education ($p$=0.001) and in English compared with Afrikaans respondents ($p$=0.033). Treatment was intensified in 48% (892/1 872) of patients with uncontrolled blood pressure at baseline, which was more likely in patients with higher blood pressure at baseline ($p$<0.001), concurrent diabetes ($p$=0.013), more education ($p$=0.020), and those who attended clinics offering off-site drug supply ($p$=0.009), with a doctor every day ($p$=0.004), or with more nurses ($p$<0.001).
**Conclusion.** Patient and clinic factors influence blood pressure control and treatment in primary care clinics in SA. Potential modifiable factors include ensuring effective communication of health messages, providing convenient access to medications, and addressing staff shortages in primary care clinics.

*S Afr Med J* 2016;106(12):1241-1246. DOI:10.7196/SAMJ.2016.v106i12.12005

High blood pressure is a leading cause of mortality and disability worldwide.[1] In South Africa (SA), the prevalence of hypertension is estimated to be 21% in people aged ≥15 years,[2] and in a survey performed in public sector clinics in four provinces, hypertension was the most common diagnosis and reason for attendance.[3] Several reports point to poor levels of blood pressure control and low levels of treatment.[4-6]

The burden of ill-health and of chronic diseases such as hypertension is strongly influenced by socioeconomic status.[7-9] Few publications have considered the impact of socioeconomic status on control of blood pressure and potentially modifiable factors associated with better blood pressure control in SA.

We studied a cohort of primary care clinic attenders with hypertension, recruited as part of a randomised controlled trial. The objective of this study was to investigate the extent to which patient-related and socioeconomic factors, and characteristics of primary healthcare facilities, were associated with blood pressure control and with intensified hypertension treatment in patients with uncontrolled blood pressure.

## Methods

### Study population

The study population comprised adults ≥18 years of age residing in the Eden District and two sub-districts in the Overberg, Western Cape, SA, who were participating in a pragmatic cluster randomised controlled trial to evaluate the effectiveness of a training programme for primary healthcare providers in the use of the Primary Care 101 (PC101) patient management tool.[10,11] The study focused on improving the quality of care for four specified chronic diseases. The study population for this article was confined to patients who reported current use of a medication for hypertension, in both the intervention and control arms.

Patients were recruited from the largest 38 public sector primary care clinics in the Eden District and two Overberg sub-districts, each of which report more than 10 000 client visits per year. Services in these clinics are nurse led, with varying levels of doctor involvement (often part-time). The communities served by these clinics are characterised by high levels of unemployment and socioeconomic deprivation, typical of many rural and small urban areas in SA.

Patients who reported current use of a medication for hypertension were eligible for inclusion if they were likely to reside in the same health district for the duration of the study and were capable of engaging in an interviewer-administered questionnaire in their preferred language (English, Afrikaans or isiXhosa). Participants were recruited in clinic waiting rooms and, if eligible, provided informed consent prior to study procedures. Their blood pressure was measured and prescription data were collected at baseline (in 2011) and 14 months later.[11]

### Data collection

At baseline, trained fieldworkers administered an electronic questionnaire and took clinical measurements. The baseline questionnaire covered demographic characteristics, level of education, employment status, income during the last month, language, and presence of comorbidities.

Fieldworkers photocopied all available prescription charts for the year preceding the interview. These were reviewed by a medically qualified researcher (NF) to identify hypertension medications prescribed at baseline.

Blood pressure was measured with the patient in the seated position after at least 5 minutes' rest, using a calibrated automatic monitor, the Omron M6 Comfort (OMRON Healthcare, The Netherlands). The second and third of three readings were averaged and recorded.[12]

Follow-up assessment involved completion of a questionnaire, clinical measurements and collection of prescription data in a similar manner to assessment at baseline. Baseline data were collected from March to November 2011 and follow-up data from May to December 2012.

Uncontrolled blood pressure was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. The assessment of treatment intensification for hypertension was based on treatment steps in the PC101 clinical management tool, which conformed to prescribing policies of the relevant health authorities, an approach used in previous reported studies employing treatment intensification as an outcome measure.[10,13,14] Treatment intensification was defined as: (*i*) an increase in dose of an antihypertensive; or (*ii*) a switch to an antihypertensive in another medication class; or (*iii*) the addition of an antihypertensive in the same or different class; or (*iv*) a switch of an antihypertensive within a class but at a higher dose; or (*v*) the addition of aspirin; or (*vi*) the addition of or increase in statin dose.

### Statistical methods

The statistical analyses investigated associations between participants' health and socioeconomic indicators, their blood pressure control, characteristics of their clinics, and intensification of hypertension treatment during the study.

Differences in the characteristics of patients with and without blood pressure control at baseline, and of their clinics, were first tested with logistic regression models, with control as outcome, each characteristic as the explanatory variable, and a separate model for each characteristic. The patient and clinic characteristics included in these models are shown in Table 1.

Independent predictors of uncontrolled blood pressure at baseline and at follow-up were investigated with multiple logistic regression models, first including all potential predictors as covariates, and then retaining only those covariates that were independent predictors at the 5% significance level. Models to identify predictors of change in hypertension control between baseline and follow-up used analysis of covariance (ANCOVA), with control at follow-up as outcome and control at baseline as a covariate. This was done to account for regression to the mean.

Analyses identifying predictors of treatment intensification among patients with uncontrolled blood pressure at baseline included the same patient and clinic characteristics used in the blood pressure control models, and also baseline blood pressure level. We report on the full model, including all characteristics as covariates, and a restricted model, including only covariates that were independent predictors at the 5% significance level. These analyses were repeated in all patients, including those with controlled blood pressure at baseline.

In all analyses the study's cluster sampling design was accounted for in regression models with robust adjustment for intraclinic cluster correlation of outcomes, using Stata version 13.0 (StataCorp LP, USA) statistical software. The *p*-values for education were estimated by modelling education as a continuous variable, with values of 0, 1, 2 and 3 indicating higher levels of education. A *p*-value ≤0.05 was considered statistically significant. The intervention v. the control arm of the randomised controlled trial was included as a covariate in all longitudinal analyses to account for the study design.

The trial was registered with Current Controlled Trials (ISRCTN 20283604). Ethical approval for the trial was obtained from the University of Cape Town Human Research Ethics Committee (HREC 119/2010) and the Western Cape Provincial Department of Health. All participants provided written informed consent to participate in the study.

## Results

A total of 3 220 participants with hypertension and baseline blood pressure readings were enrolled in the study, of whom 91% were interviewed at follow-up. Prescription data were available for 3 197 (99%) participants at baseline and for 3 137 (97%) at follow-up.

The sociodemographic characteristics of patient and clinic participants at baseline, and the difference between patients with and without blood pressure control at baseline, are reported in Table 1. The majority of participants (75%) were women and half were aged ≥50 years. The majority of participants had not completed secondary school education (56%), were unemployed (77%) and were receiving a welfare grant (61%). The average monthly income of participants, of whom 23% reported having no income, was ZAR1 105 (USD160).

Sixty per cent (1 917) of participants had uncontrolled blood pressure at baseline. Table 1 shows that at baseline a higher level of formal education was associated with blood pressure control ($p$=0.001), and participants with controlled blood pressure were more likely to have secondary or tertiary education (47% of patients with controlled v. 42% with uncontrolled blood pressure). Participants with controlled blood pressure were more likely to attend larger clinics ($p$=0.033) or clinics with a larger complement of nurses ($p$=0.037).

Logistic regression analyses identified independent associations between health and socioeconomic indicators and blood pressure control (Table 2). At baseline, a higher level of education, and English v. Afrikaans language, were associated with lower odds of uncontrolled blood pressure. There was no interaction between education and language ($p$=0.76) when an interaction term was added to the model. At follow-up, patients with higher incomes had lower odds of uncontrolled blood pressure in the full model with all covariates. In the restricted model, from which all other covariates except baseline control and the trial arm were removed, this association became non-significant ($p$=0.086). No clinic-related

**Table 1. Participants' baseline characteristics**

| Characteristics | Patients (*N*=3 220), *n* (%) | BP controlled* at baseline (*N*=1 303), *n* (%) | BP uncontrolled† at baseline (*N*=1 917), *n* (%) | *p*-value‡ |
|---|---|---|---|---|
| Participant characteristics | | | | |
| Age (years): mean (SD)§ | 54.81 (12.0) | 54.36 (12.5) | 55.11 (11.7) | 0.092 |
| Sex | | | | 0.546 |
| Female | 2 419 (75.1) | 986 (75.7) | 1 433 (74.8) | |
| Male | 801 (24.9) | 317 (24.3) | 484 (25.2) | |
| Diabetes | 1 538 (47.8) | 647 (49.7) | 891 (46.5) | 0.162 |
| Known cardiovascular disease¶ | 848 (26.3) | 347 (26.6) | 501 (26.1) | 0.698 |
| Language | | | | 0.054 |
| Afrikaans | 2 732 (84.8) | 1 095 (84.0) | 637 (85.4) | |
| isiXhosa | 220 (6.8) | 79 (6.1) | 141 (7.4) | |
| English | 268 (8.3) | 129 (9.9) | 139 (7.3) | |
| Highest education | *n*=2 938 | *n*=1 184 | *n*=1 754 | 0.001 |
| None | 242 (8.2) | 86 (7.3) | 156 (8.9) | |
| Primary | 1 397 (47.5) | 538 (45.4) | 589 (49.0) | |
| Secondary | 1 244 (42.3) | 526 (44.4) | 718 (40.9) | |
| Tertiary | 55 (1.87) | 34 (2.9) | 21 (1.2) | |
| Total monthly income (ZAR): mean (SD)§ | 1 104.9 (1 120.0) (*n*=3 215) | 1 142.5 (1 226.1) (*n*=1 301) | 1 079.3 (1 041.2) (*n*=1 914) | 0.125 |
| Unemployed | 2 472 (76.9) (*n*=3 215) | 1 002 (77.0) (*n*=1 301) | 1 470 (76.8) (*n*=1 914) | 0.865 |
| Welfare grant received | 1 967 (61.2) (*n*=3 215) | 808 (62.1) (*n*=1 301) | 1 159 (60.6) (*n*=1 914) | 0.382 |
| Clinic characteristics | | | | |
| Pharmacist in clinic | 1 487 (46.2) | 622 (47.7) | 865 (45.1) | 0.456 |
| Drug supply available away from clinic | 2 124 (66.0) | 840 (64.5) | 1 284 (67.0) | 0.437 |
| Doctor at clinic every day | 1 333 (41.4) | 562 (43.1) | 771 (40.2) | 0.405 |
| Clinic location | | | | 0.951 |
| Urban | 1 977 (61.4) | 804 (61.7) | 1 173 (61.2) | |
| Peri-urban | 511 (15.9) | 202 (15.5) | 309 (16.1) | |
| Rural | 732 (22.7) | 297 (22.8) | 435 (22.7) | |
| Clinic patients/year/1 0000: mean (SD)§ | 3.7 (3.7) | 3.9 (3.9) | 3.6 (3.5) | 0.033 |
| Clinic nurses: mean (SD)§ | 5.4 (2.9) | 5.6 (2.9) | 5.2 (2.9) | 0.037 |
| Clinic nurses (*n*) | | | | 0.051 |
| <5 | 1 564 (48.6) | 581 (44.6) | 983 (51.3) | |
| ≥5 | 1 656 (51.4) | 722 (55.4) | 934 (48.7) | |
| Intervention v. control clinic | | | | 0.234 |
| Intervention | 1 553 (48.2) | 660 (50.7) | 893 (6.6) | |
| Control | 1 667 (51.8) | 643 (49.4) | 1 024 (53.4) | |

HPT = hypertension; BP = blood pressure; SD = standard deviation; CVD = cardiovascular disease.
* Controlled: systolic BP <140 mmHg and diastolic BP <90 mmHg.
† Uncontrolled: systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg.
‡ *p*-values from logistic regression models adjusted for intraclinic correlation of outcome.
§ Mean and SD for continuous variables.
¶ History of angina, heart attack or stroke.

factors were independently associated with blood pressure control at baseline or at follow-up.

Hypertension treatment was intensified in 48% of 1 872 patients in whom blood pressure was uncontrolled at baseline. In participants whose blood pressure was uncontrolled at baseline, treatment intensification was independently more probable in those who had a higher mean systolic blood pressure at baseline ($p<0.001$), diabetes ($p=0.013$), a higher level of education ($p=0.020$), and attended a clinic with the option of off-site drug supply ($p=0.009$), with a doctor present daily ($p=0.004$), with a larger number of nurses ($p<0.001$) or in the intervention arm of the trial ($p<0.001$) (Table 3). There was no interaction between education and language ($p=0.92$) when an interaction term was added to the model. When all patients, including those with controlled blood pressure at baseline, were included in the analysis, the association with number of clinic nurses remained significant.

## Discussion

This study, performed in a cohort of hypertensive low-income patients with generally low levels of formal education attending public sector

**Table 2. Predictors of uncontrolled blood pressure in participants with hypertension at baseline**

| Outcome | Uncontrolled* BP at baseline: full model (*N*=3 220) | | | Uncontrolled BP* at baseline: limited model (*N*=3 220) | | | Uncontrolled BP* at follow-up: full model (*N*=3 220) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Explanatory baseline variable** | **OR** | **95% CI** | ***p*-value** | **OR** | **95% CI** | ***p*-value** | **OR** | **95% CI** | ***p*-value** |
| Age (per year) | 1.01 | 1.00 - 1.01 | 0.170 | | | | 1.00 | 0.99 - 1.01 | 0.469 |
| Male v. female | 1.08 | 0.90 - 1.30 | 0.412 | | | | 1.11 | 0.95 - 1.29 | 0.178 |
| Uncontrolled blood pressure* | | | | | | | 3.88 | 3.30 -4.56 | <0.001 |
| Diabetes | 0.93 | 0.76 - 1.14 | 0.508 | | | | 1.04 | 0.88 - 1.22 | 0.654 |
| Known cardiovascular disease | 0.98 | 0.84 - 1.13 | 0.758 | | | | 1.05 | 0.86 - 1.28 | 0.616 |
| Language | | | 0.008† | | | 0.033† | | | 0.794† |
| Afrikaans (reference) | 1.00 | | | 1.00 | | | 1.00 | | |
| isiXhosa | 1.38 | 0.99 - 1.94 | 0.057 | 1.11 | 0.86 - 1.44 | 0.432 | 1.10 | 0.76 - 1.59 | 0.623 |
| English | 0.78 | 0.55 - 1.09 | 0.145 | 0.74 | 0.57 - 0.96 | 0.026 | 0.93 | 0.60 - 1.42 | 0.724 |
| Highest education | | | 0.002‡ | | | 0.001‡ | | | 0.822‡ |
| None (reference) | 1.00 | | | 1.00 | | | 1.00 | | |
| Primary | 0.89 | 0.67 - 1.19 | 0.439 | 0.88 | 0.68 - 1.16 | 0.367 | 1.17 | 0.87 - 1.57 | 0.294 |
| Secondary | 0.77 | 0.57 - 1.03 | 0.081 | 0.76 | 0.58 - 0.99 | 0.042 | 1.08 | 0.80 - 1.46 | 0.623 |
| Tertiary | 0.33 | 0.17 - 0.65 | 0.001 | 0.35 | 0.18 - 0.68 | 0.002 | 1.04 | 0.56 - 1.92 | 0.905 |
| Total monthly income (ZAR) | 0.97 | 0.88 - 1.06 | 0.441 | | | | 0.90 | 0.82 - 0.99 | 0.027 |
| Unemployed v. employed | 0.92 | 0.74 - 1.12 | 0.368 | | | | 0.82 | 0.64 - 1.06 | 0.128 |
| Welfare grant received | 0.91 | 0.75 - 1.12 | 0.382 | | | | 0.99 | 0.80 - 1.23 | 0.962 |
| Pharmacist in clinic | 1.01 | 0.70 - 1.46 | 0.944 | | | | 1.00 | 0.76 - 1.33 | 0.985 |
| Drug supply available away from clinic | 1.19 | 0.86 - 1.66 | 0.297 | | | | 0.80 | 0.57 - 1.13 | 0.206 |
| Doctor at clinic every day | 1.10 | 0.80 - 1.52 | 0.541 | | | | 0.99 | 0.68 - 1.45 | 0.978 |
| Clinic location | | | 0.760† | | | | | | 0.623† |
| Urban (reference) | 1.00 | | | | | | 1.00 | | |
| Peri-urban | 1.02 | 0.74 - 1.42 | 0.900 | | | | 0.84 | 0.57 - 1.22 | 0.357 |
| Rural | 0.87 | 0.56 - 1.34 | 0.528 | | | | 0.97 | 0.65 - 1.45 | 0.868 |
| Clinic patients/year/1 000 | 1.03 | 0.98 - 1.08 | 0.235 | | | | 1.00 | 0.94 - 1.06 | 0.992 |
| Clinic nurses (*n*) | 0.93 | 0.87 - 1.01 | 0.079 | | | | 0.98 | 0.89 - 1.07 | 0.594 |
| Intervention v. control clinic | | | | | | | 1.06 | 0.76 -1.48 | 0.748 |

OR = odds ratio; CI = confidence interval.
*Uncontrolled BP: systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg.
†Wald test for all categories of variable.
‡Test for trend.

primary care clinics, confirms both patient and clinic-related factors that are associated, first, with the likelihood of blood pressure control (patient factors), and secondly, treatment intensification during the study period (patient and clinic-related factors). The importance of these findings is that some of these predictors may be modifiable, and should be considered in the planning of chronic disease control strategies and in the organisation of clinical services.

Patient factors associated with uncontrolled blood pressure at baseline included lower levels of education and communication in either isiXhosa or Afrikaans, rather than English. These associations need to be interpreted with caution for several reasons. First, while statistically significant, the absolute differences in blood pressure control associated with these risk factors were relatively small, reflecting the large sample size. Secondly, the association with patients' choice of language may have been influenced by issues relating to the conduct of the trial. Communication might have been poor, as not all interviewers were fluent in isiXhosa. Furthermore, language selection might serve as a proxy for factors not measured in this study, such as household conditions, informal education, and less prior exposure to health messages in patients' language of choice. Health literacy has complex associations, extending beyond formal education, and is rooted in the conditions under which patients live and the support they receive to accept and adhere to health advice. Murphy *et al.*,[15] in a qualitative study of hypertensive and diabetic patients attending three public sector community health centres in Cape Town, concluded that patients experienced 'multiple impediments to effective self-management and behaviour change, including poor health literacy, a lack of self-efficacy and perceived social support'. Although the introduction of PC101 seeks to address some of these needs, the results at baseline in our study are consistent with this assessment.

Perhaps more relevant are the features associated with treatment intensification, as the latter is likely to result in improved health outcomes in patients with hypertension. Again, in our study, a lower level of formal education was associated with a lower probability of treatment intensification. This finding might reflect

**Table 3. Predictors of treatment intensification in participants with uncontrolled blood pressure at baseline**

| Outcome | Treatment intensification of HPT if uncontrolled BP at baseline:* full model† (*N*=1 872) | | | Treatment intensification of HPT if uncontrolled BP at baseline:* limited model† (*N*=1 872) | | |
|---|---|---|---|---|---|---|
| **Explanatory baseline variable** | **OR** | **95% CI** | ***p*-value** | **OR** | **95% CI** | ***p*-value** |
| Patient characteristics | | | | | | |
| Age (per year) | 1.00 | 0.98 - 1.01 | 0.391 | | | |
| Male v. female | 0.94 | 0.74 - 1.21 | 0.650 | | | |
| Mean systolic BP | 1.01 | 1.01 - 1.02 | <0.001 | 1.01 | 1.01 - 1.02 | <0.001 |
| Diabetes | 1.30 | 1.05 - 1.62 | 0.018 | 1.31 | 1.06 - 1.62 | 0.013 |
| Known cardiovascular disease | 0.97 | 0.74 - 1.28 | 0.835 | | | |
| Language | | | 1.00‡ | | | |
| Afrikaans (reference) | 1.01 | | | | | |
| isiXhosa | 0.78 | 0.67 - 1.50 | 0.980 | | | |
| English | 1.01 | 0.70 - 1.47 | 0.946 | | | |
| Highest education | | | 0.040§ | | | 0.020§ |
| None (reference) | 1.00 | | | 1.00 | | |
| Primary | 1.50 | 0.98 - 2.27 | 0.059 | 1.45 | 0.97 - 2.17 | 0.072 |
| Secondary | 1.63 | 1.05 - 2.54 | 0.030 | 1.63 | 1.07 - 2.49 | 0.024 |
| Tertiary | 1.95 | 0.66 - 5.74 | 0.228 | 2.24 | 0.78 - 6.43 | 0.134 |
| Total monthly income | 1.04 | 0.91 - 1.18 | 0.565 | | | |
| Unemployed v. employed | 1.12 | 0.86 - 1.44 | 0.402 | | | |
| Welfare grant received | 0.91 | 0.70 - 1.19 | 0.500 | | | |
| Clinic characteristics | | | | | | |
| Pharmacist in clinic | 0.78 | 0.54 - 1.13 | 0.192 | | | |
| Drug supply available away from clinic | 1.40 | 1.06 - 1.86 | 0.018 | 1.44 | 1.10 - 1.89 | 0.009 |
| Doctor at clinic every day | 1.73 | 1.25 - 2.40 | 0.001 | 1.64 | 1.17 - 2.31 | 0.004 |
| Clinic location | | | 0.070‡ | | | |
| Urban (reference) | 1.00 | | | | | |
| Peri-urban | 1.05 | 0.74 - 1.48 | 0.779 | | | |
| Rural | 0.66 | 0.45 - 0.97 | 0.034 | | | |
| Clinic patients/year/1 000 | 0.95 | 0.89 - 1.01 | 0.089 | | | |
| Clinic nurses (*n*) | 1.22 | 1.10 - 1.34 | <0.001 | 1.15 | 1.08 - 1.23 | <0.001 |
| Intervention v. control clinic | 1.80 | 1.34 - 2.40 | <0.001 | 1.78 | 1.31 - 2.41 | <0.001 |

*Uncontrolled BP: systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg.
†Change modelled with ANCOVA, i.e. with baseline as covariate.
‡Wald test for all categories of variable.
§Test for trend.

the fact that effective communication and health literacy increase the likelihood of treatment changes – whether through increased willingness of clinicians to change treatment, or patients to accept it.[16] Of concern, and contrary to expectations, is that the known presence of cardiovascular disease was not associated with treatment intensification, suggesting that clinicians missed the opportunity to provide secondary prevention for cardiovascular events. However, higher blood pressure and comorbid diabetes did increase the likelihood of treatment intensification, which is clinically appropriate.

The finding that housing density, receipt of welfare grants and total monthly income did not predict blood pressure control or treatment intensification may reflect the relative homogeneity of the study population, the majority of whom were poor (mean monthly income ZAR1 100 and 98% earning less than ZAR5 000 per month) and 61% receiving welfare grants. It is also partly because these factors are associated with education and language, which were controlled for.

An increased risk of hypertension has previously been associated with low socioeconomic indicators, with associations particularly evident for level of education.[8] In SA, a higher level of education has been found to predict lower values of both diastolic and systolic blood pressure in women, while higher income predicted lower systolic blood pressure.[9] Interestingly, this did not hold true for men. Our study, which comprised predominantly women, adds new evidence for an association between low levels of education and poorer hypertension control and treatment intensification in SA.

The poor levels of blood pressure control in this study (60% of participants uncontrolled) are in keeping with previous studies. A 1999 survey in 18 community health centres in the Cape Peninsula, SA, found that 67% of hypertensive patients had uncontrolled blood pressure (>140/90 mmHg).[5] In a 2009 - 2010 study of goldminers in Gauteng Province, SA, only 42% of patients diagnosed with hypertension had received antihypertensive medication, and 69% of those on antihypertensive medication were poorly controlled.[6]

Our study has several strengths. The sample size was large, high rates of follow-up were achieved, and a range of socioeconomic variables were investigated. Furthermore, the longitudinal design enabled analysis of change in control and treatment. There were, however, several limitations. Patients were included in the hypertension group on the basis of self-reported use of medication for hypertension. On review of baseline prescription records, evidence of hypertension

treatment was not found in 5% (153) of participants. Secondly, no assessments of adherence were performed at baseline – clinicians who suspected significant non-adherence may have elected not to intensify treatment. A further potential limitation was language of communication, i.e. the possibility that interviewers might not have communicated effectively in the participant's language of choice. Finally, the homogeneity (limited range of socioeconomic status) of the population may have limited the assessment of the impact of individual determinants of blood pressure control.

In spite of these limitations, our findings have implications for clinicians and policymakers. Health services need to be sensitive to the impact of socioeconomic factors, and, in particular, lower levels of education. Emphasis must be placed on effective communication in the patient's language of choice, using educational materials and programmes prepared and presented in forms that are appropriate to their levels of education and health literacy. Secondly, our study points to clinic factors that may be addressed to improve the care of hypertensive patients. Besides attempting to improve staffing of clinics (preferably with doctors in attendance), this includes off-site access to maintenance medications. The latter finding is likely to be relevant to the care of all chronic diseases, and points to the need for expansion of drug delivery services in SA. Together, these measures should be viewed as achievable opportunities for improving the management of hypertension in primary care in SA.

**Acknowledgements.** The authors thank all clinic nurses, doctors, managers, pharmacists and pharmacy assistants at participating study facilities; the Western Cape Department of Health; the Eden and Overberg district management; and Primary Care 101 trainers and fieldworkers.

**Funding.** This project has been funded in part with federal funds, National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract no.: HHSN268200900030C), USA. Funding was also received from United Health, USA; the Western Cape Department of Health, SA; the Department of Medicine, University of Cape Town, SA; the UK Department for International Development; and the University of Cape Town Lung Institute, SA. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2224-2260. http://dx.doi.org/10.1016/S0140-6736(12)61766-8
2. Steyn K, Gaziano TA, Bradshaw D, Laubscher R, Fourie J. Hypertension in South African adults: Results from the Demographic and Health Survey, 1998. J Hypertens 2001;19(10):1717-1725. http://dx.doi.org/10.1097/00004872-200110000-00004
3. Mash B, Fairall L, Adejayan O, et al. A morbidity survey of South African primary care. PLoS ONE 2012;7(3):e32358. http://dx.doi.org/10.1371/journal.pone.0032358
4. Rayner B. Hypertension: Detection and management in South Africa. Nephron Clin Pract 2010;116(4):c269-c273. http://dx.doi.org/10.1159/000318788
5. Steyn K, Levitt NS, Patel M, et al. Hypertension and diabetes: Poor care for patients at community health centres. S Afr Med J 2008;98(8):618-622. http://dx.doi.org/10.1080/22201009.2008.10872172
6. Maepe LM, Outhoff K. Hypertension in goldminers. S Afr Med J 2012;102(1):30-33.
7. Ataguba JE, Akazili J, McIntyre D. Socioeconomic-related health inequality in South Africa: Evidence from general household surveys. Int J Equity Health 2011;10(1):48. http://dx.doi.org/10.1186/1475-9276-10-48
8. Leng B, Jin Y, Li G, Chen L, Jin N. Socioeconomic status and hypertension: A meta-analysis. J Hypertens 2015;33(2):221-229. http://dx.doi.org/10.1097/HJH.0000000000000428
9. Cois A, Ehrlich R. Analysing the socioeconomic determinants of hypertension in South Africa: A structural equation modelling approach. BMC Public Health 2014;14:414. http://dx.doi.org/10.1186/1471-2458-14-414
10. Health Systems Trust. Primary Health Care 101. 2013. http://www.hst.org.za/publications/primary-health-care-101 (accessed 27 July 2016).
11. Folb N, Timmerman V, Levitt NS, et al. Multimorbidity, control and treatment of noncommunicable diseases among primary healthcare attenders in the Western Cape. S Afr Med J 2015;105(8):642-664. http://dx.doi.org/10.7196/SAMJnew.7882
12. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) Health Tech/Blood Pressure Procedures Manual. 2009. http://www.cdc.gov/nchs/data/nhanes/nhanes_09_10/BP.pdf (accessed 30 May 2016).
13. Van Bruggen R, Gorter K, Stolk R, Klungel O, Rutten G. Clinical inertia in general practice: Widespread and related to the outcome of diabetes care. Fam Pract 2009;26(26):428-436. http://dx.doi.org/10.1093/fampra/cmp053
14. Schmittdiel JA, Uratsu CS, Karter AJ, et al. Why don't diabetes patients achieve recommended risk factor targets? Poor adherence versus lack of treatment intensification. J Gen Intern Med 2008;23(5):588-594.
15. Murphy K, Chuma T, Mathews C, Steyn K, Levitt N. A qualitative study of the experiences of care and motivation for effective self-management among diabetic and hypertensive patients attending public sector primary health care services in South Africa. BMC Health Serv Res 2015;15:303. http://dx.doi.org/10.1186/s12913-015-0969-y
16. Zolnierek KB, DiMatteo MR. Physician communication and patient adherence to treatment: A meta-analysis. Med Care 2009;47(8):826-634.

*Accepted 26 September 2016.*

## 3.3 Socioeconomic predictors and consequences of depression among primary care attenders with non-communicable diseases in the Western Cape, South Africa: cohort study within a randomised trial

### Paper overview

Mental disorders are an important but neglected cause of disease burden in South Africa. This paper investigates the extent to which socioeconomic position predicts depression symptoms over time, and the extent to which socioeconomic position and health service characteristics predict treatment of depression over time. The results show that socioeconomic disadvantage appears to be both a cause and consequence of depression, and may also be a barrier to treatment.

### Contribution to the thesis and novelty

This study addresses the third aim of the thesis and provides new evidence from South Africa in support of the bidirectional relationship between poverty and depression, supporting both the 'social causation' and 'social selection' theories. The majority of past studies looking at socio-economic associations with depression in LMICs have been cross-sectional, making it difficult to draw conclusions on direction of causal effects (Lund et al. 2010). Few studies have addressed predictors of change in depression symptoms, and predictors of change in treatment for depression over time. In addition, few studies have explored the health and economic impact of depression over time.

The findings suggest that addressing potentially modifiable clinic factors such as the availability of pharmacists and providing community-based medication supply could improve management of depression in primary care. Further, the evidence in support of a

bidirectional link between depression symptoms and social disadvantage reinforces arguments for the expansion of mental health services and for improving the prevention, detection and treatment of depression in primary health care settings in South Africa.

## Role of the candidate

I oversaw data collection for the study and was responsible for data management, including cleaning the data and preparing it for analysis. I carried out the analyses, supported by Professor Max Bachmann. I drafted the manuscript, incorporating input from co-authors and was responsible for finalising and submitting the final version of the manuscript for publication.

## Role of the co-authors

LF, MB and CLun conceptualised the paper with NF and assisted with the original draft. MB provided support with analyses. VT was the data architect. All authors reviewed the manuscript and approved it for submission.

## Publication status

Published in BMC Public Health 2015.

*Folb N, Lund C, Fairall LR, Timmerman V, Levitt NS, Steyn K, Bachmann MO. Socioeconomic predictors and consequences of depression among primary care attenders with non-communicable diseases in the Western Cape, South Africa: cohort study within a randomised trial. BMC Public Health. 2015;15:1194. DOI 10.1186/s12889-015-2509-4.*

Folb et al. BMC Public Health (2015) 15:1194
DOI 10.1186/s12889-015-2509-4

BMC Public Health

RESEARCH ARTICLE Open Access

# Socioeconomic predictors and consequences of depression among primary care attenders with non-communicable diseases in the Western Cape, South Africa: cohort study within a randomised trial

Naomi Folb[1*], Crick Lund[2], Lara R. Fairall[1], Venessa Timmerman[1], Naomi S. Levitt[3], Krisela Steyn[3] and Max O. Bachmann[4]

## Abstract

**Background:** Socioeconomic predictors and consequences of depression and its treatment were investigated in 4393 adults with specified non-communicable diseases attending 38 public sector primary care clinics in the Eden and Overberg districts of the Western Cape, South Africa.

**Methods:** Participants were interviewed at baseline in 2011 and 14 months later, as part of a randomised controlled trial of a guideline-based intervention to improve diagnosis and management of chronic diseases. The 10-item Center for Epidemiologic Studies Depression Scale (CESD-10) was used to assess depression symptoms, with higher scores representing more depressed mood.

**Results:** Higher CESD-10 scores at baseline were independently associated with being less educated ($p = 0.004$) and having lower income ($p = 0.003$). CESD-10 scores at follow-up were higher in participants with less education ($p = 0.010$) or receiving welfare grants ($p = 0.007$) independent of their baseline scores. Participants with CESD-10 scores of ten or more at baseline (56 % of all participants) had 25 % higher odds of being unemployed at follow-up ($p = 0.016$), independently of baseline CESD-10 score and treatment status. Among participants with baseline CESD-10 scores of ten or more, antidepressant medication at baseline was independently more likely in participants who had more education ($p = 0.002$), higher income ($p < 0.001$), or were unemployed ($p = 0.001$). Antidepressant medication at follow up was independently more likely in participants with higher income ($p = 0.023$), and in clinics with better access to pharmacists ($p = 0.053$) and off-site drug delivery ($p = 0.013$).

**Conclusions:** Socioeconomic disadvantage appears to be both a cause and consequence of depression, and may also be a barrier to treatment. There are opportunities for improving the prevention, diagnosis and treatment of depression in primary care in inequitable middle income countries like South Africa.

**Trial registration:** The trial is registered with Current Controlled Trials (ISRCTN20283604).

**Keywords:** South Africa, Primary care, Depression, Social determinants

* Correspondence: naomi.folb@uct.ac.za
[1]Knowledge Translation Unit, University of Cape Town Lung Institute, Cape Town, South Africa
Full list of author information is available at the end of the article

## Background

Depression is a common mental disorder, causing a high level of disease burden. There were an estimated 298 million cases of major depressive disorder worldwide in 2010 [1] and this disorder was ranked the second leading cause of years lived with disability (YLD) [1, 2].

Mental disorders are also an important cause of disease burden in South Africa. The South African Stress and Health (SASH) study indicated a lifetime prevalence of major depression of 9.7 % and a 12 month prevalence of 4.9 % [3].

Approximately 80 % of South Africans are estimated to be dependent on public health sector services [4], which are inadequately equipped to address the high prevalence of mental disorders. There is marked undertreatment of mental disorders in primary care in South Africa. Three quarters of adults with a mental disorder in the SASH study received no treatment in the year of the interview [5]. This treatment gap is consistent with evidence from many low and middle income countries (LMICs) [6].

South Africa is one of the most unequal countries in the world [7], with wide disparities in wealth and health [8]. Income inequality has been shown to be positively associated with mental illness [9–11]. A study among older Americans found those living in counties with higher income inequality were more depressed, independent of their demographic characteristics, socioeconomic status, and physical health [10]. In South Africa, the burden of ill-health has been demonstrated to be greater among lower socio-economic groups [12].

A number of studies in LMICs have shown an association between indicators of poverty and mental disorders [11, 13]. A systematic review of the relationship between poverty and common mental disorders in LMICs found a relatively consistent and strong association between common mental disorders and education, food insecurity, housing, social class, socio-economic status and financial stress; whereas income, employment and consumption were found to be more equivocal [11]. A second systematic review of poverty and common mental disorders in developing countries found most studies showed an association between risk of common mental disorders and low levels of education, and many studies also showed a relationship with other indicators of poverty such as poor housing or low income [13].

Associations have been found between depression and non-communicable diseases. High depression scores have been found to be an independent risk factor for hypertension, and there is evidence for an association between mental disorder and diabetes. In addition, depression has been shown to be associated with poor glycaemic control [14].

Depression has been shown to be associated with more frequent exacerbations in patients with chronic obstructive pulmonary disease (COPD), worse short-term survival, and higher rates of post-exacerbation readmission to hospital. An interaction effect has also been reported between symptoms of depression and death among patients with COPD [15].

The majority of past studies looking at socioeconomic associations with depression in LMICs have been cross-sectional, making it difficult to draw conclusions on causality [11]. Two explanations have been proposed for the inverse relationship between psychiatric disorders and socioeconomic status. Social causation postulates that adversity and stress due to conditions of poverty increase the risk of mental illness, whereas social selection/drift postulates that people with mental illness are at increased risk of drifting into or remaining in poverty due to factors such as loss of employment, reduced productivity, stigma and increased health expenditure [16]. Although these causal pathways are complex, evidence suggests social causation may be more important for common mental disorders such as depression, particularly in women, while social selection/drift processes may be more important for schizophrenia [17].

Few studies have addressed predictors of change in depression symptoms, and predictors of change in treatment for depression over time in LMICs. In addition, few studies have explored the health and economic impact of depression over time.

The aims of this cohort study were to investigate the extent to which socioeconomic position and physical illness (hypertension, diabetes, chronic respiratory disease) predict depression symptoms over time among primary care attenders, and the extent to which these factors and health service characteristics predict treatment of depression over time.

## Methods

### Study design and context

This paper reports on a cohort study within a cluster randomised controlled trial (RCT), including cross-sectional baseline data and longitudinal data on changes from baseline to follow up. The aim of the RCT was to evaluate the effectiveness of the Primary Care 101 guideline training programme for primary health care providers [18, 19], and to assess whether the programme improved quality of care for specified chronic diseases. Primary Care 101 consists of three elements: a 101-page algorithmic guideline that covers common symptoms and conditions in adults; an educational outreach programme in which nurse trainers deliver interactive training sessions on-site to all staff at a facility, using the Primary Care 101 guideline and case scenarios; and additional prescribing provisions for nurses who successfully complete their training.

Thirty-eight clinics in the Eden and Overberg districts of the Western Cape, South Africa, were cluster randomised either to receive the Primary Care 101 training programme for health care providers, or to continue with usual care. Eligible patients, defined below, who provided consent were interviewed at baseline in 2011 and once more, 14 months later [19]. The analyses for this study included data from the whole RCT cohort at baseline and follow-up, combining the intervention and control arms.

### Study population and sample

The study population comprised adults attending public sector primary care clinics in two districts of the Western Cape province of South Africa. The communities served by the public sector clinics in these two districts are characterised by high levels of unemployment and socio-economic deprivation. In 2011, unemployment rates were 22.5 and 17.0 % in the Eden and Overberg districts respectively [20], and the Eden district was rated as the poorest in the Western Cape province [21]. The study site is typical of many low resource rural and small urban settings in South Africa, in which the public sector primary health care clinics are nurse-led with some doctor support.

Thirty-eight of the largest primary care clinics in the Eden district and two Overberg sub-districts were selected. Each clinic services at least 10 000 attendances per year and they are staffed by nurse practitioners, doctors and community health workers. The study population was restricted to adults 18 years or older, planning to reside in the area for the next year, and capable of actively engaging in an interviewer-administered questionnaire at the time of recruitment.

Among patients who met these criteria, four groups representing patients with hypertension, diabetes, chronic respiratory disease and depression were identified. Patients were eligible for the hypertension and diabetes groups if they reported being on medication for hypertension or diabetes respectively. They were eligible for the respiratory group if they reported being on medication for chronic respiratory disease, or had symptoms of chronic respiratory disease and were not on treatment for tuberculosis. Patients were eligible for the depression group if they scored ten or more on the 10-item Centre for Epidemiologic Studies Depression Scale (CESD-10) [22]. Patients may have fulfilled inclusion criteria for more than one disease group. Participants were sampled consecutively within each clinic and invited to participate in the study, until the sample size required for each clinic was obtained. They were screened for eligibility by orally questioning them and, if they met the eligibility criteria, were then asked to provide informed consent to participate.

### Data collection and coding

At baseline trained fieldworkers administered the electronic questionnaire and took clinical measurements after eligible participants provided informed consent. The baseline questionnaire included questions about demographic characteristics, comorbidities, and socio-economic factors. Participants were asked about the highest level of education they had achieved (no schooling, grade 1–7, grade 8–12 or tertiary/diploma), their employment status (employed, self-employed, student/learner or unemployed), and their employed and pension/grant income in the last month.

The presence of depression symptoms was assessed with the 10-item CES-D scale which was administered to all participants. The 20-item CES-D was originally developed by Radloff (1977) to measure symptoms of depression in the general population [23, 24]. A shortened 10-item version was created by Andresen et al. [22] The CESD-10 items are: "1. I was bothered by things that usually don't bother me. 2. I had trouble keeping my mind on what I was doing. 3. I felt depressed. 4. I felt that everything I did was an effort. 5. I felt hopeful about the future. 6. I felt fearful. 7. My sleep was restless. 8. I was happy. 9. I felt lonely. 10. I could not get going." The individual items are scored from 0 (rarely or none of the time) to 3 (most of the time) and a score is assigned by totalling all item scores. The possible range of scores is 0–30 for the 10-item scale, with higher scores representing greater degrees of depressed mood [22]. Both the 10- and 20- item CES-D have been used and validated in a number of countries including among HIV infected individuals in South Africa [25, 26].

All participants were asked if they had received psychological counselling in the year leading up to their baseline interview. Counselling was defined as talking with someone in a way that helps to find solutions to problems, or receive emotional support, and not just receiving advice on how to take medication. Participants who reported receiving counselling from a mental health nurse, clinic counsellor, social worker, psychiatrist or psychologist were considered to have received counselling. Participants who reported receiving counselling from a mental health nurse, psychiatrist or psychologist were considered to have been referred to psychiatric services.

Chronic medication prescribed at the time of each participant's interview for depression, hypertension, diabetes and respiratory disease was recorded. Fieldworkers photocopied all available prescription charts for the year preceding the interview. The trial manager (NF) analysed the prescription charts to identify medication for chronic conditions prescribed for each participant at the time of their interview.

It is common practice in the Eden and Overberg districts for amitriptyline or imipramine to be prescribed at a low dose (25 mg daily) for pain management and insomnia. We considered amitriptyline and imipramine at a dose less than 50 mg daily to be sub-therapeutic for depression [6]. Other antidepressants were not prescribed at sub-therapeutic doses [27]. We therefore defined being on an antidepressant at a therapeutic dose as prescription of amitriptyline or imipramine of 50 mg or more daily, or on any other antidepressant.

Disease-specific control indicators were measured at baseline and follow-up [19]. Systolic and diastolic blood pressure were measured in all participants. Ten year risk of cardiovascular deaths was calculated, based on age, sex, systolic blood pressure, smoking status, reported diabetes and body mass index [28]. The severity of respiratory disease was assessed with the Symptom and Activity domains of the St Georges Respiratory Questionnaire (SGRQ) [29] in participants enrolled in the respiratory disease group. Glycated haemoglobin (HbA1c) was measured in a sub-sample of 704 diabetic participants from 20 randomly selected clinics.

The following clinic characteristics were identified at baseline: availability of a pharmacist, availability of drug supply away from clinic, psychiatric nurse at clinic, doctor at clinic every day, clinic location, clinic patients per year, clinic patients per nurse per year, and intervention versus control clinic.

At follow-up the questionnaire, clinical measurements and prescription data were collected and recorded as for the baseline data. Baseline data collection began in March 2011 and ended in October 2011. Follow-up data collection started in May 2012 and ended in January 2013.

### Statistical methods

The statistical analyses investigated associations between participants' health and socioeconomic indicators, and their symptoms and treatment of depression. We also investigated associations between depression symptoms reported at baseline and subsequent changes in participants' income and employment, ten year risk of death from cardiovascular disease and, in participants with hypertension, diabetes, or respiratory disease, in blood pressure control, glycaemic control and respiratory symptoms respectively. Analyses of treatments included the following clinic characteristics as potential explanatory variables: pharmacist in clinic, drug supply available away from clinic, psychiatric nurse at clinic, doctor at clinic every day, clinic location, clinic patients per year, clinic patients per nurse per year, and intervention versus control clinic. These clinic characteristics were investigated because they could potentially influence access to necessary treatment directly, or be indirect indicators of the quality of care.

In all analyses the study's cluster sampling design was accounted for in regression models with robust adjustment for intra-clinic cluster correlation of outcomes, using Stata version 12.0 statistical software [30]. A $p$ value 0.05 or less was considered statistically significant.

Intervention or control arm of the randomised controlled trial was accounted for in all longitudinal analyses. Variables independently associated with the outcome in each model were selected using backwards stepwise selection. At each step, explanatory variables with a p value of less than 0.10 were removed from each model. The purpose of stepwise selection of explanatory variables for each model was to estimate the effects of each socioeconomic indicator without confounding by other socioeconomic indicators or patient characteristics. Even though all of the socioeconomic indicators could theoretically have causally influenced depression and its care, it was not appropriate to keep all of them in every model because of the likelihood that overadjustment for collinear variables would obscure relevant associations.

The primary analyses of variables associated with depression symptoms were multiple linear regression models with CESD-10 score as the continuous outcome variable. Secondary analyses of depression symptoms used multiple logistic regression models with CESD-10 scores coded as high (greater than or equal to ten) or low (less than ten).

Analyses with treatments (antidepressant medication, counselling, or referral to psychiatric services) as outcomes were confined to participants with CESD-10 scores greater than or equal to ten at baseline and used multiple logistic regression models. Primary analyses of antidepressant medication coded treatment as present only if drug doses were defined as therapeutic. Secondary analyses coded antidepressant treatment as present at any dose.

Longitudinal data analysis was as follows. Changes between baseline and follow-up in depression symptoms, antidepressant medication, employment or income used analysis of covariance (ANCOVA) in the multiple regression models, that is, with the follow-up variable as outcome and with the baseline variable as a covariate. This was done to account for regression to the mean, that is, individuals with exceptionally high or low values at baseline would at follow-up tend to have values closer to the mean, due to chance alone [31]. Analyses of changes all included trial arm as a potential explanatory variable.

The trial is registered with Current Controlled Trials (ISRCTN20283604). Ethical approval for the trial was obtained from the University of Cape Town Human Research Ethics Committee and the Western Cape

Provincial Department of Health. All participants provided informed consent to participate in the study.

## Results

A total of 4393 participants were enrolled at baseline, of whom 90.5 % were followed up. Prescription records were available for 4364 (99.3 %) participants at baseline and 4284 (97.5 %) participants at follow up.

Table 1 shows the socio-demographic characteristics of participants at baseline. The majority of participants (73 %) were women and half were over the age of 50 years. Seventy-four percent had hypertension, 42 % had diabetes, 26 % had chronic respiratory disease or symptoms and 56 % had CESD-10 scores of ten or more. The majority of participants had not completed secondary school education (52 %), were unemployed (75 %) and receiving a welfare grant (58 %). The average monthly income was equivalent to about US$4.90 per day in 2011 [32], but this includes 26 % who reported having no income. These socioeconomic indicators were all significantly associated with each other, except that non-grant income was not associated with language group.

Baseline CESD-10 scores had a mean value of 10.8 units (standard deviation (SD) 6.4, median 11, interquartile range 6 to 15). Change in CESD-10 scores had a mean value of 3.1 units (SD 7.0, median 7, interquartile range −1 to 8). Both baseline and change in CESD-10 score had symmetrical bell-shaped distributions, except that the baseline score was truncated at zero. However both distributions were significantly different from Normal according to Stata's combined skewness and kurtosis tests for Normality. At baseline, CESD-10 scores were positively associated with female sex, chronic respiratory disease, antidepressant use and housing density, and were inversely associated with age, hypertension, diabetes and income.

Linear regression models estimated the independent associations of CESD-10 scores with the health and socioeconomic indicators (Table 2). Baseline CESD-10 scores were higher in participants who had chronic respiratory disease, were unemployed or receiving a welfare grant, and were lower in participants who were older, male, had hypertension or diabetes, were more educated or had higher incomes at baseline. CESD-10 scores at follow-up had increased since baseline in participants who had chronic respiratory disease, spoke Xhosa, or received welfare grants. CESD-10 scores at follow-up were lower in participants who were older, male, had hypertension, or were more educated at baseline.

The secondary analyses mostly confirmed the robustness of the results reported in Table 2, as follows. An equivalent logistic regression model with higher (greater than or equal to ten) versus lower baseline CESD-10 scores as binary outcome found the same variables as in Table 2 to be significant predictors, except that language was not significant ($p = 0.360$), and employment was ($p = 0.013$). Housing density was not independently associated with CESD-10 score as a continuous outcome variable ($p = 0.148$), but was associated with higher CESD-10 score modelled as a binary outcome variable ($p = 0.05$). Logistic regression with higher CESD-10 score at follow-up as a binary outcome variable, adjusted for baseline CESD-10 score, found age, sex, chronic respiratory disease, education and welfare grant, but not hypertension, to be significant predictors. Greater housing density was independently associated with increasing CESD-10 scores in linear and in logistic regression models.

Participants with CESD-10 scores of ten or more at baseline had 25 % higher odds of being unemployed at follow-up, and had R55 higher income per month from welfare grants at follow-up, independently of their employment status or grant income at baseline, and other confounding variables (Table 3). Baseline CESD-10 scores were not independently associated with changes in non-grant income or total income.

Baseline CESD-10 score, whether coded as a continuous or binary variable, was not associated with changes in blood pressure control, glycaemic control, respiratory symptom score or ten year risk of death from cardiovascular disease.

Logistic regression models estimated the independent effects of participant and clinic characteristics on antidepressant medication at baseline and follow-up, among participants with baseline CESD-10 scores of ten or more, and who consequently may have benefited from diagnosis and treatment of their depression symptoms (Table 4). Receipt of any treatment (antidepressant medication, counselling or psychiatric referral) was more likely in participants with higher CESD-10 scores in every model. Antidepressant medication at therapeutic doses at baseline was more likely in participants with more education, higher income, unemployed, or in clinics with a pharmacist, and was less likely in males and Xhosa speakers, independently of their baseline CESD-10 score. In the case of education, there appeared to be a dose–response relationship, indicated by a steady increase in treatment access with more years of education. Receipt of therapeutic doses of antidepressant drug at follow-up was more likely in women, participants with higher income or in clinics with a pharmacist, drugs supplied off-site, daily doctor support, lower patient to nurse ratios, or peri-urban or rural location, independently of baseline CESD-10 score and antidepressant medication.

**Table 1** Participants' baseline characteristics and associations with baseline CESD-10[a] scores

| | Number[b] | Percent[b] | CESD-10 Mean | CESD-10 SD | $p^c$ |
|---|---|---|---|---|---|
| Health indicators | | | | | |
| Age (years): mean (SD) | 51.6 (13.5) $n = 4393$ | | | | <0.001 |
| Sex | | | | | <0.001 |
| • Women | 3193 | 72.7 | 11.2 | 6.4 | |
| • Men | 1199 | 27.3 | 9.7 | 6.2 | |
| Hypertension | | | | | <0.001 |
| • No | 1166 | 26.6 | 12.8 | 6.2 | |
| • Yes | 3226 | 73.5 | 10.0 | 6.3 | |
| Diabetes | | | | | <0.001 |
| • No | 2551 | 58.1 | 11.8 | 6.4 | |
| • Yes | 1841 | 41.9 | 9.3 | 6.0 | |
| Chronic respiratory Disease | | | | | <0.001 |
| • No | 3235 | 73.7 | 10.2 | 6.3 | |
| • Yes | 1157 | 26.3 | 12.2 | 6.4 | |
| CESD-10 score ≥10 | | | | | |
| • <10 | 1926 | 43.9 | 4.9 | 2.8 | |
| • ≥10 | 2466 | 56.2 | 15.3 | 4.3 | |
| Antidepressant, any dose | | | | | <0.001 |
| • No | 3545 | 81.3 | 10.2 | 6.1 | |
| • Yes | 818 | 18.8 | 13.2 | 7.0 | |
| Antidepressant, therapeutic dose | | | | | <0.001 |
| • No | 3971 | 91.0 | 10.3 | 6.1 | |
| • Yes | 392 | 9.0 | 15.1 | 7.3 | |
| Socioeconomic indicators | | | | | |
| Language | | | | | 0.88 |
| • Afrikaans | 3679 | 83.8 | 10.8 | 6.6 | |
| • Xhosa | 337 | 7.7 | 10.1 | 5.3 | |
| • English | 376 | 8.6 | 10.6 | 5.3 | |
| Highest education | | | | | 0.35 |
| • None | 291 | 7.3 | 10.8 | 6.2 | |
| • Primary | 1757 | 44.2 | 11.0 | 6.2 | |
| • Secondary | 1853 | 46.6 | 10.6 | 6.5 | |
| • Tertiary | 75 | 1.9 | 9.9 | 6.4 | |
| Total monthly income (Rand): mean (SD) | 1084 (1254) $n = 4378$ | | | | <0.001 |
| Unemployed | | | | | 0.12 |
| • No | 1096 | 25.0 | 10.4 | 6.4 | |
| • Yes | 3282 | 75.0 | 10.9 | 6.4 | |
| Welfare grant | | | | | 0.87 |
| • No | 1850 | 42.3 | 10.7 | 6.4 | |
| • Yes | 2528 | 57.7 | 10.8 | 6.4 | |
| Housing density (occupants/rooms): mean (SD) | 1.8 (1.2) $n = 2930$ | | | | <0.001 |

[a] *CESD-10* 10-item Center for Epidemiologic Studies Depression Scale
[b] Except mean and standard deviation (SD) for continuous variables
[c] Linear regression models adjusted for cluster sample design

**Table 2** Patients' baseline characteristics independently associated with CESD-10[a] score at baseline and with change[b] in CESD-10 score: linear regression models

| Outcome | Baseline CESD-10[a] score | | | | Follow-up CESD-10[a] score[b] | | | |
|---|---|---|---|---|---|---|---|---|
| Explanatory variable | Coefficient | 95 % CI[a] | | *p* | Coefficient | 95 % CI[a] | | *p* |
| Age (per year) | −0.06 | −0.08 | −0.04 | <0.001 | −0.06 | −0.08 | −0.04 | <0.001 |
| Men vs. women | −1.66 | −2.19 | −1.13 | <0.001 | −0.96 | −1.46 | −0.46 | <0.001 |
| Hypertension | −1.93 | −2.60 | −1.27 | <0.001 | −0.53 | −1.07 | 0.00 | 0.052 |
| Diabetes | −1.75 | −2.27 | −1.24 | <0.001 | | | | |
| Chronic respiratory disease | 1.21 | 0.51 | 1.91 | <0.001 | 1.06 | 0.58 | 1.54 | <0.001 |
| Highest education | | | | 0.004[c] | | | | 0.010[c] |
| • None (reference) | 1.00 | | | | 1.00 | | | |
| • Primary | −0.24 | −1.31 | 0.84 | 0.656 | −0.35 | −1.34 | 0.63 | 0.473 |
| • Secondary | −1.19 | −2.33 | −0.05 | 0.042 | −1.48 | −2.50 | −0.47 | 0.005 |
| • Tertiary | −0.93 | −2.70 | 0.83 | 0.291 | −1.64 | −3.03 | −0.25 | 0.022 |
| Language | | | | | | | | 0.038[c] |
| • Afrikaans (reference) | | | | | 1.00 | | | |
| • Xhosa | | | | | 1.90 | 0.42 | 3.37 | 0.013 |
| • English | | | | | 1.66 | −0.66 | 3.98 | 0.156 |
| Income (per 1000 Rand per month) | −0.23 | −0.37 | −0.08 | 0.003 | | | | |
| Unemployed | 0.53 | −0.08 | 1.15 | 0.086 | | | | |
| Welfare grant baseline | 0.54 | −0.02 | 1.10 | 0.060 | 0.66 | 0.19 | 1.13 | 0.007 |
| Baseline CESD-10 score[b] | NA | | | | 0.32 | 0.27 | 0.37 | <0.001 |

[a] *CESD-10* 10-item Center for Epidemiologic Studies Depression Scale, *CI* confidence interval, *NA* not applicable
[b] Change modelled with analysis of covariance, that is, with baseline value as covariate
[c] Wald test for all categories of variable

Psychiatric referral between baseline and follow-up was more likely in participants with tertiary education or higher income and was less likely in participants who were older, male, Xhosa-speaking or in intervention clinics.

Counselling between baseline and follow-up was more likely in participants with more education or receiving welfare grants, and in clinics that supplied drugs away from the clinics, and was less likely in participants who were older or had hypertension, and in intervention clinics or clinics with a psychiatric nurse.

## Discussion

This study shows that depression symptoms in adults attending primary care clinics in two districts of South Africa, most of whom had common chronic conditions, were strongly and independently associated with several indicators of disadvantaged socioeconomic position. Depression symptoms, as indicated by higher CESD-10 scores at baseline, were independently associated with being less educated and having lower income. CESD-10 scores at follow-up had increased since baseline in participants who were less educated or receiving welfare grants. Level of education was however not associated with baseline CESD-10 score in the crude analysis, being confounded by the other socioeconomic indicators. This is consistent with findings from several other LMICs, where education was less frequently associated with common mental disorders in bivariate analyses than in multivariate analyses [11].

Previous studies, the majority of which have been community based, have similarly demonstrated associations between common mental disorders and socioeconomic factors, including less education [11, 13, 33, 34], low socio-economic status [11] and low income [13, 34].

Our study population comprised patients already using primary care facilities, and therefore relatively easy to reach for diagnosis and treatment of depression. It showed that, at baseline, participants were less likely to have received treatment with antidepressants if they were socially disadvantaged, in particular if they had lower income or less education. However, participants were more likely to receive treatment if they were unemployed. This may be because it is easier for unemployed participants to attend clinics for treatment. In contrast, the SASH study found no significant associations between receiving treatment for mental disorders and income or level of education [35]. At follow-up, clinic characteristics were more important than socioeconomic factors in predicting depression treatment,

**Table 3** Patient characteristics independently associated with changes[a] in unemployment and welfare grant income: logistic and linear regression models

| Outcome | Unemployed at follow-up[b] | | | | Monthly welfare grant income at follow up (Rand)[c] | | | |
|---|---|---|---|---|---|---|---|---|
| Explanatory variable | OR[d] | 95 % CI | | *p* | Coefficient | 95 % CI[d] | | *p* |
| CESD-10 score ≥10 at baseline | 1.25 | 1.04 | 1.51 | 0.016 | 55 | 18 | 91 | 0.004 |
| Age (per year) | 1.05 | 1.04 | 1.06 | <0.001 | 9 | 7 | 11 | <0.001 |
| Men vs. women | 0.70 | 0.57 | 0.86 | 0.001 | | | | |
| Chronic respiratory disease | | | | | 66 | 25 | 108 | 0.003 |
| Diabetes | | | | | 27 | 0 | 55 | 0.048 |
| Highest education | | | | <0.001[e] | | | | 0.017 [e] |
| • None (reference) | 1.00 | | | | 0 | | | |
| • Primary | 0.78 | 0.54 | 1.13 | 0.186 | −38 | −85 | 8 | 0.105 |
| • Secondary | 0.59 | 0.38 | 0.90 | 0.014 | −67 | −115 | −19 | 0.007 |
| • Tertiary | 0.19 | 0.10 | 0.35 | <0.001 | 3 | −212 | 218 | 0.975 |
| Language | | | | 0.052[e] | | | | <0.001[e] |
| • Afrikaans (reference) | 1.00 | | | | 0 | | | |
| • Xhosa | 0.68 | 0.46 | 1.00 | 0.047 | −158 | −228 | −88 | <0.001 |
| • English | 1.21 | 0.85 | 1.73 | 0.288 | −99 | −162 | −37 | 0.003 |
| Unemployed at baseline[a] | 13.9 | 10.7 | 18.2 | <0.001 | | | | |
| Grant income at baseline (per 1000 Rand per month)[a] | | | | | 602 | 522 | 682 | <0.001 |

[a] Change modelled with analysis of covariance, that is, with baseline value as covariate
[b] Logistic regression model
[c] Linear regression model
[d] *OR* odds ratio, *CI* confidence interval
[e] Wald test for all categories of variable

with participants less likely to have received antidepressant medication if they attended less resourced clinics, without a pharmacist or off-site drug delivery, or if they had lower income. Primary care clinics should be adequately staffed and have pharmacists on site but also enable patients to collect their repeated medicines at more convenient locations. Strategies to deal with the shortage of doctors and nurses in the South African public sector, especially in rural areas, have included community service for doctors, monetary incentives, introducing a cadre of mid-level workers such as pharmacists, contracting non-professional health workers to take on various responsibilities such as counselling and adherence support, and introducing innovative clinical guidelines to enable nurses to manage patients who would otherwise be seen by doctors [36]. Nevertheless, our results reflect the effects of variation in patient:staff ratios within a resource-constrained system, and suggest the need to equalise workloads between clinics, with existing resources. Our finding that patients in clinics with a psychiatric nurse were less likely to receive counselling at follow-up is counter-intuitive. It may be that psychiatric nurses are managing patients with more severe psychiatric disease, that is, psychoses mostly treated with drugs, and do not have the time or skills to provide counselling for depression.

Patients who were more depressed at baseline were more likely to receive antidepressant medication subsequently. Causal inference about the cross-sectional association between depression symptoms at baseline and treatment at baseline is not as clear, but it is more plausible that depression led to treatment rather than that treatment led to depression. Women were more likely than men to have higher CESD-10 scores and to receive treatment with antidepressants at baseline and follow-up. These findings are consistent with work from HIV cohorts in Southern Africa which have shown that proportionally more women than men are on antiretroviral therapy [37], and highlights the need to identify barriers to men accessing healthcare [38, 39]. The role of gender in the causation, experience, reporting and care of depression is however an enormous subject which was beyond the scope of this study.

Depression could potentially have affected participants' physical health through biological mechanisms, or through their health care use, treatment adherence or interpretation of physical symptoms. However, we found that depression symptoms at baseline were not associated with changes in blood pressure control, glycaemic control, respiratory symptom score or ten year risk of death from cardiovascular disease. This differs from studies which have shown a positive association between

**Table 4** Baseline health, socioeconomic and clinic characteristics independently associated with mental health treatments at baseline and at follow-up[a], in patients with CESD-10 score of ten or more: logistic regression models

| Outcome | Therapeutic dose of antidepressant drug at baseline | | | | Therapeutic dose of antidepressant drug at follow-up[a] | | | | Psychiatric referral between baseline and follow-up | | | | Counselling between baseline and follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Explanatory variable | OR[b] | 95 % CI[b] | | *P* | OR | 95 % CI | | *P* | OR | 95 % CI | | *P* | OR | 95 % CI | | *P* |
| Patient characteristics | | | | | | | | | | | | | | | | |
| Age (per year) | | | | | | | | | 0.97 | 0.95 | 0.98 | <0.001 | 0.97 | 0.96 | 0.98 | <0.001 |
| Men vs. women | 0.31 | 0.19 | 0.49 | <0.001 | 0.34 | 0.22 | 0.53 | <0.001 | 0.67 | 0.43 | 1.03 | 0.069 | | | | |
| Hypertension | | | | | | | | | | | | | 0.75 | 0.60 | 0.95 | 0.016 |
| Diabetes | 0.72 | 0.49 | 1.06 | 0.094 | 0.71 | 0.48 | 1.04 | 0.079 | | | | | | | | |
| Highest education | | | | 0.002[c] | | | | | | | | 0.006[c] | | | | 0.022[c] |
| • None (reference) | 1.00 | | | | | | | | 1.00 | | | | 1.00 | | | |
| • Primary | 1.36 | 0.75 | 2.47 | 0.314 | | | | | 1.11 | 0.51 | 2.38 | 0.797 | 0.85 | 0.51 | 1.41 | 0.529 |
| • Secondary | 1.98 | 1.10 | 3.55 | 0.022 | | | | | 1.37 | 0.62 | 2.99 | 0.435 | 0.81 | 0.49 | 1.33 | 0.401 |
| • Tertiary | 2.06 | 0.91 | 4.66 | 0.082 | | | | | 4.00 | 1.57 | 10.15 | 0.004 | 1.99 | 1.08 | 3.68 | 0.028 |
| Language | | | | <0.001[c] | | | | | | | | 0.003[c] | | | | |
| • Afrikaans (reference) | 1.00 | | | | | | | | 1.00 | | | | | | | |
| • Xhosa | 0.23 | 0.15 | 0.35 | <0.001 | | | | | 0.16 | 0.05 | 0.45 | 0.001 | | | | |
| • English | 0.85 | 0.54 | 1.35 | 0.488 | | | | | 1.10 | 0.64 | 1.90 | 0.732 | | | | |
| Income (per 1000 rand per month) | 1.31 | 1.18 | 1.44 | <0.001 | 1.21 | 1.03 | 1.43 | 0.023 | 1.19 | 1.05 | 1.34 | 0.005 | | | | |
| Unemployed | 2.01 | 1.32 | 3.09 | 0.001 | | | | | | | | | | | | |
| Welfare grant | | | | | | | | | 1.35 | 0.96 | 1.90 | 0.082 | 1.36 | 1.13 | 1.64 | 0.001 |
| Baseline CESD-10 score (per unit) | 1.15 | 1.12 | 1.19 | <0.001 | 1.06 | 1.00 | 1.11 | 0.033 | 1.11 | 1.06 | 1.15 | <0.001 | 1.06 | 1.03 | 1.10 | <0.001 |
| Therapeutic dose of antidepressant at baseline[a] | NA[b] | | | | 136.90 | 77.25 | 242.61 | <0.001 | NA | | | | NA | | | |
| Clinic characteristics | | | | | | | | | | | | | | | | |
| Pharmacist in clinic | 1.86 | 1.25 | 2.78 | 0.002 | 1.58 | 0.99 | 2.51 | 0.053 | | | | | | | | |
| Drug supply available away from clinic | | | | | 1.67 | 1.11 | 2.50 | 0.013 | | | | | 1.59 | 0.95 | 2.66 | 0.078 |
| Psychiatric nurse at clinic | | | | | | | | | | | | | 0.32 | 0.13 | 0.80 | 0.015 |
| Doctor at clinic every day | | | | | 1.48 | 0.95 | 2.30 | 0.084 | | | | | | | | |
| Clinic location | | | | | | | | 0.038[c] | | | | | | | | |
| • Urban (reference) | | | | | 1.00 | | | | | | | | | | | |

**Table 4** Baseline health, socioeconomic and clinic characteristics independently associated with mental health treatments at baseline and at follow-up[a], in patients with CESD-10 score of ten or more: logistic regression models *(Continued)*

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| • Peri-urban | 1.17 | 0.66 | 2.08 | 0.599 | | | | | | | | |
| • Rural | 2.60 | 1.18 | 5.76 | 0.018 | | | | | | | | |
| Clinic patients per year/10,000 | | | | | | | | | 1.04 | 0.99 | 1.10 | 0.081 |
| Clinic patients per nurse per year/1000 | 0.93 | 0.88 | 0.99 | 0.022 | | | | | | | | |
| Intervention vs. control clinic | 1.39 | 0.97 | 1.98 | 0.073 | 0.57 | 0.35 | 0.91 | 0.020 | 0.54 | 0.33 | 0.88 | 0.013 |

[a] Change modelled with analysis of covariance, that is, with baseline value as covariate
[b] *OR* odds ratio, *CI* confidence interval, *NA* not applicable
[c] Wald test for all categories of variable

depression and poor glycaemic control in diabetic patients [14].

Our findings suggest that the association between depression symptoms and socio-economic position is bidirectional. That is, in addition to disadvantaged social position predicting worse depression symptoms at follow-up, participants who had depression symptoms at baseline were more socially disadvantaged at follow-up, showing 25 % higher odds of being unemployed. The bidirectional link between depression symptoms and social disadvantage therefore supports both the social causation and social selection theories. Our findings suggest that, in this study setting, socioeconomic disadvantage is both a cause and a consequence of depression, and may also be a barrier to treatment, with participants less likely to receive treatment if they had a lower income (baseline and follow-up) or less education (baseline).

The study had a number of strengths. The sample size was large, high rates of follow-up were achieved, and a wide range of socio-economic variables were investigated. A key strength of the study was the longitudinal design, which allowed potential causal relationships to be identified, demonstrating that the relationship between socioeconomic position and depression worked in both directions.

There were a number of limitations to the study. The CESD-10 questionnaire was used to identify participants with depression symptoms, but not to confirm the clinical diagnosis of depression. It was originally derived and validated on an older adult population [22] but has subsequently been validated in a younger population on antiretroviral therapy [25]. Participants were only enrolled into the study if they had hypertension, diabetes, chronic respiratory disease or depression symptoms, so the results may not be generalisable to primary care attenders without these conditions. Thirty-four percent of participants in the depression group did not answer the question at baseline on whether they had received counselling in the past year. This was due to an error in the electronic questionnaire that resulted in this question being skipped during several weeks of fieldwork before it was detected and corrected. Socioeconomic factors that could influence depression symptoms that were not measured include food insecurity, poor housing, lack of social support, and disability.

Further research is needed to investigate the relative contributions of both social causation and social selection/drift mechanisms to the well documented association between socio-economic disadvantage and depression in LMICs; to identify what specific intervention strategies are needed to reach vulnerable low socioeconomic populations living with depression; and to evaluate the effectiveness of interventions that are designed to target each of the above mechanisms. Feasible examples might include brief psychological interventions with financial risk protection as part of universal health coverage.

## Conclusion

This study provides new evidence from South Africa in support of the bidirectional relationship between poverty and depression. Mental health interventions have been shown to be associated with improved economic outcomes in LMICs [16]. This study reinforces arguments for the expansion of mental health services and improving the prevention, detection and treatment of depression in primary health care settings in South Africa and other LMICs, for clinical and economic reasons. While there is currently an emphasis on integrating communicable and non-communicable chronic disease care in South Africa, we must not lose sight of the importance of ensuring better management and access to mental health care.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

All authors contributed to the design of the study. NF, LF, VT, KS and NL oversaw data collection, data cleaning, merging of datasets and preparation of extracts for analysis. MB led the analysis with assistance from NF. All authors contributed to interpretation of findings and preparation of the manuscript. All authors read and approved the final manuscript.

#### Acknowledgements

The authors wish to thank all clinic nurses, doctors, clinic managers, pharmacists and pharmacy assistants at participating study facilities; the Department of Health of the Provincial Government of the Western Cape; the Eden and Overberg district management; Primary Care 101 trainers and fieldworkers; and the National Health Laboratory Service.
This project has been funded in part with Federal funds by the United States National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN268200900030C. Funding was also received from United Health, USA; the Department of Health of the Provincial Government of the Western Cape; the Department of Medicine, University of Cape Town, South Africa; the United Kingdom Department for International Development; the University of Cape Town Lung Institute, South Africa; and the University of East Anglia, UK. The study funders did not contribute to the design of the study, the collection, analysis and interpretation of data, or to the writing of this article or decision to submit it for publication. The researchers were independent from funders and sponsors, and researchers involved in the collection, analysis and interpretation of the data had access to all the data.

#### Author details

[1]Knowledge Translation Unit, University of Cape Town Lung Institute, Cape Town, South Africa. [2]Alan J Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa. [3]Department of Medicine, University of Cape Town, Cape Town, South Africa. [4]Norwich Medical School, University of East Anglia, Norwich, UK.

Received: 12 February 2015 Accepted: 17 November 2015
Published online: 30 November 2015

#### References

1. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013;10:e1001547.

2. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163–96.
3. Tomlinson M, Grimsrud AT, Stein DJ, Williams DR, Myer L. The Epidemiology of Major Depression in South Africa: Results from the South African Stress and Health Study. S Afr Med J. 2009;99:367–73.
4. Health Systems Trust. South African Health Review 2010. Durban: Health Systems Trust, 2010. http://www.hst.org.za/publications/south-african-health-review-2010. Accessed 14 August 2014.
5. Williams DR, Herman A, Stein DJ, Heeringa SG, Jackson PB, Moomal H, et al. Twelve-month mental disorders in South Africa: prevalence, service use and demographic correlates in the population-based South African Stress and Health Study. Psychol Med. 2008;38:211–20.
6. World Health Organisation. Mental Health Gap Action Programme (mhGAP) 2010. http://www.who.int/mental_health/mhgap/en/. Accessed 11 November 2014.
7. Tregenna F, Tsela M. Inequality in South Africa: The distribution of income, expenditure and earnings. Dev South Afr. 2012;29:35–61.
8. Benatar SR. The challenges of health disparities in South Africa. S Afr Med J. 2013;103:154–5.
9. Messias E, Eaton WW, Grooms AN. Economic Grand Rounds: Income Inequality and Depression Prevalence Across the United States: An Ecological Study. Psychiatr Serv. 2011;62:710–2.
10. Muramatsu N. County-level income inequality and depression among older Americans. Health Serv Res. 2003;38:1863–83.
11. Lund C, Breen A, Flisher AJ, Kakuma R, Corrigall J, Joska JA, et al. Poverty and common mental disorders in low and middle income countries: A systematic review. Soc Sci Med. 2010;71:517–28.
12. Ataguba JE, Akazili J, McIntyre D. Socioeconomic-related health inequality in South Africa: evidence from General Household Surveys. Int J Equity Health. 2011;10:48.
13. Patel V, Kleinman A. Poverty and common mental disorders in developing countries. Bull World Health Organ. 2003;81:609–15.
14. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. Lancet. 2007;370:859–77.
15. Parreira VF, Kirkwood RN, Towns M, Aganon I, Barrett L, Darling C, et al. Is There an Association between Symptoms of Anxiety and Depression and Quality of Life in Patients with Chronic Obstructive Pulmonary Disease? Can Respir J. 2015;22:37–41.
16. Lund C, De Silva M, Plagerson S, Cooper S, Chisholm D, Das J, et al. Poverty and mental disorders: breaking the cycle in low-income and middle-income countries. Lancet. 2011;378:1502–14.
17. Dohrenwend BP, Levav I, Shrout PE, Schwartz S, Naveh G, Link BG, et al. Socioeconomic status and psychiatric disorders: the causation-selection issue. Science. 1992;255:946–52.
18. Health Systems Trust. Primary Health Care 101. 2013. http://www.hst.org.za/publications/primary-health-healthcare-101. Accessed 22 November 2015.
19. Folb N, Timmerman V, Levitt NS, Steyn K, Bachmann MO, Lund C, et al. Multimorbidity, control and treatment of non-communicable diseases among primary healthcare attenders in the Western Cape, South Africa. S Afr Med J. 2015;105:642–7.
20. Statistics South Africa. Census 2011 Municipal factsheet. http://www.statssa.gov.za/census/census_2011/census_products/Census_2011_Municipal_fact_sheet.pdf. Accessed 22 November 2015.
21. Eden District Municipality. Eden District Municipality Integrated Development Plan (IDP) Annual Review for 2010/11. Eden District Municipality, 2010. http://mfma.treasury.gov.za/Documents/01.%20Integrated%20Development%20Plans/2010-11/03.%20District%20Municipalities/DC4%20Eden/DC4%20Eden%20-%20IDP%20-%201011.pdf. Accessed 21 August 2014.
22. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med. 1994;10:77–84.
23. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1:385–401.
24. Miller WC, Anton HA, Townson AF. Measurement properties of the CESD scale among individuals with spinal cord injury. Spinal Cord. 2008;46:287–92.
25. Zhang W, O'Brien N, Forrest JI, Salters KA, Patterson TL, Montaner JSG, et al. Validating a shortened depression scale (10 item CES-D) among HIV-positive people in British Columbia, Canada. PLoS One. 2012;7:e40793.
26. Myer L, Smit J, Roux LL, Parker S, Stein DJ, Seedat S. Common mental disorders among HIV-infected individuals in South Africa: prevalence, predictors, and validation of brief psychiatric rating scales. AIDS Patient Care STDs. 2008;22:147–58.
27. Rossiter D, editor. South African Medicines Formulary (SAMF). Health and Medical Publishing Group of the South African Medical Association. Cape Town, South Africa. 11th edition; 2014.
28. Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. Lancet. 2008;371:923–31.
29. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991;85(Suppl B):25–31.
30. StataCorp. Stata Statistical Software: Release 12. College Station: StataCorp LP; 2011.
31. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol. 2005;34:215–20.
32. OANDA currency converter. http://www.oanda.com/currency/historical-rates/. Accessed 24 December 2013.
33. Araya R, Lewis G, Rojas G, Fritsch R. Education and income: which is more important for mental health? J Epidemiol Community Health. 2003;57:501–5.
34. Patel V, Araya R, de Lima M, Ludermir A, Todd C. Women, poverty and common mental disorders in four restructuring societies. Soc Sci Med. 1999;49:1461–71.
35. Seedat S, Stein DJ, Herman A, Kessler R, Sonnega J, Heeringa S, et al. Twelve-month treatment of psychiatric disorders in the South African Stress and Health Study (World Mental Health Survey Initiative). Soc Psychiatry Psychiatr Epidemiol. 2008;43:889–97.
36. Daviaud E, Chopra M. How Much Is Not Enough? Human Resources Requirements for Primary Health Care: A Case Study from South Africa. Bull World Health Organ. 2008;86:46–51.
37. Muula AS, Ngulube TJ, Siziya S, Makupe CM, Umar E, Prozesky HW, et al. Gender distribution of adult patients on highly active antiretroviral therapy (HAART) in Southern Africa: a systematic review. BMC Public Health. 2007;7:63.
38. Galdas PM, Cheater F, Marshall P. Men and Health Help-Seeking Behaviour: Literature Review. J Adv Nurs. 2005;49:616–23.
39. Möller-Leimkühler AM. Barriers to Help-Seeking by Men: A Review of Sociocultural and Clinical Literature with Particular Reference to Depression. J Affect Disord. 2002;71:1–9.

## 3.4 Educational outreach with an integrated clinical tool for nurse-led non-communicable chronic disease management in primary care in South Africa: a pragmatic cluster randomised controlled trial

### Paper overview

This paper reports on the RCT evaluating the PC101 programme. The programme was found to be feasible and safe but was not associated with the primary outcomes of treatment intensification for NCDs or case detection for depression. This notwithstanding, the intervention, with adjustments to improve its effectiveness, has been adopted for implementation in primary care clinics throughout South Africa.

### Contribution to the thesis and novelty

This paper addresses the fourth aim of the thesis. The benefits of nurse substitution and supplementation in NCD care in high income settings are well recognised, but evidence from low- and middle-income countries is limited.

The PC101 intervention is a further development of the PALSA PLUS programme, which focussed on HIV/AIDS and respiratory disease including tuberculosis. PC101 includes all common symptoms and conditions among adults attending primary care services and is designed to support and expand nurses' roles in NCD care.

Our trial covered all three NCDs profiled in the series of implementation science calls from the Global Alliance for Chronic Diseases (hypertension, diabetes, chronic respiratory disease) (GACD 2016), and also addressed depression, the second leading cause of years lived with disability worldwide (Vos et al. 2012).

While no primary outcomes showed significant benefit, the upper confidence limits included the possibility of meaningful clinical improvements, and the direction of results in three of the four primary endpoints in the study was consistent and positive. Furthermore, there was no evidence of harm and the programme was perceived to be a highly feasible and acceptable approach to the expansion of skills for NCDs. The National Department of Health has adopted the programme for implementation in primary care clinics throughout South Africa.

## Role of the candidate

I oversaw data collection for the study and was responsible for data management, including cleaning the data and preparing it for analysis. I collaborated with Professor Carl Lombard and Associate Professor Lara Fairall in the statistical design and analyses. I drafted the manuscript with co-lead author Associate Professor Lara Fairall, incorporating input from co-authors, and was responsible for finalising and submitting the final version of the manuscript for publication.

## Role of the co-authors

LF, NF, KS, RC, GF, and NL developed and implemented the intervention. NF, LF, VT, KS and NL oversaw data collection. CLom led the analysis with assistance from NF, LF and MB. LF and NF wrote the original draft. All authors contributed to preparation of the manuscript and approved the final manuscript.

## Publication status

Published in PLOS Medicine 2016

*Fairall LR, Folb N, Timmerman V, Lombard C, Steyn K, Bachmann MO, et al. Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-communicable Chronic Disease Management in Primary Care in South Africa: A Pragmatic Cluster Randomised Controlled Trial. PLoS Med. 2016;13(11): e1002178. doi:10.1371/journal.pmed.1002178*

PLOS | MEDICINE

RESEARCH ARTICLE

# Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-communicable Chronic Disease Management in Primary Care in South Africa: A Pragmatic Cluster Randomised Controlled Trial

**Lara R. Fairall[1,2,3☯]*, Naomi Folb[1,2,3☯], Venessa Timmerman[1], Carl Lombard[4], Krisela Steyn[2,3], Max O. Bachmann[5], Eric D. Bateman[1,2], Crick Lund[6], Ruth Cornick[1], Gill Faris[1], Thomas Gaziano[3,7], Daniella Georgeu-Pepper[1], Merrick Zwarenstein[8], Naomi S. Levitt[2,3]**

**1** Knowledge Translation Unit, University of Cape Town Lung Institute, Cape Town, South Africa, **2** Department of Medicine, University of Cape Town, Cape Town, South Africa, **3** Chronic Disease Initiative for Africa, Department of Medicine, University of Cape Town, Cape Town, South Africa, **4** Biostatistics Unit, Medical Research Council, Cape Town, South Africa, **5** Norwich Medical School, University of East Anglia, Norwich, United Kingdom, **6** Alan J Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa, **7** Division of Cardiovascular Medicine, Brigham & Women's Hospital, Boston, Massachusetts, United States, **8** Centre for Studies in Family Medicine, Department of Family Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

☯ These authors contributed equally to this work.
* Lara.Fairall@uct.ac.za



OPEN ACCESS

**Citation:** Fairall LR, Folb N, Timmerman V, Lombard C, Steyn K, Bachmann MO, et al. (2016) Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-communicable Chronic Disease Management in Primary Care in South Africa: A Pragmatic Cluster Randomised Controlled Trial. PLoS Med 13(11): e1002178. doi:10.1371/journal.pmed.1002178

**Academic Editor:** Margaret E Kruk, Harvard University, UNITED STATES

**Received:** May 19, 2016

**Accepted:** October 19, 2016

**Published:** November 22, 2016



**Data Availability Statement:** Relevant data are within the paper and the S1 Data Supporting Information file.

**Funding:** This project has been funded in part with Federal funds by the United States National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN268200900030C (http://www.nhlbi.nih.gov/). Funding was also received from United Health, USA; the Department of Health

## Abstract

### Background

In many low-income countries, care for patients with non-communicable diseases (NCDs) and mental health conditions is provided by nurses. The benefits of nurse substitution and supplementation in NCD care in high-income settings are well recognised, but evidence from low- and middle-income countries is limited. Primary Care 101 (PC101) is a programme designed to support and expand nurses' role in NCD care, comprising educational outreach to nurses and a clinical management tool with enhanced prescribing provisions. We evaluated the effect of the programme on primary care nurses' capacity to manage NCDs.

### Methods and Findings

In a cluster randomised controlled trial design, 38 public sector primary care clinics in the Western Cape Province, South Africa, were randomised. Nurses in the intervention clinics were trained to use the PC101 management tool during educational outreach sessions delivered by health department trainers and were authorised to prescribe an expanded range of drugs for several NCDs. Control clinics continued use of the Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS) management tool and usual

of the Provincial Government of the Western Cape; the Department of Medicine, University of Cape Town, South Africa; the United Kingdom Department for International Development; and the University of Cape Town Lung Institute, South Africa. Funding was received by NL. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing Interests:** The authors have declared that no competing interests exist.

**Abbreviations:** ART, antiretroviral therapy; BMI, body mass index; CESD-10, 10-item Center for Epidemiologic Studies Depression Scale; COPD, chronic obstructive pulmonary disease; LMICs, low- and middle-income countries; NCD, non-communicable disease; PALSA PLUS, Practical Approach to Lung Health and HIV/AIDS in South Africa; PC101, Primary Care 101; RR, risk ratio; TB, tuberculosis.

training. Patients attending these clinics with one or more of hypertension (3,227), diabetes (1,842), chronic respiratory disease (1,157) or who screened positive for depression (2,466), totalling 4,393 patients, were enrolled between 28 March 2011 and 10 November 2011. Primary outcomes were treatment intensification in the hypertension, diabetes, and chronic respiratory disease cohorts, defined as the proportion of patients in whom treatment was escalated during follow-up over 14 mo, and case detection in the depression cohort. Primary outcome data were analysed for 2,110 (97%) intervention and 2,170 (97%) control group patients. Treatment intensification rates in intervention clinics were not superior to those in the control clinics (hypertension: 44% in the intervention group versus 40% in the control group, risk ratio [RR] 1.08 [95% CI 0.94 to 1.24; $p = 0.252$]; diabetes: 57% versus 50%, RR 1.10 [0.97 to 1.24; $p = 0.126$]; chronic respiratory disease: 14% versus 12%, RR 1.08 [0.75 to 1.55; $p = 0.674$]), nor was case detection of depression (18% versus 24%, RR 0.76 [0.53 to 1.10; $p = 0.142$]). No adverse effects of the nurses' expanded scope of practice were observed. Limitations of the study include dependence on self-reported diagnoses for inclusion in the patient cohorts, limited data on uptake of PC101 by users, reliance on process outcomes, and insufficient resources to measure important health outcomes, such as HbA1c, at follow-up.

## Conclusions

Educational outreach to primary care nurses to train them in the use of a management tool involving an expanded role in managing NCDs was feasible and safe but was not associated with treatment intensification or improved case detection for index diseases. This notwithstanding, the intervention, with adjustments to improve its effectiveness, has been adopted for implementation in primary care clinics throughout South Africa.

## Trial Registration

The trial is registered with Current Controlled Trials (ISRCTN20283604)

## Author Summary

### Why Was This Study Done?

- Non-communicable diseases (NCDs) are the leading cause of deaths worldwide, even in low- and middle-income countries (LMICs) that continue to battle to control communicable diseases like HIV and tuberculosis (TB).
- Effective and affordable treatments prevent complications from NCDs like heart attacks and strokes, but access is limited by the variable availability and limited capacity of primary care health workers to detect and effectively manage these conditions. In many LMICs, non-physicians such as nurses provide primary care for NCDs.
- Over the past 16 years, we have developed, evaluated, and refined integrated clinical management tools and training programmes that employ problem-based approaches to common symptoms like cough and priority health conditions

including TB, HIV, asthma, and emphysema. We have shown them to be effective in improving the quality and outcomes of care for communicable diseases.

- We have expanded this programme to include almost all NCDs and mental health. This study evaluated the impact, both benefits and harms, of introducing the expanded programme, called Primary Care 101 (PC101), in terms of the quality of primary care for four common chronic diseases: hypertension, diabetes, chronic respiratory disease, and depression.

## What Did the Researchers Do and Find?

- We compared the care offered to patients with one of these four chronic diseases in 18 clinics in which primary care health workers were trained in the use of PC101 with that in 18 clinics where nurses continued to use the predecessor tool, which focused on communicable diseases.
- The trial had a pragmatic design, meaning it was conducted under usual conditions of health system operational constraints. Clinics in urban and rural areas serving people living in socio-economically deprived areas of South Africa were selected.
- We enrolled 4,393 patients with one or more of the NCDs of interest and followed them up for 14 mo after introduction of PC101 at the intervention clinics. The primary outcome of interest was intensification of treatment (or diagnosis, in the case of depression) for the four NCDs, analysed separately.
- The results confirmed very high rates of multimorbidity (patients having more than one condition at a time), under-diagnosis, under-treatment, and poor disease control.
- Introducing PC101 did not result in intensification of treatment for the four NCDs, but neither was there evidence of harm from the nurses' expanded scope of practice.

## What Do These Findings Mean?

- The trial confirmed that multimorbidity and poor detection and control of NCDs and depression are common in this setting. Interventions are necessary to limit the impact of these conditions on people's health and quality of life.
- PC101 offered a practical and acceptable tool to help expand the scope of practice of non-physician clinicians to include NCD care, but we were not able to show improvements in care, as we have previously done for communicable diseases.
- The study illustrates the limitations of trials designed to study the effects of complex system interventions in real life, where even small changes across many endpoints, as seen in our study, may be useful to decision-makers under pressure to respond constructively to the rise of multimorbidity and NCDs.
- PC101 has been adopted for country-wide implementation in primary care clinics in South Africa.

## Introduction

South Africa is facing a quadruple burden of disease: HIV and tuberculosis (TB); non-communicable diseases (NCDs), including mental health conditions; injury and violence; and maternal, neonatal, and childhood illnesses [1]. The past 15 years have seen concentrated efforts to strengthen the capacity of the public health system to treat HIV and TB. These investments seem at last to be paying off, with a rise in life expectancy, a decline in mortality [2], and fewer new HIV infections [3]. Yet the burden of NCDs and mental health remains unchecked; cardiovascular disease is now the second leading cause of death in South Africans after communicable diseases [4,5].

In South Africa, responsibility for the detection and treatment of NCDs lies at the primary care level, with nurses seeing nine out of ten patients, most of whom have more than one presenting condition [6]. However, the quality of NCD care is generally poor, characterised by under-diagnosis, under-treatment, and poor clinical control [1,7,8]. We have previously successfully piloted and trialled task-sharing interventions for communicable diseases, increasing the capacity of nurses to take on assessment and prescribing roles for HIV and TB previously restricted to doctors [9–15]. This programme has been scaled up throughout South Africa as part of the national government's accelerated response to HIV and TB launched in 2010 [16]. A similar programme has been developed for use in other countries including Malawi, Botswana, Brazil, and Mexico [17]. We have since expanded this programme, now called Primary Care 101 (PC101), to include NCDs and mental health, hoping to leverage the health system reforms that accompanied the scale-up of antiretroviral therapy (ART) to improve the quality of primary care for other priority conditions.

These integrated programmes of care seek to overcome the limitations of vertical services that tend to neglect multimorbidity [18–23], and to expand the roles of nurses, increasing the number and distribution of health workers providing treatment for common NCD conditions.

While the benefits of nurse substitution and supplementation for a limited number of NCDs in high-income settings are well recognised [24], evidence from low- and middle-income countries (LMICs) is sparse and limited to a few pilot studies [25–28]. Fewer studies still have sought to improve care across several NCDs simultaneously. Meta-analyses of complex interventions in health systems confirm only small effect sizes (ranging from 0.4% to 6.3%) for carer behaviour (improved care), but given the size of the populations affected, these effect sizes are considered important, provided the interventions are introduced without harm. We report here the findings of the PC101 Trial, a pragmatic cluster randomised study evaluating the effectiveness of the PC101 intervention, which combines provision of an integrated management tool with educational outreach to nurses. The primary outcomes of interest were intensification of treatment for hypertension, diabetes, and chronic respiratory disease and case detection of depression in overlapping cohorts of patients with these conditions.

## Methods

Ethical approval for the trial was obtained from the University of Cape Town Human Research Ethics Committee (reference number 119/2010) and the Western Cape Department of Health.

### Study Design

This was a pragmatic, parallel-group cluster randomised controlled trial performed in the Eden and Overberg districts of the Western Cape Province. Clusters were public sector primary healthcare clinics randomised within six sub-district strata. Outcome measures in each of four cohorts were assessed in individual patients. Patient cohorts overlapped; patients with more than one condition of interest were included in each applicable cohort, and cohorts were

powered and analysed separately. This study design, with multiple cohorts, each with its own primary outcome evaluated simultaneously, aimed to reflect the realities in primary care clinics that nurses are required to diagnose and manage a wide range of conditions, that NCDs are associated with multimorbidity, and that a focus on one condition may compromise the management of others [29]. The Western Cape Department of Health provided consent for the inclusion and randomisation of clinics, before randomisation was performed. Patients provided written consent for data collection after randomisation of clinics and prior to data collection.

## Participants

**Clinics.** The study was conducted in the predominantly rural districts of Eden and Overberg, where public sector clinics serve a population of around 800,000, mainly people with lower socio-economic status. Busy town clinics had fulltime doctors, but most clinics were nurse led, with doctors in attendance on a sessional basis (Table A in S1 Appendix).

Eligible clinics provided services, including for NCDs, at least five days a week and reported more than 10,000 attendances per year, so were likely able to contribute sufficient numbers of patients to the study. Of 124 clinics in the Eden district, 33 clinics in five sub-districts met these criteria. We supplemented this sample with five clinics from a sub-district in an adjacent district (Overberg), to increase the number of clinics available for randomisation and strengthen the study's power.

The health districts in the study are representative of health services offered to more than 80% of the population of South Africa, comprising clinics both from medium-sized towns and rural areas [6].

**Patients.** The study population comprised patients with one or more of the following: hypertension, diabetes, chronic respiratory disease, or depression. Initial eligibility criteria were being 18 y or older, likely to reside in the area for the next year, and capable of actively engaging in an interviewer-administered questionnaire at the time of recruitment. Inclusion criteria for the four cohorts were as follows (Table 1): for the hypertension and diabetes cohorts, if patients reported being on medication for hypertension or diabetes, respectively; for the respiratory disease cohort, if they reported receiving medication for chronic airway disease (asthma or chronic obstructive pulmonary disease [COPD]) or reported a cough and/or difficult breathing for 2 wk or more prior to enrolment and were not on treatment for TB [30]; for the depression cohort, if they scored ten or more on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10) [31,32]. We selected this instrument because the 20-item version has been validated in a similar setting in South Africa [33], and the 10-item version in primary care populations elsewhere [34–36]. The shorter version was necessary to limit the length of the screening process for all four conditions. Patients were eligible even if at the time of enrolment they had no record of current treatment for their condition.

In keeping with the study's pragmatic design, enrolment was not restricted to patients with uncontrolled disease or to patients considered to be adherent to current treatment [40]. Although encouraging adherence was included in the management tool, it was not monitored.

**Randomisation.** Clinics within each of six health sub-district strata were randomised to avoid potential confounding resulting from geographically determined differences in management of clinical services. Two strata contained equal numbers of clinics, meaning that randomisation could be done in a 1:1 ratio. The four strata containing odd numbers of clinics were randomly allocated to have either one more or one fewer intervention clinic than control clinics, to achieve an equal number of clinics in each group (19 per group, 38 in total).

**Table 1. Eligibility criteria, primary outcome definitions, and required sample size estimates for each cohort.**

| Cohort | Eligibility Criteria | Primary Outcome | Primary Outcome Definition | Required Sample Size Parameters[1] | | | |
|---|---|---|---|---|---|---|---|
| | | | | Cluster Size | Intervention Proportion | Control Proportion | ICC |
| Hypertension | Self-reported antihypertensive medication[2] | Treatment intensification | (1) an increase in the number of antihypertensive medication classes and/or (2) an increase in dose of at least one antihypertensive and/or (3) a switch to an antihypertensive in another medication class and/or (4) a switch to an antihypertensive in the same medication class provided that the new dose is equivalent to a higher dose of the previous antihypertensive and/or (5) addition of aspirin and/or (6) the addition or increase in dose of a statin. | 57 | 0.36 | 0.25 | 0.04 [37][3] |
| Diabetes | Self-reported hypoglycaemic medication[4] | Treatment intensification | (1) the addition or increase in dose of metformin and/or (2) the addition or increase in dose of a sulphonylurea and/or (3) the addition or increase in dose of insulin and/or (4) the addition or increase in dose of an ACE inhibitor and/or (5) addition of aspirin and/or (6) the addition or increase in dose of a statin. | 57 | 0.36 | 0.25 [38][3] | 0.04 [37][3] |
| Chronic respiratory disease | Self-reported respiratory medication OR cough and/or difficult breathing >2 wk (and not on TB treatment)[5] | Treatment intensification | (1) the addition or increase in dose of an inhaled corticosteroid and/or (2) addition of a beta-agonist and/or (3) addition of ipratropium bromide and/or (4) addition of theophylline. | 36 | 0.30 | 0.15 | 0.02 [15][3] |
| Depression | CESD-10 $\geq$ 10 | Case detection | (1) addition of antidepressant medication and/or (2) receipt of counselling by a mental health practitioner and/or (3) referral to mental health services. | 60 | 0.10 | 0.04 | 0.04 [39][3] |

[1]All calculations are for two-sided tests and are powered at 90%. Sample sizes have been inflated by 20% to allow for loss to follow-up at 14 mo.

[2]Patients included in this cohort responded yes to the following question: "Are you taking medicine for high blood pressure (hypertension)?"

[3]These parameters were derived from earlier publications.

[4]Patients included in this cohort responded yes to the following question: "Are you taking medicine for diabetes ("sugar")?"

[5]Patients included in this cohort responded yes to either of the following questions: "Are you taking medicine for asthma or chronic bronchitis or emphysema?" or "Do you have cough or difficult breathing which has lasted for more than two weeks?"

CESD-10, 10-item Center for Epidemiologic Studies Depression Scale; ICC, intraclass correlation coefficient.

doi:10.1371/journal.pmed.1002178.t001

Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention.

## Setting and Programme

**Usual care for non-communicable and communicable diseases (control group).** South African primary care clinics provide free services for communicable disease and NCDs. Patients are seen by a clinician, usually a nurse, and stable patients with NCDs are seen at intervals of 3–6 mo, but are required to collect medications each month either from the clinic or from an off-site medication pick-up point. The clinical load borne by nurses is great; in 2008 the median number of patients per nurse seen each working day in the clinics studied

was 25. Although all clinics were attended by doctors, in more than half this was on a part-time basis rather than daily (Table A in S1 Appendix). National regulations require that prescriptions be renewed and co-signed by a doctor at least every 6 mo, a process that is time-consuming, reducing opportunities for the doctor to review complex cases and mentor nurses. The selection of medications and level of prescribing provisions (nurse versus doctor) are governed by the South African national essential medicines list and standard treatment guidelines [41], which are revised by the National Department of Health every 5 y. Nurse prescribing provisions differ by province and, prior to the trial, were limited in the Western Cape to first-line medications such as thiazide diuretics for hypertension, metformin for diabetes, and low-dose inhaled corticosteroids for asthma. Prescription of antidepressants, which is governed by regulatory conditions for high schedule medications, is restricted to doctors.

Guidelines and policies for communicable diseases change more frequently than those for NCDs. Guidelines for both tend to be lengthy and text-heavy, at times containing confusing differences in recommendations for the same condition. To address this issue, we developed and implemented the Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS), a management tool that integrates guidelines and configures them concisely and simply in an algorithmic format that more closely aligns with presentations in primary care (symptoms and follow-up for chronic conditions) and ensures harmonisation of disease-specific guidelines. It also clarifies prescriber levels (nurse versus doctor) [13,17,42]. It was implemented in two provinces in 2006 (Western Cape and Free State), and in all nine provinces of South Africa between 2010 and 2011. Since 2007 it has included provision for nurse initiation and re-prescription of ART. This inclusion was based on the results of a large pragmatic randomised controlled trial performed in the Free State Province that showed that nurses were as effective as doctors in providing ART care [9,11,12], and on a second trial in the Western Cape and Gauteng Provinces that evaluated nurse re-prescription of ART [43]. This development was prompted by the urgent need to expand ART services in South Africa. Use of the latest (2011/2012) version of PALSA PLUS was the standard of care in control clinics during the PC101 Trial. Prior to the development of PC101, nurses were required to manage NCDs, but they received relatively little training and support, resources for NCD management were not user-friendly, and initiation or intensification of NCD medications was largely dependent on the availability of doctors. The introduction of PALSA PLUS was the first attempt to change this pattern; providing more user-friendly management tools that expanded nurses' scope of practice and prescribing with increasing "diagonal" integration.

A second key component of the PALSA PLUS programme is training clinicians to use the management tool. This component employs an educational outreach model [44] in which facility trainers, typically nurse middle managers, are trained and equipped to deliver repeated short (1.5 h), onsite, interactive training sessions using carefully constructed case scenarios [42]. Clinicians are trained to use the tool as a care pathway in case management and to use it during each consultation. Follow-up "refresher" training accompanied distribution of the revised management tool each year. By 2011, around 70% of all nurses working in the trial districts had received initial training in PALSA PLUS, and training continued as usual in the control clinics.

An unanticipated change in usual care in the health districts under study was a shift in focus from communicable disease care to NCD care. Midway through the trial, the district health department launched a 3-mo campaign called Chronic Disease Season in all clinics to improve NCD recognition and care. Chronic Disease Season focused on hypertension and diabetes and involved both community and clinic health workers. The community-level interventions included several "health screening days" in which free blood pressure and finger-prick glucose measurements were offered at venues such as shopping centres and town halls. People with high values were referred to local clinics. In addition, around 10% of community health

workers (33 in total) were equipped to provide basic education on lifestyle measures including diet and physical activity.

**Intervention rationale.** The PC101 intervention was a further development of the PALSA PLUS programme, aimed to include all common symptoms and conditions, including NCDs, among adults attending primary care services. This expanded scope was strongly motivated by input from primary care nurses and managers, who reported that coverage for NCDs in PALSA PLUS, particularly hypertension and diabetes, would greatly improve its usefulness. The implementation of PC101 aimed to use the same educational outreach approach as used for PALSA PLUS. This educational approach was shown in three pragmatic trials to be effective for the management of communicable diseases. Beneficial effects included reproducible and substantial improvements in TB case detection [9,13,15]; increases in appropriate prescribing, including inhaled corticosteroids for asthma [15], co-trimoxazole prophylaxis for HIV [13], and appropriate switching to second-line ART [9]; and appropriate referral of severe [15] and complex cases [9]. Changes in healthcare utilisation included fewer and shorter hospital admissions and a higher number of primary care visits [9,13,15]. The impact on health worker morale was also documented in parallel qualitative evaluations, with nurses reporting a sense of empowerment and emphasising the value of combining simplified diagnostic and treatment algorithms, onsite training, and expansions in prescribing provisions [12,42]. No harmful effects of the intervention were noted.

**Intervention materials.** The main intervention material was a 101-page evidence- and policy-informed algorithmic management tool. Based on PALSA PLUS, it was developed over a period of 5 y (2006–2011) with input from specialist clinicians, primary care doctors and nurses, allied health professionals, managers, and representatives of patient advocacy groups. The selection of content was based on the results of a cross-sectional survey in 18,000 consultations in primary care clinics across four provinces in South Africa of the most common reasons for attendance. The first half of PC101 covers 40 of the most common symptoms in adults attending primary care and prompts screening for the 20 chronic conditions included in the second half of the tool [6]. The selection of chronic conditions took a health services approach, including those that required regular planned follow-up in primary care. Included were communicable diseases (HIV, TB, sexually transmitted infections), NCDs (diabetes, hypertension, asthma, COPD, epilepsy), mental health conditions (depression, substance abuse, schizophrenia, dementia), and women's health (contraception, antenatal care). Content was extracted from existing disease and policy guidelines and structured in a simple summative form: one page for "diagnosis" and one to two pages for follow-up "routine care" (organised under the headings of "assess", "advise", and "treat") for each condition. Promotion of integrated care was a key objective. Extensive use was made of algorithms and checklists to optimise presentation of content, and provide actionable support that is readily applied during consultations. Content for diverse conditions was organised in a standard format; symptom pages prompted screening for multiple chronic conditions, and pages on the routine care of chronic conditions included screening for common comorbidities. In addition, care was taken to ensure that recommendations that were applicable to multiple pages of the tool, such as blood pressure thresholds for diagnosis, treatment, and lifestyle advice, were harmonised and consistently reflected. The management tool was provided as a ring-bound, high-quality, full-colour illustrated booklet to every clinician (nurse and doctor) responsible for primary care in the 19 intervention clinics. The tool is updated annually to reflect changes in evidence, policy, and feedback from clinicians and managers. For examples of updated content, see http://knowledgetranslation.co.za/programmes/pack-adult/.

The case scenarios used for training built on a set that had been extensively used during PALSA PLUS implementation. An illustration of a typical waiting room scene provided a cast of characters, each of whom was fleshed out in a case scenario (Table B in S1 Appendix). The

cases were carefully constructed to build familiarity with use of the management tool, grow knowledge specifically related to NCDs and depression, and scaffold development of knowledge and skills [45], moving from straightforward clinical presentations toward greater complexity and multimorbidity. The cases formed the basis for the educational training sessions (Table B in S1 Appendix). A desk-blotter with a calendar illustrating key messages for priority conditions was provided to all staff in intervention clinics, to facilitate booking of follow-up appointments and to remind clinicians of essential elements of care.

**Training.** Six health department nurse trainers with experience in primary care and with responsibility for existing training initiatives within the study districts—including Integrated Management of Childhood Illness, PALSA PLUS, and ad hoc training in the TB programme—and with a support role for nurses were employed as facility trainers for the study. They were initially trained in PC101 during a 5-d live-in training course in May 2011. This course was led by an experienced adult education practitioner with a background in nursing (G. F.) and the family doctor who had led the expansion of the management tool (R. C.). The programme adopted a strong experiential focus, and gave as much attention to equipping the nurse trainers to be educators as it did to the expanded content of the management tool. It included multiple practice sessions during which the nurse trainers facilitated case-scenario-based training sessions with their peers, followed by critical feedback. It included exercises to help each trainer understand their own learning style [46] and to learn reflective practice. Facility trainers delivered eight short (1.5 h), on-site, interactive educational outreach sessions using the PC101 management tool and case scenarios to all clinical staff at intervention clinics over several weeks. In all, 155 face-to-face educational outreach sessions were held at the 19 intervention clinics, eight sessions in each clinic. Owing to clinical demands and absences due to night duties or annual sick or study leave, not all staff were able to attend every session. In total, 81 nurses (who each participated in a median of six sessions), five pharmacists, and four doctors were trained. The trainers received no payment from the research team. In addition to on-site training, nurse trainers provided support to staff through regular visits during which they would discuss difficult cases, review folders of patients whose care nurses had changed using PC101, or jointly see patients.

The nurse trainers themselves were supported through quarterly 1-d workshops, facilitated by G. F. These workshops included opportunities to report back on training at the clinic, troubleshoot difficulties in scheduling or completing educational outreach sessions, resolve queries related to the clinical content of the management tool, and practise facilitation skills. They also aimed to continue the community of practice that had been established during the initial live-in training.

**Expanded prescribing provisions.** Professional nurses who successfully completed the educational outreach were authorised by the district manager to prescribe an additional seven medications for NCDs previously restricted to doctors: enalapril and amlodipine for hypertension, glibenclamide and gliclazide for diabetes, simvastatin for increased cardiovascular risk, inhaled budesonide for asthma, and short courses of oral prednisone for exacerbations of COPD (Table C in S1 Appendix). These expansions were clearly reflected in the management tool, which colour-coded all medications to reflect whether they could be prescribed by a doctor or a nurse or only by a doctor, and were also communicated to clinic managers by way of a circular from the district managers. The expanded prescribing provisions initially resulted in some tensions between nurses, doctors, and pharmacists. These were resolved through a facilitated group session and informal communication within clinics, sometimes involving the nurse trainer. This intervention was the only modification to the training during the trial.

**Intervention monitoring.** The integrity of the intervention was assessed in several ways. Nurse trainers were observed during the initial live-in course and at quarterly follow-up workshops. Two nurse trainers were interviewed, and, in December 2011, focus group discussions

were held with nurses in four intervention clinics. Nurses representing both rural and small town locations were enthusiastic about the management tool and recognised that it was a new way of strengthening care for NCDs. In particular they appreciated the format and the standardised framework for providing routine care, and the familiar features shared with PALSA PLUS. Consistent with our previous experience with PALSA PLUS, some variation in uptake of the management tool by nurses was reported. There was a tendency for nurses who formerly used PALSA PLUS to adopt PC101 and use it regularly, whereas nurses who had not used PALSA PLUS were less likely to begin to use the new management tool routinely [11,12]. Uptake by the trainers was considered excellent, and trainers completed planned sessions in all intervention clinics, some repeating sessions to ensure coverage of most staff.

## Data Collection

Fieldworkers recruited from local communities were trained to collect the trial data. They invited patients seated in the waiting rooms to be considered for the study and screened them using a structured questionnaire. Patients who met the eligibility criteria (Table 1) and provided informed consent were enrolled in the trial and completed the baseline questionnaire in Afrikaans, isiXhosa, or English, administered by the fieldworker using a handheld electronic device. Anthropometry (weight, height, waist circumference) and blood pressure were recorded [47]. Patients were asked to attend a follow-up interview 14 mo after their baseline interview. The lengthy period between interviews was intended to allow adequate opportunity for health workers to intervene in the care of trial patients, given that chronic disease patients are seldom reviewed at clinics more often than every 3–6 mo.

The questionnaire included questions on medical history, smoking status, mental health, health-related quality of life, and socio-economic status. The severity of respiratory symptoms among patients in the respiratory cohort was assessed using the symptom and activity domains of the St George's Respiratory Questionnaire [48]. Patients who chose to complete the interview in isiXhosa were excluded from this section of the interview as there is no tested isiXhosa translation of this instrument. The presence of symptoms of depression was assessed with the CESD-10, administered to all patients enrolled in the study [32].

Depression treatment was defined as having received counselling, having been referred to psychiatric services, or being on an antidepressant at a therapeutic dose. Low-dose amitriptyline and imipramine are widely prescribed in South Africa for pain management or insomnia. We therefore defined antidepressant use at a therapeutic dose as prescription of amitriptyline or imipramine $\geq$50 mg daily and/or any other antidepressant. Counselling was defined as "talking with someone in a way that helps to find solutions to problems, or receive emotional support, and not just receiving advice on how to take medication."

Fieldworkers extracted and photocopied patients' prescription charts from their folders, clinic stores, and pharmacies for the year preceding the baseline interview. The medically qualified trial manager (N. F.) analysed all prescription charts and recorded prescriptions of chronic medication for each patient at the time of their interview. A data capturer entered the prescription data (medication, dose, and frequency) into a database, and the total daily dose for each medication was calculated. Prescription, interview, and laboratory data were imported and stored in a SQL server database, and a single longitudinal record constructed for every patient by the study database scientist (V. T.).

Reminder letters and cell phone text messages were sent to patients in the month preceding their scheduled follow-up interview. Patients who failed to attend this appointment were traced by phone or home visit. Patients received a gift voucher for a local grocery store with a value of ZAR100 (US$12.25) on completion of the follow-up interview, to compensate for

travel costs and time. The follow-up questionnaire was similar to the baseline questionnaire, and fieldworkers repeated the anthropometry and blood pressure measurements. At follow-up, prescription data for the period since baseline were extracted, photocopied, analysed, and documented in the same way as at baseline.

Quality control measures included supervision of fieldworkers, electronic alert messages for fieldworkers if unusually high or low values were entered into the electronic questionnaire, monitoring of the data to identify unusual values or trends, and double entry of prescription data. At follow-up, prescription data were queried if they were missing, if the date of the prescription fell outside of a 1-mo window period based on the scheduled re-interview date, or if cohort-specific medications were excluded.

Blinding of the intervention was not possible at the clinic level due to the nature of the intervention.

## Outcome Measures

The primary outcome for hypertension, diabetes, and chronic respiratory disease was treatment intensification, reflected by an increase in dose or number of medications or change in medication class. This outcome was chosen after considering research identifying clinician inertia as a key reason for failure to control these conditions [49,50]; treatment intensification is associated with improved control [51–53]; was likely appropriate for the study population, where under-treatment was highly prevalent [1,7,8]; fitted well with the focus of the intervention on the clinical practices of nurses and the expansion of their prescribing with training; and could be applied across three of the four chronic conditions of interest. Definitions of treatment intensification by cohort are summarised in Table 1. For the depression cohort, case detection was selected as the primary outcome because depression is recognised to be under-diagnosed and under-treated in primary care [54].

Secondary outcome measures were as follows: disaggregation of primary outcomes by type of medication; cardiovascular disease risk and risk factors such as blood pressure, body mass index (BMI), and smoking status; health-related quality of life measured using the EuroQol-5D [55] and the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) [56]; mortality; and healthcare utilisation. These last four outcomes were designed to detect evidence of harm resulting from shifting clinical responsibility from doctors to nurses, an often overlooked consideration in evaluations of task-shifting [57].

## Sample Size and Statistical Power

The study was powered to detect clinically important differences in primary outcomes within each cohort, accounting for the cluster randomisation design. With 38 clinics available for randomisation, we calculated the number of patients needed per clinic for each cohort to detect differences in primary outcomes of between 10% and 15%, with 90% power, 5% significance, and intraclass correlations of outcome based on previous studies, and assuming 20% loss to follow-up (Table 1). Baseline rates of treatment intensification were not available in South Africa, and so we used rates from studies completed in high-income settings [50,58].

HbA1c was measured as part of the pre-planned blood sampling strategy in a subgroup of clinics because resource limitations meant that we could not measure it in all diabetic patients in all 38 clinics. We estimated that HbA1c tests were needed from 30 diabetic patients in 10 clinics in each group (i.e., 600 diabetic patients from 20 clinics in total) in order to a show a difference of 0.5% (HbA1c of 8.8% in the control group versus HbA1c of 8.3% in the intervention group, assuming a standard deviation of 3.4%).

## Analysis

We compared baseline clinic and patient characteristics between treatment groups. All clinics and patients were analysed in the treatment group to which they were randomly assigned. Primary and secondary outcomes were analysed at the patient level, separately within each cohort. No adjustment was made for the multiple disease-specific primary outcomes. The cluster randomisation design was accounted for using robust cluster variance-covariance estimates. Intervention effects were estimated using binomial regression models with treatment as the main effect, adjusted for stratification, and are reported with 95% confidence intervals. Secondary analyses were further adjusted for potentially confounding baseline characteristics such as treatment status and disease control at baseline, smoking status, age, sex, and co-morbidity with one of the study diseases.

We carried out pre-specified subgroup analyses of the primary outcomes stratified by baseline level of disease control using binomial regression models including baseline disease control as a covariate. Baseline disease control of hypertension was defined as blood pressure $< 140/90$ (or, in patients with diabetes or a history of cardiovascular disease, $<130/80$), and for diabetes, as HbA1c $< 7\%$. For depression, since the outcome was detection, "control" was defined as any patient receiving treatment for depression as follows: being on antidepressant medication at therapeutic dosage or having received counselling in the past year or having been referred to psychiatric services in the last year. No definition of disease control was applied to patients with chronic respiratory disease. Heterogeneity of the intervention effect was assessed by looking at the interaction between treatment and baseline disease control. In addition, we pre-specified secondary analyses of the primary outcomes disaggregated by component. For the primary outcomes, missing data were considered not to have occurred.

We used linear regression to compare changes between baseline and follow-up in blood pressure, waist circumference, weight, BMI, HbA1c, and health status measures between the treatment groups, adjusted for stratification. Similarly, we used ordinal logistic regression to compare readiness to quit smoking, and Poisson regression to compare rates of healthcare utilisation between the treatment groups. Stata version 13.0 statistical software was used for all analyses.

## Results

Fig 1 shows the trial profile. All 38 randomised clinics completed the trial. In all, 4,904 patients were screened, of whom 4,393 patients met the eligibility criteria and were enrolled in the trial. Recruitment targets were exceeded for all cohorts except for diabetes, where recruitment fell short of targets. Enrolment of patients took place between 28 March 2011 and 10 November 2011 and was completed in intervention clinics before educational outreach sessions to nurses began. Follow-up data collection began on 21 May 2012 and ended on 13 December 2012.

In all, 1,927 patients in the intervention group were interviewed at follow-up (1,927/2,166; 89%), and 2,050 in the control group (2,050/2,227; 92%). Reasons for not being re-interviewed were similar between groups: death (63 in the intervention group versus 54 in the control group); relocation (42 in the intervention group versus 26 in the control group); too ill to be re-interviewed (two in the intervention group versus zero in the control group); and could not be traced (132 in the intervention group versus 97 in the control group). Prescription charts could be traced, and thus the primary outcome ascertained, for 206 patients who were not re-interviewed in the intervention group, and 151 in the control group, accounting for the very high rates of patients contributing data to the primary endpoint analysis (Fig 1).

Baseline patient characteristics are presented in Table 2 and detailed in a separate publication [47]. Baseline clinic characteristics are provided in Table A in S1 Appendix. Intervention

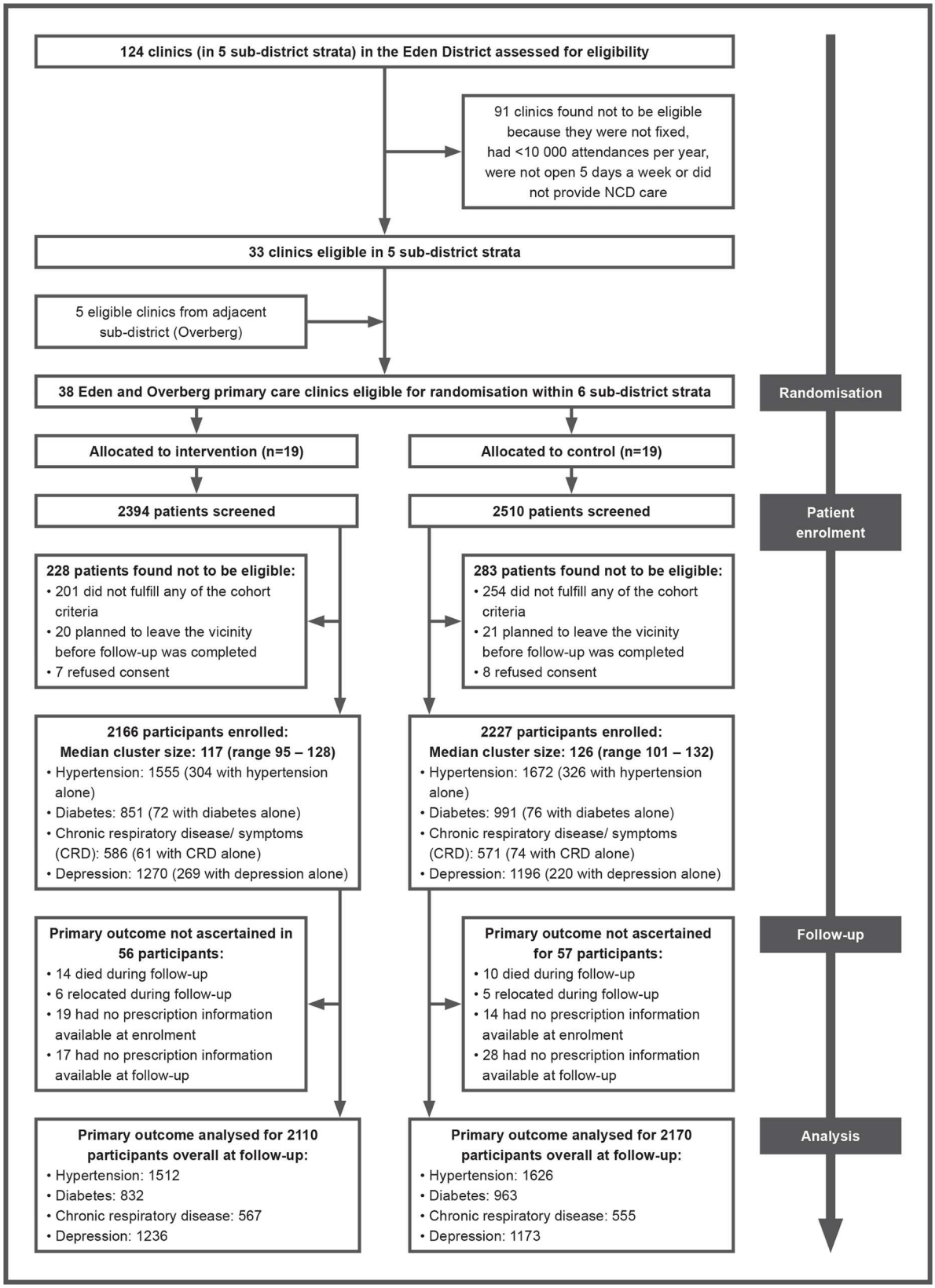



**Fig 1. Trial profile.** NCD, non-communicable disease.

doi:10.1371/journal.pmed.1002178.g001

**Table 2. Characteristics of patients allocated to an educational outreach programme (intervention group) or no new training (control group).**

| Characteristic | Intervention | Control |
|---|---|---|
| Patients recruited | 2,166 (49) | 2,227 (51) |
| Women | 1,573 (73) | 1,621 (73) |
| Age (years): median (IQR) | 51 (42–61) | 53 (44–62) |
| Language selected for the interview | | |
| • Afrikaans | 1,794 (83) | 1,885 (85) |
| • isiXhosa | 145 (7) | 192 (9) |
| • English | 227 (11) | 150 (7) |
| Highest education level achieved | | |
| • Tertiary education | 40 (2) | 35 (2) |
| • Secondary school education | 923 (43) | 930 (42) |
| • Primary school education | 818 (38) | 940 (42) |
| • No schooling | 146 (7) | 145 (7) |
| • Not obtained | 239 (11) | 177 (8) |
| Employed or self-employed | 557 (26) | 531 (24) |
| Receiving a social government grant | 1,205 (56) | 1,323 (59) |
| Housing density[1]: median (IQR) | 2 (1–2), *n* = 1,426 | 2 (1–2), *n* = 1,505 |
| Multimorbidity | | |
| • Hypertension only | 304 (14) | 326 (15) |
| • Diabetes only | 72 (3) | 76 (3) |
| • Chronic respiratory disease only | 61 (3) | 74 (3) |
| • Depression only | 269 (12) | 220 (10) |
| • Two conditions | 911 (42) | 949 (43) |
| • Three or four conditions | 549 (25) | 582 (26) |
| Past medical history | | |
| • Known cardiovascular disease (heart attack, angina, stroke) | 605 (28) | 505 (23) |
| • Previous tuberculosis | 237 (11) | 255 (12) |
| • History of hypertension | 1,590 (73) | 1,718 (77) |
| • History of diabetes | 854 (39) | 998 (45) |
| • History of depression | 525 (24) | 558 (25) |
| Smoking history | | |
| • Current | 652 (30) | 731 (33) |
| • Past | 464 (21) | 550 (25) |
| • Never | 1,022 (47) | 921 (41) |
| • Not obtained | 28 (1) | 25 (1) |
| Pack-year history for current and ex-smokers: median (IQR) | 7 (3–15), *n* = 869 | 7 (3–13), *n* = 1,064 |
| Hospitalisation in 3-mo period preceding interview | 134 (6) | 136 (6) |
| BP 140/90 mm Hg[2] | 1,055 (49) | 1,216 (55) |
| BP 180/110 mm Hg[2] | 166 (8) | 193 (8) |
| Weight (kg): mean (SD) | 77 (20), *n* = 2,111 | 77 (19), *n* = 2,179 |
| BMI (kg/m$^2$): mean (SD) | 30 (8), *n* = 2,060 | 30 (8), *n* = 2,104 |
| Obese (BMI 30 kg/m$^2$) | 972 (45) | 1,008 (45) |
| Waist circumference (cm): mean (SD) | 98 (16), *n* = 2,140 | 98 (16), *n* = 2,205 |
| Waist circumference more than ideal[2] | 1,316 (61) | 1,381 (62) |
| 10-y non-laboratory-based cardiovascular disease death risk (percent)[3]: mean (SD) | 22 (20), *n* = 1,335 | 26 (21), *n* = 1,327 |

(*Continued*)

**Table 2.** (*Continued*)

| Characteristic | Intervention | Control |
|---|---|---|
| HbA1c (percent): mean (range), median (IQR) | 9 (4–17), 8 (7–10), *n* = 310 | 9 (5–17), 9 (7–11), *n* = 394 |
| HbA1c 7% | 227 (73), *n* = 310 | 317 (81), *n* = 394 |

Values are *n* (percent) unless stated otherwise.

[1]Housing density: number of occupants/number of rooms.

[2]Waist circumference >88 cm for women, >104 cm for men.

[3]Ten-year risk of cardiovascular disease death (sudden cardiac or stroke death). Score calculated for patients with no known cardiovascular disease.

BMI, body mass index; BP, blood pressure; IQR, interquartile range; SD, standard deviation.

doi:10.1371/journal.pmed.1002178.t002

and control clinics had similar numbers of nurses and doctors. Control clinics tended to be larger and, by chance, had more psychiatric services and on-site pharmacy facilities.

Baseline patient characteristics were generally well balanced between arms. Seventy-three percent of patients were women, and the median age was 52 y. There were high levels of unemployment and receipt of social welfare grants. Multimorbidity was common: 42% of patients had two conditions, and 26% more than two. The percentage of patients with a single condition of interest was as follows: hypertension, 20% (630 of 3,227); depression, 20% (489 of 2,466); diabetes, 8% (148 of 1,842); and chronic respiratory disease, 12% (135 of 1,157). A quarter of patients reported established cardiovascular disease. Eleven percent reported previous TB, and 2% reported being on ART. There were signs of under-treatment and under-diagnosis, with 18% of hypertensive patients reporting no or only one current antihypertensive medication, only 51% of diabetic patients receiving statins, only 50% of those with chronic respiratory disease or symptoms receiving any respiratory medication, and only 25% of those who screened positive for depression reporting some form of relevant treatment for the condition.

There was poor control of hypertension and diabetes despite treatment: blood pressure was ≥140/90 mm Hg in 59% of hypertensive patients, and HbA1c was ≥7% in 77% of those with diabetes in whom HbA1c was measured at baseline (704/1,842; 38%).

Treatment intensification in the hypertension and diabetes cohorts across both the intervention and control groups was common during the study period (Table 3), slightly favouring the intervention group (44% versus 40% for hypertension and 57% versus 50% for diabetes), although these differences were not significant when adjusted for stratification by sub-district and clustering. For hypertension, the risk ratio (RR) was 1.08 (95% CI 0.94 to 1.24; $p = 0.252$); for diabetes, the RR was 1.10 (95% CI 0.97 to 1.24; $p = 0.126$). Rates of treatment intensification in the chronic respiratory disease cohort were low (14% in the intervention group versus 12% in the control group) and not significantly different between groups (RR 1.08; 95% CI 0.75 to 1.55; $p = 0.674$). Fewer patients who screened positive for depression in the intervention group reported receiving treatment for depression at follow-up than their control group counterparts (18% versus 24%), but there was no difference between groups after adjustment for the trial's design (RR 0.76; 95% CI 0.53 to 1.10; $p = 0.142$). Adjustment for baseline characteristics (Table 2) did not materially alter these results. The full regression models are presented in Table D in S1 Appendix.

Pre-specified subgroup analyses by baseline level of disease control (Table 4) showed that, in the diabetic cohort, the intervention was associated with treatment intensification only among patients with baseline HbA1c of 7%–10% (RR 1.30; 95% CI 1.16 to 1.47; *p*-value for interaction = 0.010). In the other cohorts, there were no significant differences in effectiveness

**Table 3. Primary outcomes for each disease cohort.**

| Disease Cohort | Outcome | Intervention, *n*/*N* (Percent) | Control, *n*/*N* (Percent) | Effect Estimate: Risk Ratio | | | | ICC |
|---|---|---|---|---|---|---|---|---|
| | | | | Crude Model | | Adjusted Model | | |
| | | | | Estimate (95% CI) | *p*-Value | Estimate (95% CI) | *p*-Value | |
| Hypertension | Treatment intensification | 685/1,555 (44) | 673/1,672 (40) | 1.08 (0.94 to 1.24) | 0.252 | 1.10[1] (0.96 to 1.27) | 0.165 | 0.043 |
| Diabetes | Treatment intensification | 481/851 (57) | 498/991 (50) | 1.10 (0.97 to 1.24) | 0.126 | 1.11[2] (0.99 to 1.26) | 0.083 | 0.030 |
| Chronic respiratory disease | Treatment intensification | 81/586 (14) | 68/571 (12) | 1.08 (0.75 to 1.55) | 0.674 | 1.22[3] (0.88 to 1.68) | 0.228 | 0.011 |
| Depression | Case detection | 224/1,253 (18) | 283/1,186 (24) | 0.76 (0.53 to 1.10) | 0.142 | 0.80[4] (0.57 to 1.10) | 0.167 | 0.077 |

[1]Adjusted for age, sex, body mass index, smoking status, diabetes, chronic respiratory disease, blood pressure control, maximal medical therapy at baseline, history of cardiovascular disease.

[2]Adjusted for sex, body mass index, smoking status, hypertension, history of cardiovascular disease at baseline.

[3]Adjusted for age, smoking status, diabetes, history of tuberculosis, whether or not receiving respiratory medication at baseline.

[4]Adjusted for sex, smoking status, hypertension, history of depression, 10-item Center for Epidemiologic Studies Depression Scale score at baseline, whether or not receiving antidepressant medication at baseline.

ICC, intraclass correlation coefficient.

doi:10.1371/journal.pmed.1002178.t003

between subgroups. However, treatment intensification tended to be more common, in both arms, in subgroups with poorer control at baseline. The non-significant difference in depression treatment, which favoured the control group, was mostly among those already receiving treatment for depression at baseline.

Disaggregated primary outcomes are presented in Table E in S1 Appendix. Notable findings include apparently significantly higher rates of aspirin initiation among patients with hypertension and diabetes attending intervention clinics, even though aspirin prescribing was restricted to doctors. Angiotensin-converting enzyme (ACE) inhibitor use was significantly higher among intervention group patients with known cardiovascular disease, as was sulphonylurea use among intervention group diabetic patients with BMI $\geq$ 30 kg/m$^2$. In the depression cohort, the higher rate of depression treatment in the control arm was because more control group patients reported receiving counselling (15% in the intervention arm versus 22% in the control arm) and referral to psychiatric services (5% in the interventional arm versus 9% in the control arm). There was no significant difference between groups in the use of antidepressants, which was very low (<5%).

Table 5 reports differences in cardiovascular risk factors between baseline and follow-up. There were no differences between groups in terms of blood pressure, waist circumference, BMI, or HbA1c. Smoking quit rates were high overall, but similar between groups. However, readiness to quit smoking was significantly higher in the intervention group (odds ratio 1.73; 95% CI 1.17 to 2.57).

There were no differences between groups in health outcomes measured with the EuroQol-5D [55], CESD-10 [32], or World Health Organization Disability Assessment Schedule 2.0 [56] (Table 6). Mortality did not differ between groups (Table 6). Healthcare utilisation, as measured by clinic visits and hospital admissions during the 3 mo before the follow-up visit, was similar between groups, but there was a statistically non-significant higher number of hospital admissions in the intervention group (Table 7).

**Table 4. Subgroup analyses: primary outcomes stratified by level of disease control at baseline.**

| Baseline Subgroup (Pre-specified) | Intervention, *n*/*N* (Percent) | Control, *n*/*N* (Percent) | Effect Estimate: Risk Ratio | | WALD *p*-Value[1] |
|---|---|---|---|---|---|
| | | | Estimate (95% CI) | *p*-Value | |
| **Hypertension** | | | | | 0.444 |
| BP uncontrolled[2] | 546/1,127 (49) | 545/1,268 (43) | 1.12 (0.97 to 1.28) | 0.113 | |
| BP controlled[2] | 139/426 (33) | 128/399 (32) | 1.01 (0.76 to 1.33) | 0.954 | |
| **Diabetes** | | | | | 0.010 |
| HbA1c < 7% | 34/83 (41) | 29/77 (38) | 1.08 (0.77 to 1.52) | 0.638 | |
| HbA1c 7%–10% | 97/140 (69) | 93/170 (55) | 1.30 (1.16 to 1.47) | <0.001 | |
| HbA1c > 10% | 62/87 (71) | 107/147 (73) | 0.97 (0.81 to 1.16) | 0.703 | |
| **Chronic respiratory disease: symptom score subgroup** | | | | | 0.532 |
| SGRQ symptom score ≤ median | 20/189 (11) | 19/228 (8) | 1.17 (0.66 to 2.07) | 0.581 | |
| SGRQ symptom core > median | 37/221 (17) | 35/195 (18) | 0.95 (0.65 to 1.39) | 0.802 | |
| **Chronic respiratory disease: activity score subgroup** | | | | | 0.693 |
| SGRQ activity score ≤ median | 36/256 (14) | 34/273 (13) | 1.07 (0.7 to 1.65) | 0.744 | |
| SGRQ activity score > median | 40/271 (15) | 31/254 (12) | 1.21 (0.77 to 1.92) | 0.412 | |
| **Depression** | | | | | 0.632 |
| Receiving any treatment for depression[3] | 76/278 (27) | 127/336 (38) | 0.74 (0.54 to 1.02) | 0.063 | |
| Not receiving any treatment for depression[3] | 148/990 (15) | 156/860 (18) | 0.84 (0.49 to 1.42) | 0.510 | |

[1] *p*-Values for arm-subgroup interaction.

[2] BP uncontrolled defined as ≥130/80 mm Hg for patients with diabetes or a history of cardiovascular disease, and ≥140/90 mm Hg for all other patients.

[3] Receiving treatment for depression defined as being on antidepressant medication at therapeutic dosage or having received counselling in the past year or having been referred to psychiatric services in the last year.

BMI, body mass index; BP, blood pressure; SGRQ, St George's Respiratory Questionnaire.

doi:10.1371/journal.pmed.1002178.t004

## Discussion

This paper reports our evaluation of the clinical effectiveness of a complex health systems intervention, based on task-shifting by adding nurse-led NCD and depression care to a proven effective, and scalable, integrated care model for nurse-led care of communicable diseases, in the context of limited availability of physicians to treat a high burden of multimorbid and poorly controlled NCDs in a middle-income country.

The primary analyses found no statistically significant effects of the intervention on the primary outcomes for any of the four disease cohorts. These cohorts were analysed separately, equivalent to four parallel trials; adjustment for having four primary outcomes instead of one would only have decreased statistical differences. Health status outcomes also did not differ between the intervention and control groups. But neither was there evidence of harm for any of these endpoints, or in terms of reduced well-being or excess hospitalisations or deaths. In

**Table 5. Effect on cardiovascular disease risk and risk factors; all four cohorts pooled.**

| Risk/Risk Factor | Measurement at Follow-Up | | Change between Baseline and Follow-Up | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Intervention[1] | Control[1] | Intervention[1] | Control[1] | Effect Estimate | | *p*-Value | ICC |
| | | | | | Type | Estimate (95% CI) | | |
| CVD risk[2] | 22.1 (20.0), *n* = 1,550 | 24.9 (20.6), *n* = 1,417 | −0.4 (8), *n* = 1,365 | −1.1 (8), *n* = 1,303 | Diff in means | 0.54 (−0.51 to 1.59) | 0.310 | 0.038 |
| SBP (mm Hg) | 134 (23.0), *n* = 1,927 | 135 (21.7), *n* = 2,049 | 1.2 (21.8), *n* = 1,925 | −1.1 (21.7), *n* = 2,044 | Diff in means | 2.00 (−0.87 to 4.87) | 0.172 | 0.038 |
| DBP (mm Hg) | 88 (13.2), *n* = 1,927 | 87 (12.7), *n* = 2,049 | 0.0 (13.5), *n* = 1,925 | −1.8 (13.4), *n* = 2,044 | Diff in means | 1.58 (−0.56 to 3.72) | 0.148 | 0.058 |
| Proportion with uncontrolled BP[3] | 1,267/2,166 (58%) | 1,325/2,227 (60%) | N/A | N/A | Risk ratio | 1.02[4] (0.96 to 1.09) | 0.464 | 0.024 |
| Waist circumference (cm) | 98.3 (16.7), *n* = 1,886 | 99.6 (16.8), *n* = 1,998 | 0.3 (8.4), *n* = 1,867 | 0.8 (8.8), *n* = 1,981 | Diff in means | −0.53 (−2.30 to 1.25) | 0.563 | 0.131 |
| Weight (kg) | 77.2 (19.7), *n* = 1,872 | 77.2 (19.2), *n* = 1,992 | −0.1 (6.5), *n* = 1,866 | −0.3 (6.5), *n* = 1,985 | Diff in means | 0.15 (−0.52 to 0.82) | 0.665 | 0.024 |
| BMI (kg/m$^2$) | 30.1 (7.6), *n* = 1,866 | 30.5 (7.5), *n* = 1,981 | 0.0 (2.5), *n* = 1,863 | −0.1 (2.6), *n* = 1,979 | Diff in means | 0.06 (−0.21 to 0.32) | 0.672 | 0.024 |
| HbA1c (percent) | 9.1 (2.6), *n* = 285 | 9.5 (2.6), *n* = 333 | 0.0 (2.4), *n* = 161 | −0.2 (2.1), *n* = 218 | Diff in means | 0.21 (−0.43 to 0.85) | 0.508 | 0.055 |
| Proportion who smoke | 480/2,166 (22%) | 577/2,227 (26%) | N/A | N/A | Risk ratio | 0.88[5] (0.74 to 1.06) | 0.178 | 0.037 |
| Proportion who quit smoking | 167/574 (29%) | 194/668 (29%) | N/A | N/A | Risk ratio | 1.01 (0.71 to 1.42) | 0.971 | 0.049 |
| Number of units smoked per day | 6.8 (6.1), *n* = 479 | 6.6 (5.1), *n* = 578 | −0.7 (5.7), *n* = 406 | −0.6 (5.7), *n* = 578 | Diff in means | −0.08 (−1.07 to 0.91) | 0.869 | 0.047 |
| Readiness to quit smoking | | | | | Odds ratio | 1.73 (1.17 to 2.57) | 0.006 | 0.104 |
| • Thinking of quitting in next 30 d | 73/480 (15%) | 66/577 (11%) | N/A | N/A | | | | |
| • Thinking of quitting in next 6 mo | 318/480 (66%) | 337/577 (58%) | N/A | N/A | | | | |
| • Not thinking of quitting | 89/480 (19%) | 174/577 (30%) | N/A | N/A | | | | |

[1]Mean (standard deviation) or *n/N* (percent).

[2]Ten-year risk of cardiovascular disease death (sudden cardiac or stroke death). Score calculated for patients with no known cardiovascular disease.

[3]Uncontrolled BP defined as ≥130/80 mm Hg for patients with diabetes or a history of cardiovascular disease, and ≥140/90 mm Hg for all other patients.

[4]Adjusted for uncontrolled BP at baseline, age, and sex.

[5]Adjusted for insulin at baseline, uncontrolled BP at baseline, BMI, sex, hypertension, and history of cardiovascular disease.

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; Diff, difference; DBP, diastolic blood pressure; ICC, intraclass correlation coefficient; N/A, not applicable; SBP, systolic blood pressure.

doi:10.1371/journal.pmed.1002178.t005

addition, the intervention was not associated with higher healthcare utilisation at the primary care or hospital level. A pre-planned subgroup analysis by baseline level of diabetes control showed a benefit of the intervention in the subgroup of patients with moderately uncontrolled diabetes (HbA1c 7%–10% at baseline), but the two other pre-specified subgroup analyses (for hypertension and depression by baseline level of disease control) did not show a significant difference between groups.

While no primary outcomes showed a significant benefit of the intervention, the upper confidence limits included the possibility of meaningful clinical improvements, and the direction of results in three of the four primary endpoints in the study was consistent and positive. Also,

**Table 6. Effect on quality of life, depression, and mortality.**

| Outcome | Measurement at Follow-Up | | Change between Baseline and Follow-Up | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Intervention[1] | Control[1] | Intervention[1] | Control[1] | Effect Estimate | | *p*-Value | ICC |
| | | | | | Type | Estimate (95% CI) | | |
| EuroQol 5D index score[2] | 0.8 (0.3), *n* = 1,927 | 0.8 (0.2), *n* = 2,050 | 0.0 (0.3), *n* = 1,924 | 0.0 (0.3), *n* = 2,045 | Diff in means | 0.00 (−0.05 to 0.06) | 0.855 | 0.078 |
| EuroQol 5D visual analogue scale[3] | 75.1 (20.3), *n* = 1,927 | 74.0 (19.0), *n* = 2,050 | 12.1 (29.8), *n* = 1,924 | 6.4 (26.9), *n* = 2,045 | Diff in means | 6.06 (−3.25 to 15.36) | 0.202 | 0.290 |
| 10-item Center for Epidemiologic Studies Depression Scale[4] | 8.0 (6.3), *n* = 1,927 | 7.4 (6.1), *n* = 2,050 | −3.1 (6.8), *n* = 1,926 | −3.1 (7.3), *n* = 2,050 | Diff in means | −0.12 (−1.72 to 1.48) | 0.882 | 0.111 |
| World Health Organization Disability Assessment Schedule 2.0[5] | 17.1 (7.0), *n* = 1,740 | 17.6 (6.3), *n* = 1,933 | N/A | N/A | Diff in means | −0.09 (−1.27 to 1.09) | 0.878 | 0.113 |
| Mortality | 64/2,166 (3%) | 64/2,227 (3%) | N/A | N/A | Risk ratio | 1.11 (0.79 to 1.56) | 0.564 | 0.003 |

[1]Mean (standard deviation) or *n/N* (percent).

[2]The EuroQol-5D index score is a weighted total between 0 and 1, where 0 = death and 1 = perfect health.

[3]The EuroQol-5D visual analogue scale is a score between 0 and 100 where 0 = worst imaginable state of health and 100 = best imaginable state of health.

[4]The 10-item Center for Epidemiologic Studies Depression Scale is scored from 0 to 30, with higher scores representing greater degrees of depressed mood.

[5]The World Health Organization Disability Assessment Schedule 2.0 is scored from 12 to 60, with higher scores representing greater degrees of disability.

Diff, difference; ICC, intraclass correlation coefficient; N/A, not applicable.

doi:10.1371/journal.pmed.1002178.t006

the pre-specified secondary analysis of patients with diabetes and uncontrolled HbA1c measurements at baseline demonstrated a positive effect. After disaggregation of the disease groups, other significant findings were higher rates of aspirin initiation among patients with hypertension and diabetes, higher use of ACE inhibitors in patients with known cardiovascular disease, and more prescriptions of sulphonylureas in patients with diabetes and a high BMI (Table E in S1 Appendix).

The non-significant findings for the primary outcomes contrast with positive findings in our three previous pragmatic randomised controlled trials using a similar integrated management tool and the same training approach, focused on a narrower range of mainly communicable conditions [9–15,30,42,59]. These trials showed modest, but consistent, improvements across a range of process indicators and health and healthcare utilisation outcomes.

There are several potential reasons for the non-significant findings on the primary outcomes of our study. One is the level of uptake of PC101 into daily clinical practice. Owing to limited research funding, a complete and suitably detailed process evaluation of the uptake of PC101 into clinical practice was not possible. However, limited focus group discussions and

**Table 7. Effect on healthcare utilisation.**

| Outcome | Intervention, Mean (SD) | Control, Mean (SD) | Effect Estimate | | | ICC |
|---|---|---|---|---|---|---|
| | | | Type | Estimate (95% CI) | *p*-Value | |
| Number of hospital admissions in 3 mo before follow-up interview | 0.1 (0.4), *n* = 1,927 | 0.1 (0.3), *n* = 2,050 | IRR | 1.25 (0.91 to 1.71) | 0.162 | 0.004 |
| Number of inpatient days in 3 mo before follow-up interview | 0.4 (2.8), *n* = 1,927 | 0.3 (2.4), *n* = 2,050 | IRR | 1.43 (0.83 to 2.48) | 0.201 | 0.003 |
| Number of clinic visits in 3 mo before follow-up interview | 2.5 (1.7), *n* = 1,456 | 2.5 (1.4), *n* = 1,665 | IRR | 1.02 (0.93 to 1.13) | 0.678 | 0.070 |

ICC, intraclass correlation coefficient; IRR, incidence rate ratio.

doi:10.1371/journal.pmed.1002178.t007

observations in clinics by members of the research team confirmed heterogeneous uptake of PC101 within and between clinics, as might be expected in a pragmatic trial intervention. Overall low levels of uptake would seem unlikely, given the enthusiastic response and high uptake of the method by clinic staff reported in our previous implementation studies with the PALSA PLUS management tool [12,42]. Other factors should be considered, such as training. The addition of NCD care to the training programme may have proved a step too far—the content of the PC101 management tool was twice as substantial as that of the PALSA PLUS tool—and potentially overwhelming for nurses who were still learning to implement nurse-initiated and -managed antiretroviral treatment when the trial started. Furthermore, NCDs have long been managed by nurses in primary care clinics throughout South Africa, albeit with minimal training or intervention. As seen in the baseline characteristics, poor NCD care may have become entrenched, and markers of poor disease control routinely ignored [60]. The challenge of "undoing" these clinical habits and effecting a change in clinical behaviour is well described and may take repeated training sessions to achieve. Although training was provided throughout the trial, the comprehensive nature of PC101 made it difficult to cover the curriculum for NCDs sufficiently within the time frame of the study. Owing to limited research funding, but consistent with a pragmatic trial design, formal assessments of adequacy of training and uptake (use) of PC101 were not performed.

A further potential reason for the failure to show differences between groups was the effect of a co-intervention, the concurrent Chronic Disease Season campaign, instituted by the clinic managers in both control and intervention clinics. The impact of this unforeseen development is seen in the higher rates of treatment intensification for hypertension and diabetes (the focus of the campaign) than for chronic respiratory disease or depressive symptoms in both the intervention and control clinics. Whereas only 13% of patients with chronic respiratory disease and 3% of those with depression had medication intensified at follow-up, nearly half of those with hypertension and diabetes had intensified treatment (42% and 53%, respectively). These rates of intensification of antihypertensive and diabetic medications are similar to or slightly higher than those reported in high-income country settings [50,58].

Another consideration concerns methodology. We recruited all patients with the diseases of interest rather than only those requiring treatment intensification, and failed to assess adherence and exclude patients who did not adhere to previously prescribed medications and who might therefore have been less likely to have been prescribed additional treatment. However, the eligibility criteria were adopted on the assumption that decision-makers wanted evidence of effectiveness of the intervention across broad groups of patients, rather than for subgroups, and that, as lack of disease control was highly prevalent at baseline, the majority of patients would qualify for treatment intensification.

Other limitations of the study design include dependence on self-reported diagnoses for inclusion in the patient cohorts, reliance on process outcomes, and insufficient resources to measure important health outcomes, such as HbA1c, at follow-up. Also, the duration and timing of the follow-up data collection might not have been optimal for a study of chronic diseases, where follow-up visits being only every 3–6 mo limited opportunities for treatment intensification. This is illustrated by the low number of clinic visits during the follow-up period, a mean of around 2.5 per patient over a period of 14 mo (Table 7).

The main strength of the study was that it was a pragmatic trial, implemented under routine circumstances in a real-world setting with the intervention delivered by usual health department trainers, with minimal research-related distortions of care delivery. Observing this real-world implementation appears to have given relevant policy-makers sufficient confidence to make a decision on the suitability of the intervention for their health systems. Other strengths of the study include the cluster randomised design (appropriate to reduce the risk of

contamination in an intervention directed at groups of nurses working in clinics), high follow-up rates for both patient interviews and prescription data, the inclusion of four different chronic diseases in a context characterised by high rates of multimorbidity, and identification and follow-up of patient participants by fieldworkers independent of clinical care.

So what are the implications of the trial for decision-makers in South Africa and other LMICs who are faced with overstretched health services and the need to address NCDs and mental health? In October 2013, even before the trial results were finalised, decision-makers were increasingly enthusiastic about the PC101 intervention, and both the Western Cape Department of Health and the National Department of Health in South Africa elected to commence implementation. Later dissemination of the trial findings on the effectiveness of this intervention to these local and national policy-makers did not change this decision. The decision, we were told, was much more influenced by demand from frontline clinicians and managers for what was perceived to be a highly feasible and acceptable approach to expanding skills for NCDs. Further factors that may have influenced decision-makers were the benefits of the new mode of clinician training reported in our prior studies [9,13,15], an independent report supporting the integrated Chronic Care Model as a feasible component of health system reform in South Africa [61], and the findings of a non-randomised evaluation of PC101 performed in 42 primary care clinics in three additional health districts [62]. The PC101 management tool is correctly seen as a means of overcoming the "silo" approach to individual disease management in which recommendations for different conditions may vary and even conflict and, more importantly, ensures that NCDs and mental health are not overlooked because of prioritisation of communicable diseases. For us, as researchers who look to rigorous research methods to guide health system development, this has been a powerful lesson in understanding that evidence of effectiveness is only one element under consideration by decision-makers [63]. Given clinicians' strong attraction to the ease of integrating PC101 into clinic practice and the positive system effects of our intervention mentioned above, it might have been more useful to focus our primary analysis on lack of harm. For example, the study was not powered to test for differences in healthcare utilisation and reasons for referrals and hospitalisations. Thus, it is not possible to evaluate the significance of the small imbalance in numbers of hospital admissions between the intervention group and the control group, since an increase in hospitalisations reflecting more appropriate referrals from primary care may be interpreted as favourable rather than as a treatment failure. Specifically designed trials are required.

We now consider that it is our responsibility as health system researchers to invest in improving the effectiveness of this intervention. There are patterns in the data from the trial that provide reassurance that the intervention is not harmful and that, with further optimisation, might demonstrate improvements in effectiveness. Several adjustments have been made to the programme that is being scaled up with the aim of increasing its impact on skills, clinician confidence, and quality of care. The PC101 content has been broken down into four training modules (communicable diseases, NCDs, mental health, and women's health) to allow staff to become familiar with one area at a time and embed changes into their clinical practice before moving to the next. We now also explicitly aim PC101 training at doctors, through dedicated workshops for professionals who would otherwise miss regular onsite training due to the sessional nature of their work. Implementation workshops, with an extra day aimed at meeting the needs of facility and middle managers, are included in the training of nurse trainers, and appointment of clinical governance teams within sub-districts allows local troubleshooting of barriers to implementation and inclusion of non-clinicians in the day-to-day running of the programme. A further cluster randomised trial in the North West province of South Africa (ClinicalTrials.gov NCT02407691) is currently evaluating the effect of the mental health module when combined with the provision of manualised depression counselling by lay

health workers delivered to ART patients with co-morbid depression. A second study is evaluating this mental health module in patients with hypertension and co-morbid depression [64]. This expansion of human resources to include lay health workers is based on our experience from the PC101 trial that nurse training alone is insufficient to close the gap in depression care when there is limited access to treatment in the form of counselling services or antidepressant prescriptions (prescribing currently restricted to doctors).

Although it will not be possible to conduct another randomised controlled trial of the adapted PC101 implementation as it is scaled up, we plan to conduct such trials for future national and international adaptations of this programme [17]. Ease of implementability appears to be a major feature for policy-makers, and we will include proxies, such as acceptability to frontline clinicians, as outcome measures in future trials.

In conclusion, this pragmatic cluster randomised trial of the effects of an integrated management tool implemented using educational outreach to nurses showed no effect on treatment intensification in patients with NCDs or on case detection of depression. But neither was there evidence of harm. Despite this lack of positive clinical outcomes, decision-makers were disposed to view PC101 as a coherent, feasible, and acceptable extension of a programme of integrated care previously shown to be effective in the South African health system, and health authorities have committed to a national rollout of an improved version of the PC101 programme. The disjuncture between the clinical outcomes of our study and the policy choice exposes the different responsibilities of researchers and decision-makers in a health system. For us, as intervention developers, this focuses our attention on longer term improvements to strengthen components of the programme in order to achieve clinical impact on care for NCDs, while, as evaluators, we see the need for ongoing audit and further randomised pragmatic controlled trials to evaluate the effectiveness of these improvements.

Health systems research and development is an interactive and deliberative process. Perhaps the greatest contribution of this study lies in the relationships developed between our team and health system decision-makers, during a series of five large randomised evaluations of health systems interventions that responded to decision-maker-defined health systems needs over 16 years [17]. To this process we have each brought our different skills and perspectives, and together have developed, and are scaling up, an iteratively improved, evidence-informed approach to nurse-led primary care that strengthens human resources and health systems, and brings better care to South Africans, as well as models that can be applied in other low- and middle-income country settings.

## Supporting Information

**S1 Appendix.**
(DOCX)

**S1 Data. Dataset.**
(XLSX)

**S1 Text. Trial protocol.**
(DOCX)

**S2 Text. CONSORT checklist.**
(DOC)

**S3 Text. Template for Intervention Description and Replication (TIDieR) checklist.**
(DOCX)

**S4 Text. Baseline questionnaire.**
(PDF)

**S5 Text. Patient information sheet and consent form.**
(PDF)

## Acknowledgments

The authors thank the intervention clinic nurses who were willing to take on additional clinical responsibilities despite their tremendous workloads; doctors, clinic managers, pharmacists, and pharmacy assistants at the study facilities; the Western Cape Department of Health; the Eden and Overberg district management: in particular, we thank Renette Crous for her leadership, and Edith Swanepoel, Este van der Berg, Joggie Hattingh, and Jimmy Ledwaba for their support and assistance; the PC101 trainers: Lynette Wilkinson, Anita Michaels, Katy Moses, Ursula Turner, Sonia Botha, and Priscilla Brauns; Serena van Haght, who co-ordinated the fieldworkers; Lisa D'Emiljo, Saria van As, Julie Dietricht, and Daniella Georgeu-Pepper, who supervised fieldworkers; the fieldworkers who collected the data; the National Health Laboratory Service for processing our samples and providing electronic blood result data; Shoprite and Pick and Pay for contributing vouchers; Richard Smith for helpful comments on the manuscript; and the patients who participated. The authors would like to recognise the contribution of the late Alan Flisher to the design of the trial and, in particular, the inclusion of mental health.

## Author Contributions

**Conceptualization:** LF NF CLo KS MB EB CLu TG MZ NL.

**Data curation:** NF VT LF CLo MB.

**Formal analysis:** CLo LF NF MB.

**Funding acquisition:** LF KS EB CLu TG NL.

**Investigation:** LF NF VT NL KS DGP.

**Methodology:** LF NF VT CLo KS MB EB CLu RC GF TG DGP MZ NL.

**Project administration:** LF NF NL KS VT.

**Resources:** LF NF.

**Software:** VT NF LF CLo MB.

**Supervision:** LF NF NL KS VT.

**Validation:** CLo LF NF MB VT NL KS.

**Visualization:** LF NF EB CLo MB NL KS.

**Writing – original draft:** LF NF.

**Writing – review & editing:** LF NF VT CLo KS MB EB CLu RC GF TG DGP MZ NL.

## References

1. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet. 2009; 374:934–47. doi: 10.1016/S0140-6736(09)61087-4 PMID: 19709736

2. Bradshaw D, Dorrington RE, Laubscher R. Rapid mortality surveillance report 2011. Cape Town: South African Medical Research Council; 2012.
3. Rehle TM, Hallett TB, Shisana O, Pillay-van Wyk V, Zuma K, Carrara H, et al. A decline in new HIV Infections in South Africa: estimating HIV incidence from three national HIV surveys in 2002, 2005 and 2008. PLoS ONE. 2010; 5:e11094. doi: 10.1371/journal.pone.0011094 PMID: 20559425
4. Bradshaw D, Groenewald P, Laubscher R, Nannan N, Nojilana B, Norman R, et al. Initial burden of disease estimates for South Africa, 2000. S Afr Med J. 2003; 93:682–88. PMID: 14635557
5. Pillay-van Wyk V, Msemburi W, Laubscher R, Dorrington RE, Groenewald P, Matzopoulos R, et al. Second national burden of disease study South Africa: national and subnational mortality trends, 1997–2009. Lancet. 2013; 381:S113.
6. Mash B, Fairall L, Adejayan O, Ikpefan O, Kumari J, Mathee S, et al. A morbidity survey of South African primary care. PLoS ONE. 2012; 7:e32358. doi: 10.1371/journal.pone.0032358 PMID: 22442666
7. Steyn K, Levitt NS, Patel M, Fourie J, Gwebushe N, Lombard C, et al. Hypertension and diabetes: poor care for patients at community health centres. S Afr Med J. 2008; 98:618–22. PMID: 18928041
8. Williams DR, Herman A, Stein DJ, Heeringa SG, Jackson PB, Moomal H, et al. Twelve-month mental disorders in South Africa: prevalence, service use and demographic correlates in the population-based South African Stress and Health Study. Psychol Med. 2008; 38:211–20. doi: 10.1017/S0033291707001420 PMID: 17903333
9. Fairall L, Bachmann MO, Lombard C, Timmerman V, Uebel K, Zwarenstein M, et al. Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial. Lancet. 2012; 380:889–98. doi: 10.1016/S0140-6736(12)60730-2 PMID: 22901955
10. Colvin CJ, Fairall L, Lewin S, Georgeu D, Zwarenstein M, Bachmann MO, et al. Expanding access to ART in South Africa: the role of nurse-initiated treatment. S Afr Med J. 2010; 100:210–2. PMID: 20459957
11. Uebel KE, Fairall LR, van Rensburg DH, Mollentze WF, Bachmann MO, Lewin S, et al. Task shifting and integration of HIV care into primary care in South Africa: the development and content of the streamlining tasks and roles to expand treatment and care for HIV (STRETCH) intervention. Implement Sci. 2011; 6:86. doi: 10.1186/1748-5908-6-86 PMID: 21810242
12. Georgeu D, Colvin CJ, Lewin S, Fairall L, Bachmann MO, Uebel K, et al. Implementing nurse-initiated and managed antiretroviral treatment (NIMART) in South Africa: a qualitative process evaluation of the STRETCH trial. Implement Sci. 2012; 7:66. doi: 10.1186/1748-5908-7-66 PMID: 22800379
13. Zwarenstein M, Fairall LR, Lombard C, Mayers P, Bheekie A, English RG, et al. Outreach education for integration of HIV/AIDS care, antiretroviral treatment, and tuberculosis care in primary care clinics in South Africa: PALSA PLUS pragmatic cluster randomised trial. BMJ. 2011; 342:d2022. doi: 10.1136/bmj.d2022 PMID: 21511783
14. Barton GR, Fairall L, Bachmann MO, Uebel K, Timmerman V, Lombard C, et al. Cost-effectiveness of nurse-led versus doctor-led antiretroviral treatment in South Africa: pragmatic cluster randomised trial. Trop Med Int Health. 2013; 18:769–77. doi: 10.1111/tmi.12093 PMID: 23480523
15. Fairall LR, Zwarenstein M, Bateman ED, Bachmann MO, Lombard C, Majara BP, et al. Effect of educational outreach to nurses on tuberculosis case detection and primary care of respiratory illness: pragmatic cluster randomised controlled trial. BMJ. 2005; 331:750–4. doi: 10.1136/bmj.331.7519.750 PMID: 16195293
16. Department of Health. National Department of Health strategic plan 2010/11–2012/13: Pretoria: Department of Health; 2010 [cited 2016 Oct 19]. Available from: http://www.nationalplanningcycles.org/sites/default/files/country_docs/South%20Africa/south_africa_strategic_health_plan_2010-2013.pdf.
17. Fairall L, Bateman E, Cornick R, Faris G, Timmerman V, Folb N, et al. Innovating to improve primary care in less developed countries: towards a global model. BMJ Innov. 2015; 1:196–203. doi: 10.1136/bmjinnov-2015-000045 PMID: 26692199
18. Coventry PA, Small N, Panagioti M, Adeyemi I, Bee P. Living with complexity; marshalling resources: a systematic review and qualitative meta-synthesis of lived experience of mental and physical multimorbidity. BMC Fam Pract. 2015; 16:171. doi: 10.1186/s12875-015-0345-3 PMID: 26597934
19. Déruaz-Luyet A, N'Goran AA, Tandjung R, Frey P, Zeller A, Haller DM, et al. Multimorbidity in primary care: protocol of a national cross-sectional study in Switzerland. BMJ Open. 2015; 5:e009165. doi: 10.1136/bmjopen-2015-009165 PMID: 26510730
20. Foguet-Boreu Q, Violán C, Rodriguez-Blanco T, Roso-Llorach A, Pons-Vigués M, Pujol-Ribera E, et al. Multimorbidity patterns in elderly primary health care patients in a south Mediterranean European region: a cluster analysis. PLoS ONE. 2015; 10:e0141155. doi: 10.1371/journal.pone.0141155 PMID: 26524599

21. Luijks H, Lucassen P, van Weel C, Loeffen M, Lagro-Janssen A, Schermer T. How GPs value guidelines applied to patients with multimorbidity: a qualitative study. BMJ Open. 2015; 5:e007905. doi: 10.1136/bmjopen-2015-007905 PMID: 26503382

22. Moffat K, Mercer SW. Challenges of managing people with multimorbidity in today's healthcare systems. BMC Fam Pract. 2015; 16:129. doi: 10.1186/s12875-015-0344-4 PMID: 26462820

23. Nicholson K, Terry A, Fortin M, Williamson T, Thind A. Understanding multimorbidity in primary health care. Can Fam Physician. 2015; 61:918. PMID: 26472799

24. Laurant M, Harmsen M, Wollersheim H, Grol R, Faber M, Sibbald B. The impact of nonphysician clinicians: do they improve the quality and cost-effectiveness of health care services? Med Care Res Rev. 2009; 66(6 Suppl):36S–89S. doi: 10.1177/1077558709346277 PMID: 19880672

25. Labhardt ND, Balo J-R, Ndam M, Grimm J-J, Manga E. Task shifting to non-physician clinicians for integrated management of hypertension and diabetes in rural Cameroon: a programme assessment at two years. BMC Health Serv Res. 2010; 10:339. doi: 10.1186/1472-6963-10-339 PMID: 21144064

26. Kengne AP, Awah PK, Fezeu LL, Sobngwi E, Mbanya J-C. Primary health care for hypertension by nurses in rural and urban sub-Saharan Africa. J Clin Hypertens (Greenwich). 2009; 11:564–72.

27. Coleman R, Gill G, Wilkinson D. Noncommunicable disease management in resource-poor settings: a primary care model from rural South Africa. Bull World Health Organ. 1998; 76:633–40. PMID: 10191559

28. Gill GV, Price C, Shandu D, Dedicoat M, Wilkinson D. An effective system of nurse-led diabetes care in rural Africa. Diabet Med. 2008; 25:606–11. doi: 10.1111/j.1464-5491.2008.02421.x PMID: 18445175

29. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008; 337:a1655. doi: 10.1136/bmj.a1655 PMID: 18824488

30. English RG, Bateman ED, Zwarenstein MF, Fairall LR, Bheekie A, Bachmann MO, et al. Development of a South African integrated syndromic respiratory disease guideline for primary care. Prim Care Respir J. 2008; 17:156–63. doi: 10.3132/pcrj.2008.00044 PMID: 18701971

31. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977; 1:385–401.

32. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med. 1994; 10:77–84. PMID: 8037935

33. Myer L, Smit J, Roux LL, Parker S, Stein DJ, Seedat S. Common mental disorders among HIV-infected individuals in South Africa: prevalence, predictors, and validation of brief psychiatric rating scales. AIDS Patient Care STDS. 2008; 22:147–58. doi: 10.1089/apc.2007.0102 PMID: 18260806

34. Zhang W, O'Brien N, Forrest JI, Salters KA, Patterson TL, Montaner JSG, et al. Validating a shortened depression scale (10 item CES-D) among HIV-positive people in British Columbia, Canada. PLoS ONE. 2012; 7:e40793. doi: 10.1371/journal.pone.0040793 PMID: 22829885

35. Miller WC, Anton HA, Townson AF. Measurement properties of the CESD scale among individuals with spinal cord injury. Spinal Cord. 2008; 46:287–92. doi: 10.1038/sj.sc.3102127 PMID: 17909558

36. Cheung YB, Liu KY, Yip PSF. Performance of the CES-D and its short forms in screening suicidality and hopelessness in the community. Suicide Life Threat Behav. 2007; 37:79–88. doi: 10.1521/suli.2007.37.1.79 PMID: 17397282

37. O'Connor PJ, Desai J, Solberg LI, Reger LA, Crain AL, Asche SE, et al. Randomized trial of quality improvement intervention to improve diabetes care in primary care settings. Diabetes Care. 2005; 28:1890–7. PMID: 16043728

38. Grant R, Adams AS, Trinacty CM, Zhang F, Kleinman K, Soumerai SB, et al. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. Diabetes Care. 2007; 30:807–12. doi: 10.2337/dc06-2170 PMID: 17259469

39. Rahman A, Malik A, Sikander S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. Lancet. 2008; 372:902–9. doi: 10.1016/S0140-6736(08)61400-2 PMID: 18790313

40. Zwarenstein M, Treweek S, Gagnier J, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008; 337:a2390. doi: 10.1136/bmj.a2390 PMID: 19001484

41. Department of Health. Standard treatment guidelines and essential medicines list for South Africa: Primary Health Care. Pretoria: Department of Health; 2008.

42. Stein J, Lewin S, Fairall L, Mayers P, English R, Bheekie A, et al. Building capacity for antiretroviral delivery in South Africa: a qualitative evaluation of the PALSA PLUS nurse training programme. BMC Health Serv Res. 2008; 8:240. doi: 10.1186/1472-6963-8-240 PMID: 19017394

43. Sanne I, Orrell C, Fox M, Conradie F, Ive P, Zeinecker J, et al. Nurse management is not inferior to doctor management of antiretroviral patients: the CIPRA South Africa randomised trial. Lancet. 2010; 376:33–40. doi: 10.1016/S0140-6736(10)60894-X PMID: 20557927

44. O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, Kristoffersen DT, et al. Educational outreach visits: effects on professional practice and health care outcomes. Cochrane Database Syst Rev. 2007; 4:CD000409.

45. Van Der Stuyf RR. Scaffolding as a teaching strategy. SlideShare; 2002 [cited 2016 Oct 19]. Available from: http://www.slideshare.net/valms1/vygotsky-17272530.

46. Swinton L. Kolb's Learning Style Inventory and Kolb's Learning Cycle explained—no fluff, no filler, just facts. Mftrou.com; 2016 [cited 2016 Oct 19]. Available from: http://www.mftrou.com/kolb-learning-style-inventory.html.

47. Folb N, Timmerman V, Levitt NS, Steyn K, Bachmann MO, Lund C, et al. Multimorbidity, control and treatment of non-communicable diseases among primary healthcare attenders in the Western Cape, South Africa. S Afr Med J. 2015; 105:642–7. PMID: 26449692

48. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991; 85(Suppl B):25–31.

49. Van Bruggen R, Gorter K, Stolk R, Klungel O, Rutten G. Clinical inertia in general practice: widespread and related to the outcome of diabetes care. Fam Pract. 2009; 26:428–36. doi: 10.1093/fampra/cmp053 PMID: 19729401

50. Schmittdiel JA, Uratsu CS, Karter AJ, Heisler M, Subramanian U, Mangione CM, et al. Why don't diabetes patients achieve recommended risk factor targets? Poor adherence versus lack of treatment intensification. J Gen Intern Med. 2008; 23:588–94. doi: 10.1007/s11606-008-0554-8 PMID: 18317847

51. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, et al. Inadequate management of blood pressure in a hypertensive population. N Engl J Med. 1998; 339:1957–63. doi: 10.1056/NEJM199812313392701 PMID: 9869666

52. Berlowitz DR, Ash AS, Glickman M, Friedman RH, Pogach LM, Nelson AL, et al. Developing a quality measure for clinical inertia in diabetes care. Health Serv Res. 2005; 40:1836–53. doi: 10.1111/j.1475-6773.2005.00436.x PMID: 16336551

53. Carter BL, Bergus GR, Dawson JD, Farris KB, Doucette WR, Chrischilles EA, et al. A cluster-randomized trial to evaluate physician/pharmacist collaboration to improve blood pressure control. J Clin Hypertens (Greenwich). 2008; 10:260–71.

54. Seedat S, Stein DJ, Herman A, Kessler R, Sonnega J, Heeringa S, et al. Twelve-month treatment of psychiatric disorders in the South African Stress and Health Study (World Mental Health Survey Initiative). Soc Psychiatry Psychiatr Epidemiol. 2008; 43:889–97. doi: 10.1007/s00127-008-0399-9 PMID: 18677573

55. Bachmann MO, Louwagie G, Fairall L. Quality of life and financial measures in HIV/AIDS in Southern Africa. In: Preedy VR, Watson RR, editors. Handbook of disease burdens and quality of life measures. New York: Springer Science + Business Media; 2010. p. 3223–3243.

56. Garin O, Ayuso-Mateos JL, Almansa J, Nieto M, Chatterji S, Vilagut G, et al. Validation of the 'World Health Organization Disability Assessment Schedule, WHODAS-2' in patients with chronic diseases. Health Qual Life Outcomes. 2010; 19:51.

57. Sheikh A, Panesar SS, Larizgoitia I, Bates DW, Donaldson LJ. Safer primary care for all: a global imperative. Lancet Glob Health. 2013; 1:e182–3. doi: 10.1016/S2214-109X(13)70030-5 PMID: 25104342

58. Billue KL, Safford MM, Salanitro AH, Houston TK, Curry W, Kim Y, et al. Medication intensification in diabetes in rural primary care: a cluster-randomised effectiveness trial. BMJ Open. 2012; 2:e000959. doi: 10.1136/bmjopen-2012-000959 PMID: 22991217

59. Fairall L, Bachmann MO, Zwarenstein M, Bateman ED, Niessen LW, Lombard C, et al. Cost-effectiveness of educational outreach to primary care nurses to increase tuberculosis case detection and improve respiratory care: economic evaluation alongside a randomised trial. Trop Med Int Health. 2010; 15:277–86. doi: 10.1111/j.1365-3156.2009.02455.x PMID: 20070633

60. Lewin S, Green J. Ritual and the organisation of care in primary care clinics in Cape Town, South Africa. Soc Sci Med. 2009; 68:1464–71. doi: 10.1016/j.socscimed.2009.02.013 PMID: 19278764

61. Mahomed OH, Asmall S. Development and implementation of an integrated chronic disease model in South Africa: lessons in the management of change through improving the quality of clinical practice. Int J Integr Care. 2015; 15:e038. PMID: 26528101

62. Mahomed OH, Naidoo S, Asmall S, Taylor M. Evaluation of PC 101 training for professional nurses in 3 districts in South Africa. Pretoria: National Department of Health; 2015.

63. Kruk ME, Yamey G, Angell SY, Beith A, Cotlear D, Guanais F, et al. Transforming global health by improving the science of scale-up. PLoS Biol. 2016; 14:e1002360. doi: 10.1371/journal.pbio.1002360 PMID: 26934704

64. Lund C, Tomlinson M, De Silva M, Fekadu A, Shidhaye R, Jordans M, et al. PRIME: a programme to reduce the treatment gap for mental disorders in five low- and middle-income countries. PLoS Med. 2012; 9:e1001359. doi: 10.1371/journal.pmed.1001359 PMID: 23300387

**S1 Appendix for Paper 4**

**Table A** Characteristics of clinics allocated to an educational outreach programme (Primary Care 101) or no new training (control group). Values are numbers (percentages) unless stated otherwise.

| **Clinics** | **Intervention** | **Control** |
|---|---|---|
| Number of clinics | 19 | 19 |
| Headcount[1]: median (IQR) | 19304 (16341-28064) | 30882 (20091-41053) |
| Setting: | | |
| Urban (%) | 11 (58) | 11 (58) |
| Peri-urban (%) | 4 (21) | 3 (16) |
| Rural (%) | 4 (21) | 5 (26) |
| Number of nurses per clinic: median (IQR) | 4 (3-5) | 6 (3-7) |
| Patient to nurse ratio (headcount/number of nurses): median (IQR) | 1:5552 (4329-9329) | 1:5835 (4412-8009) |
| Psychiatric qualified nurse available: | | |
| Weekly (%) | 6 (32) | 7 (37) |
| Monthly (%) | 10 (53) | 12 (63) |
| None (%) | 3 (16) | 0 (0) |
| Doctor support: | | |
| Daily (%) | 8 (42) | 7 (37) |
| Sessional (%) | 11 (58) | 12 (63) |
| Pharmacy on-site (%) | 6 (32) | 10 (53) |

[1] Headcount: number of attendances of patients >5 years in 2008

**Table B:** Primary Care 101 Training Cases

| Scenario | Patient name | Symptoms/ chronic diseases covered | Core learning |
|---|---|---|---|
| 1 | Godfrey | Weight loss – diabetes screen | • Expansion of familiar page<br>• Link with chronic condition screen |
| 2 | Patricia | Headache – stress | • Expansion of familiar page<br>• Approach to stress |
| 3 | Auntie Gertie | Asthma: routine care | • Introduce routine care approach of 'Assess, Advise, Treat' |
| 4 | Godfrey | Tuberculosis (TB): routine care | • Approach to routine care for complicated chronic condition<br>• Becoming familiar with new pages for TB |
| 5 | Stanley | Body pain – HIV | • Becoming familiar with new symptom page<br>• Approach to routine care for complicated chronic condition<br>• Becoming familiar with new pages for HIV |
| 6 | Thobeka | Back pain – cardiovascular disease (CVD) risk | • Using common symptom as trigger to screen for important chronic condition<br>• Approach to assessing and managing CVD risk |
| 7 | Xolani | Face problems – stroke | • Diagnosing stroke<br>• Approach to routine stroke care |
| 8 | Sipho | Chest pain – ischaemic heart disease (IHD) | • Managing the client needing urgent attention<br>• Approach to routine IHD care |
| 9 | Jane | Fatigue – depression | • Identifying the client with depression<br>• Diagnosing depression<br>• Approach to routine depression care |
| 10 | Adelaide | Abdominal pain – substance abuse | • Identifying the client with substance abuse<br>• Diagnosing substance abuse<br>• Approach to routine substance abuse care |
| 11 | Faizel | Fits - epilepsy | • Managing the client needing urgent attention<br>• Approach to routine epilepsy care |
| 12 | Melissa | HIV - pregnancy | • Look for other chronic condition in client with known chronic condition<br>• Play with alternate scenarios for routine HIV care |
| 13 | Caroline | Diabetes - hypertension | • Using routine care approach with new chronic condition<br>• Approach to routine diabetes care<br>• Diagnosing hypertension in diabetes |
| 14 | Boeta | Joint symptom – gout, CVD risk, substance abuse | • Identifying the client with gout<br>• Diagnosing gout<br>• Approach to routine gout care<br>• Identifying other chronic conditions in the client with 1 chronic condition and approach to routine care of client with several chronic conditions |

**Table C:** Expanded treatment patterns

| **Indication** | **Available for Practice Nurse (PN) prescription prior to Primary Care 101 (PC101) training** | **Available for PN prescription post PC101 training** |
|---|---|---|
| Hypertension | Hydrochlorothiazide (HCTZ) | HCTZ *and*<br>Enalapril (maximum dose 10mg daily) *or*<br>Amlodipine (maximum dose 5mg daily) |
| Diabetes | Metformin | Metformin *and*<br>Glibenclamide (2.5mg daily to maximum 5mg twice daily (bd)) *or*<br>Gliclazide (40mg daily to maximum 80mg bd *and*<br>Simvastatin (maximum dose 10mg daily) *and*<br>Enalapril (maximum dose 10mg daily) if proteinuria |
| Cardiovascular disease or cardiovascular risk >20% | Aspirin | Simvastatin (maximum dose 10mg daily) |
| Asthma | Salbutamol inhaler<br>Budesonide for Clinical Nurse Practitioners (CNPs) | Salbutamol inhaler *and*<br>Budesonide (maximum dose 200mcg bd) *and*<br>Prednisone 40mg daily for 7 days (maximum 2 courses per year) for acute exacerbations |
| COPD | Salbutamol inhaler | Salbutamol inhaler *and*<br>Prednisone 40mg daily for 7 days (maximum 2 courses per year) for acute exacerbations |

**Table D:** Analysis of primary outcomes: risk ratios of the associations of arm and patient level characteristics

**Table D Hypertension (N=3227)**

| Factor | n/N (%) | Risk ratio (95% CI) | P value |
|---|---|---|---|
| ***Arm of trial*** | | | |
| Control | 673/1672 (40) | 1 [reference] | |
| Intervention | 685/1555 (44) | 1.10 (0.96 to 1.27) | 0.165 |
| ***Stratum*** | | | |
| 1: Bitou and Knysna | 359/903 (40) | 1 [reference] | |
| 2: Hessequa and Kannaland | 190/452 (42) | 1.02 (0.77 to 1.35) | 0.888 |
| 3: Eden DMA and Oudtshoorn | 223/615 (36) | 0.90 (0.67 to 1.21) | 0.485 |
| 4: George | 222/440 (51) | 1.19 (0.93 to 1.51) | 0.165 |
| 5: Mossel Bay | 206/395 (52) | 1.27 (1.05 to 1.53) | 0.012 |
| 6: Overberg | 158/422 (37) | 0.90 (0.72 to 1.13) | 0.371 |
| ***Patient characteristics*** | | | |
| Age at enrolment[1] | | 1.00 (1.00 to 1.01) | 0.012 |
| ≤ 40 years | 135/379 (36) | | |
| 41-50 years | 320/780 (41) | | |
| 51-60 years | 458/1041 (44) | | |
| ≥ 61 years | 445/1027 (43) | | |
| Sex | | | |
| Female | 1030/2425 (43) | 1 [reference] | |
| Male | 328/802 (41) | 0.97 (0.87 to 1.08) | 0.595 |
| BMI[2] | | | |
| <=30 kg/m$^2$ | 556/1438 (39) | 1 [reference] | |
| >30 kg/m$^2$ | 735/1628 (45) | 1.15 (1.05 to 1.25 | 0.001 |
| Smoking status | | | |
| Never | 660/1519 (44) | 1 [reference] | |
| Ex | 313/790 (40) | 0.95 (0.82 to 1.11) | 0.512 |
| Current | 374/885 (42) | 1.07 (0.97 to 1.17) | 0.160 |
| Diabetes | | | |
| Not in diabetic cohort | 631/1687 (37) | 1 [reference] | |
| In diabetic cohort | 727/1540 (47) | 1.16 (1.06 to 1.27) | 0.001 |
| Chronic respiratory disease (CRD) | | | |
| Not in CRD cohort | 1061/2491 (43) | 1 [reference] | |
| In CRD cohort | 297/736 (40) | 0.97 (0.88 to 1.07) | 0.525 |
| BP control[2] | | | |
| Controlled | 267/825 (32) | 1 [reference] | |
| Not controlled | 1091/2395 (46) | 1.40 (1.20 to 1.63) | 0.000 |
| MMT at baseline[3] | | | |
| Not on MMT[3] | 1167/2721 (43) | 1 [reference] | |
| On MMT[3] | 191/482 (40) | 0.87 (0.76 to 0.99) | 0.031 |
| History of CVD[2] | | | |
| No history of CVD[2] | 1008/2378 (42) | 1 [reference] | |
| History of CVD[2] | 350/849 (41) | 0.96 (0.87 to 1.06) | 0.448 |

[1]Age at enrolment: presented as a categorical variable for descriptive purposes only

[2]BMI=body mass index; BP=blood pressure; CVD=cardiovascular disease

[3]MMT=maximal medical therapy: defined for hypertension as being on ≥ 3 antihypertensive drugs at optimal dosage

**Table D Diabetes n=1842**

| Factor | n/N (%) | Risk ratio (95% CI) | P value |
|---|---|---|---|
| ***Arm of trial: conditional on BMI***[1] | | | |
| BMI ≤ 30[1] | | | |
| Control | 202/404 (50) | 1 [reference] | |
| Intervention | 158/327 (48) | 0.97 (0.81 to 1.15) | 0.717 |
| BMI >30[1] | | | |
| Control | 273/532 (51) | 1 [reference] | |
| Intervention | 297/479 (62) | 1.20 (1.05 to 1.37) | 0.009 |
| ***Stratum*** | | | |
| 1: Bitou and Knysna | 260/504 (52) | 1 [reference] | |
| 2: Hessequa and Kannaland | 139/272 (51) | 0.99 (0.78 to 1.26) | 0.960 |
| 3: Eden DMA and Oudtshoorn | 137/327 (42) | 0.84 (0.59 to 1.18) | 0.308 |
| 4: George | 186/295 (63) | 1.21 (0.96 to 1.53) | 0.115 |
| 5: Mossel Bay | 127/199 (64) | 1.36 (1.09 to 1.71) | 0.006 |
| 6: Overberg | 130/245 (53) | 1.07 (0.86 to 1.32) | 0.549 |
| ***Patient characteristics*** | | | |
| Sex | | | |
| Female | 755/1382 (55) | 1 [reference] | |
| Male | 224/460 (49) | 0.93 (0.82 to 1.04) | 0.200 |
| Smoking status | | | |
| Never | 526/939 (56) | 1 [reference] | |
| Ex | 240/473 (51) | 0.94 (0.84 to 1.04) | 0.226 |
| Current | 208/415 (50) | 0.95 (0.83 to 1.09) | 0.490 |
| History of CVD[1] | | | |
| No history of CVD[1] | 777/1419 (55) | 1 [reference] | |
| History of CVD[1] | 202/423 (48) | 0.88 (0.80 to 0.98) | 0.019 |
| Hypertension (HPT) | | | |
| Not in HPT cohort | 149/302 (49) | 1 [reference] | |
| In HPT cohort | 830/1540 (54) | 1.08 (0.95 to 1.23) | 0.219 |

[1]BMI=body mass index; CVD=cardiovascular disease

**Table D Chronic Respiratory Disease (CRD) N=1157**

| Factor | n/N (%) | Risk ratio (95% CI) | P value |
|---|---|---|---|
| ***Arm of trial*** | | | |
| Control | 68/571 (12) | 1 [reference] | |
| Intervention | 81/586 (14) | 1.22 (0.88 to 1.68) | 0.228 |
| ***Stratum*** | | | |
| 1: Bitou and Knysna | 31/303 (10) | 1 [reference] | |
| 2: Hessequa and Kannaland | 22/166 (13) | 0.97 (0.50 to 1.89) | 0.930 |
| 3: Eden DMA and Oudtshoorn | 22/233 (9) | 0.81 (0.45 to 1.46) | 0.488 |
| 4: George | 33/155 (21) | 1.21 (0.79 to 1.87) | 0.379 |
| 5: Mossel Bay | 23/142 (16) | 1.20 (0.70 to 2.05) | 0.499 |
| 6: Overberg | 18/158 (11) | 0.84 (0.50 to 1.42) | 0.517 |
| ***Patient characteristics*** | | | |
| Age | | | |
| <=40 | 16/213 (8) | 1 [reference] | |
| 41-60 | 96/692 (14) | 1.11 (0.75 to 1.64) | 0.618 |
| 61-80 | 36/242 (15) | 1.11 (0.72 to 1.71) | 0.652 |
| 81+ | 1/10 (10) | 0.80 (0.10 to 6.34) | 0.833 |
| Smoking status | | | |
| Never | 39/394 (10) | 1 [reference] | |
| Ex | 54/290 (19) | 1.49 (0.98 to 2.28) | 0.062 |
| Current | 55/454 (12) | 1.12 (0.74 to 1.69) | 0.601 |
| Diabetes | | | |
| Not in diabetic cohort | 110/837 (13) | 1 [reference] | |
| In diabetic cohort | 39/320 (12) | 0.80 (0.59 to 1.09) | 0.161 |
| History of tuberculosis | | | |
| No history of tuberculosis at baseline | 117/943 (12) | 1 [reference] | |
| History of tuberculosis at baseline | 31/211 (15) | 1.00 (0.67 to 1.49) | 0.994 |
| Chronic Respiratory Disease (CRD) medication | | | |
| Not on CRD drugs at baseline | 27/567 (5) | 1 [reference] | |
| On CRD drugs but not MMT[1] | 81/231 (35) | 6.75 (4.11 to 11.09) | 0.000 |
| On CRD drugs at baseline and MMT[1] | 41/346 (12) | 2.38 (1.34 to 4.24) | 0.003 |

[1]MMT=maximal medical therapy: defined for chronic respiratory disease as being on inhaled corticosteroid at a dose of ≥ 800mcg daily

**Table D Depression N=2439 (2466 in depression cohort but 27 patients excluded from depression primary analysis)**

| Factor | n/N (%) | Risk ratio (95% CI) | P value |
|---|---|---|---|
| ***Arm of trial*** | | | |
| Control | 283/1186 (24) | 1 [reference] | |
| Intervention | 224/1253 (18) | 0.80 (0.57 to 1.10) | 0.167 |
| ***Stratum*** | | | |
| 1: Bitou and Knysna | 120/739 (16) | 1 [reference] | |
| 2: Hessequa and Kannaland | 51/341 (15) | 0.82 (0.45 to 1.52) | 0.533 |
| 3: Eden DMA and Oudtshoorn | 108/458 (24) | 1.27 (0.62 to 2.59) | 0.507 |
| 4: George | 83/328 (25) | 1.13 (0.67 to 1.92) | 0.651 |
| 5: Mossel Bay | 69/273 (25) | 1.14 (0.65 to 2.03) | 0.644 |
| 6: Overberg | 76/300 (25) | 1.23 (0.70 to 2.16) | 0.464 |
| ***Patient characteristics*** | | | |
| Sex | | | |
| Female | 413/1859 (22) | 1 [reference] | |
| Male | 94/580 (16) | 0.76 (0.62 to 0.94) | 0.011 |
| Smoking status | | | |
| Never | 200/1011 (20) | 1 [reference] | |
| Ex | 107/544 (20) | 0.96 (0.73 to 1.26) | 0.772 |
| Current | 193/848 (23) | 0.97 (0.78 to 1.20) | 0.764 |
| Hypertension (HPT) | | | |
| Not in HPT cohort | 218/854 (26) | 1 [reference] | |
| In HPT cohort | 289/1585 (18) | 0.72 (0.60 to 0.86) | 0.000 |
| History of depression | | | |
| No history of depression | 233/1577 (15) | 1 [reference] | |
| History of depression | 274/858 (32) | 1.73 (1.48 to 2.02) | 0.000 |
| CESD-10 score at baseline[1,2] | | 1.01 (0.99 to 1.04) | 0.197 |
| 10-15 | 257/1459 (18) | | |
| 16-20 | 145/672 (22) | | |
| 21-25 | 84/272 (31) | | |
| 26-30 | 21/63 (33) | | |
| Antidepressants at baseline at a therapeutic dose | | | |
| Not receiving antidepressants | 384/2133 (18) | 1 [reference] | |
| Receiving antidepressants | 119/292 (40) | 1.46 (1.12 to 1.89) | 0.004 |

[1]CESD-10= 10-item Centre for Epidemiologic Studies Scale

[2] Presented as a categorical variable for descriptive purposes only

**Table E:** Primary outcomes disaggregated by components

**Table E Hypertension Cohort**

| Outcome | Intervention | Control | Effect estimate | | P | Regression model | Adjusted for |
|---|---|---|---|---|---|---|---|
| | n/N (%) | n/N (%) | Type | Estimate (95% CI) | | | |
| ***Disaggregation of primary outcome*** | | | | | | | |
| Treatment intensification of antihypertensive medication | 559/ 1555 (36) | 564/ 1672 (34) | RR | 1.07 (0.92 to 1.24) | 0.375 | Binomial | MMT, BP control, sex, diabetes, CVD[1,2] |
| Addition of aspirin | 120/ 1555 (8) | 98/ 1672 (6) | RR | 1.44 (1.02 to 2.03) | 0.037 | Binomial | MMT, BP control, sex, diabetes, CVD[1,2] |
| Addition or increase in the dose of a statin | 205/ 1555 (13) | 182/ 1672 (11) | RR | 1.27 (0.87 to 1.86) | 0.218 | Binomial | MMT, BP control, sex, diabetes, CVD[1,2] |

[1]MMT=maximal medical therapy: defined for hypertension as being on ≥ 3 antihypertensive drugs at optimal dosage

[2]BP=blood pressure; CVD=cardiovascular disease

**Table E Diabetes Cohort**

| Outcome | Intervention n/N (%) | Control n/N (%) | Effect estimate Type | Effect estimate Estimate (95% CI) | P | Regression model | Adjusted for |
|---|---|---|---|---|---|---|---|
| ***Disaggregation of primary outcome*** | | | | | | | |
| Addition or increase in the dose of metformin | 156/ 851 (18) | 157/ 991 (16) | RR | 1.11 (0.83 to 1.48) | 0.472 | Binomial | |
| Addition or increase in the dose of sulphonylurea | 127/ 851 (15) | 108/ 991 (11) | RR | 1.30 (0.98 to 1.73) | 0.074 | Binomial | |
| Addition or increase in the dose of sulphonylurea if BMI ≤ 30 | 32/327 (10) | 47/404 (12) | RR | 0.87 (0.52 to 1.47) | 0.613 | Binomial | MMT, age, interaction between arm and BMI, sex, HPT, history of CVD[1,2] |
| Addition or increase in the dose of sulphonylurea if BMI >30 | 85/479 (18) | 55/532 (10) | RR | 1.68 (1.23 to 2.30) | 0.001 | Binomial | MMT, age, interaction between arm and BMI, sex, HPT, history of CVD[1,2] |
| Insulin | 189/851 (22) | 179/991 (18) | RR | 1.18 (0.92 to 1.51) | 0.194 | Binomial | |
| Addition or increase in the dose of an ACE inhibitor | 96/ 851 (11) | 91/ 991 (9) | RR | 1.23 (0.88 to 1.72) | 0.223 | Binomial | |
| Addition or increase in the dose of an ACE inhibitor if no history of CVD | 78/645 (12) | 81/774 (11) | RR | 1.13 (0.76 to 1.66) | 0.544 | Binomial | MMT, age, BMI, sex, HPT, interaction between arm and history of CVD[1,2] |
| Addition or increase in the dose of an ACE inhibitor if history of CVD | 18/206 (9) | 10/217 (5) | RR | 2.76 (1.17 to 6.49) | 0.020 | Binomial | MMT, age, BMI, sex, HPT, interaction between arm and history of CVD[1,2] |
| Addition of aspirin | 77/ 851 (9) | 60/ 991 (6) | RR | 1.73 (1.13 to 2.63) | 0.011 | Binomial | |
| | | | | 1.70 (1.08 to 2.66) | 0.021 | | MMT, BMI, age, sex, HPT, CVD[1,2] |
| Addition or increase in the dose of a statin | 156/851 (18) | 154/ 991 (16) | RR | 1.19 (0.80 to 1.78) | 0.395 | Binomial | |
| | | | | 1.15 (0.76 to 1.75) | 0.505 | | MMT, age, BMI, sex, HPT, history of CVD[1,2] |

[1]MMT=maximal medical therapy: defined for diabetes as being on insulin

[2]BMI=body mass index; HPT=hypertension; CVD=cardiovascular disease

**Table E Chronic Respiratory Disease Cohort**

| Outcome | Intervention | Control | Effect estimate | | P | Regression model | Adjusted for |
|---|---|---|---|---|---|---|---|
| | n/N (%) | n/N (%) | Type | Estimate (95% CI) | | | |
| ***Disaggregation of primary outcome*** | | | | | | | |
| Addition or increase in dose of inhaled corticosteroid | 55/586 (9) | 42/571 (7) | RR | 1.12 (0.72 to 1.73) | 0.608 | Binomial | |
| Increase in dose or addition of inhaled corticosteroid | | | RR | 1.05 (0.65 to 1.67) | 0.854 | | MMT, CRD drugs, SGRQACT, age, smoking, sex, HPT cohort[1,2] |
| Addition of beta agonist | 13/586 (2) | 13/571 (2) | RR | 0.90 (0.51 to 1.56) | 0.697 | Binomial | |
| Addition of beta agonist | | | RR | 0.78 (0.39 to 1.56) | 0.482 | Binomial | MMT, CRD drugs, SGRQACT, age, smoking, sex, HPT cohort[1,2] |
| Addition of ipratropium bromide | 13/586 (2) | 11/571 (2) | RR | 1.22 (0.66 to 2.23) | 0.526 | Binomial | |
| Addition of ipratropium bromide | | | RR | 1.27 (0.66 to 2.44) | 0.479 | Binomial | MMT, CRD drugs, SGRQACT, age, smoking, sex, HPT cohort[1,2] |
| Addition of theophylline | 19/586 (3) | 20/571 (4) | RR | 0.97 (0.48 to 1.99) | 0.943 | Binomial | |
| Addition of theophylline | | | RR | 1.21 (0.68 to 2.15) | 0.517 | Binomial | MMT, CRD drugs, SGRQACT, age, smoking, sex, HPT cohort[1,2] |

[1]MMT=maximal medical therapy: defined for chronic respiratory disease as being on inhaled corticosteroid at a dose of $\geq$ 800mcg daily

[2]CRD=chronic respiratory disease; SGRQACT=St Georges Respiratory Questionnaire activity Domain; HPT=hypertension

**Table E Depression Cohort**

| Outcome | Intervention | Control | Effect estimate | | P | Regression model | Adjusted for |
|---|---|---|---|---|---|---|---|
| | n/N (%) | n/N (%) | Type | Estimate (95% CI) | | | |
| ***Disaggregation of primary outcome*** | | | | | | | |
| Addition or increase in antidepressant in therapeutic dosages | 41/ 1270 (3) | 36/ 1196 (3) | RR | 1.07 (0.69 to 1.65) | 0.773 | Binomial | |
| | | | | 1.15 (0.77 to 1.73) | 0.500 | | Psychiatric sister, age, history of depression, hypertension, sex, baseline antidepressant, diabetes |
| Received counselling | 194/ 1270 (15) | 264/ 1196 (22) | RR | 0.74 (0.49 to 1.12) | 0.153 | Binomial | |
| | | | RR | 0.01 (0.01 to 0.02) | 0.000 | Binomial | Age, HPT, diabetes, sex, smoking, counselling at baseline[1] |
| Referral to mental health services | 67/ 1270 (5) | 108/ 1196 (9) | RR | 0.62 (0.41 to 0.93) | 0.022 | Binomial | |
| | | | | 0.64 (0.45 to 0.92) | 0.015 | | Psychiatric referral at baseline, sex, diabetes, smoking |

[1]HPT=hypertension

# Chapter 4: Discussion

## 4.1 Summary of findings

This thesis provides recent and novel evidence for high levels of multimorbidity, poor control and unmet treatment needs for NCDs in the South African primary care public sector. It confirms and provides original evidence for associations between socioeconomic position and blood pressure control and treatment intensification, and between socioeconomic position and depression symptoms and treatment. It provides new evidence in South Africa for a bidirectional link between socioeconomic position and depression symptoms, suggesting that socioeconomic position is both a cause and consequence of depression. Further, it provides original evidence for associations between patient and clinic characteristics, and the management of hypertension and depression in primary care. Finally, it reports on evidence of the effectiveness of the PC101 programme aimed at expanding nurses' role in NCD care. Although differences in the primary endpoints of the RCT did not reach statistical significance, the programme was safe and feasible and has been adopted across South Africa.

## 4.2 Multimorbidity, control and treatment of NCDs

Multimorbidity is increasingly common (Mercer et al. 2012) (Barnett et al. 2012) and presents multiple challenges for primary health care providers (Moffat and Mercer 2015).

In general, there is a paucity of current data on NCDs and their management in South Africa during a period of South African history dominated by HIV/AIDS, and the delayed response

to scaling up effective treatments for it. This has contributed to poor appreciation of the burden and impact of NCDs, and limited provision for their management. PC101 is an innovation that aims to improve this situation, but without situational analyses and evidence, such as provided in this thesis (Papers 1, 2 and 3), the need for and impact of innovations will be difficult to appreciate and assess.

Paper 1 confirms high levels of multimorbidity, and demonstrates higher levels of comorbidity between hypertension and diabetes than previous studies in South Africa (Peer et al. 2013) (Steyn et al. 2008) (Lalkhen and Mash 2015). Our findings are consistent with a study of urban South African women that demonstrated high rates of comorbid psychological distress with physical disease (Mendenhall et al. 2013). As many as 65% of participants with chronic respiratory disease (CRD), and half of participants with hypertension, diabetes or CRD screened positive for depression symptoms.

Paper 3 demonstrates depression symptoms at baseline being positively associated with chronic respiratory disease (CRD), but not with hypertension or diabetes. This might be due to CRD generally being more symptomatic and disabling than hypertension or diabetes. The association between depression symptoms and CRD is consistent with previous reports of up to 25% of people with COPD and 13–14% of people with asthma also having depression (Morrison et al. 2016). Further, paper 3 reports that baseline depression symptoms were not associated with a ten year risk of cardiovascular disease death score. However, a recent study (Kyrou et al. 2016), with a follow-up period of 10 years, showed that reported depression was positively and independently associated with 10-year CVD incidence, with depression increasing CVD risk approximately fourfold. In a meta-analysis, Pan et al found

depression to be associated with a significantly increased risk of stroke morbidity and mortality (Pan et al. 2011), and in a more recent meta-analysis, Barlinn et al found that depression increases the risk of first-ever stroke by 40% in the general population (Barlinn et al. 2014).

Papers 1 and 2 report low levels of control and treatment for NCDs. Fifty-nine percent of participants with hypertension had a blood pressure ≥140/90 mmHg. Among participants with diabetes, the mean HbA1c value was 9%, 2% above target. Only 12% of participants with symptoms of depression had been prescribed an antidepressant at a therapeutic dose. Fewer than a half of participants with CRD had received a beta2-agonist and only 34% an inhaled corticosteroid. These findings are consistent with previous reports in South Africa of poor control and treatment for NCDs, and demonstrate little improvement in NCD control since these earlier studies were conducted (Steyn et al. 2008) (Maepe and Outhoff 2012) (Williams et al. 2008).

## 4.3 Socioeconomic inequalities and the role of primary care

This thesis reports on socioeconomic and modifiable predictors of control of hypertension (Paper 2) and depression (Paper 3), two of the most common chronic conditions, and causes of morbidity, globally and in South Africa.

Lower levels of education predicted both uncontrolled blood pressure at baseline, and depression symptoms at baseline and follow-up. Lower levels of education were also found to be associated with lower probability of treatment intensification for hypertension at

follow-up, and treatment for depression with antidepressant medication at baseline. Lower income was associated with depression symptoms at baseline, and a lower probability of antidepressant medication at baseline and follow-up.

Our finding of a positive association between level of education and blood pressure control is consistent with a South African study which found higher education to predict lower blood pressure in women (Cois and Ehrlich 2014). The associations reported in Paper 3 between socioeconomic indicators (less education and lower income) and depression symptoms are consistent with previous studies, the majority of which have been community-based (Lund et al. 2010) (Patel and Kleinman 2003) (Araya et al. 2003) (Patel et al. 1999). However, our finding that depressed patients were less likely to receive treatment with antidepressant medications if they had less education or lower income, differs from the South African Stress and Health (SASH) study which found no significant associations between receiving treatment for mental disorders and level of education or income (Seedat et al. 2008).

Of particular importance is the association found between clinic characteristics and control of hypertension and depression, as these factors are potentially modifiable. Clinic factors were found to be associated with both probability of treatment intensification for hypertension (clinics with community-based medication supply, with a doctor every day or more nurses) and antidepressant medication for depressed patients at follow-up (clinics with better access to pharmacists or community-based medication supply). Few studies have addressed modifiable predictors of hypertension and depression care in South Africa and these original findings emphasise the importance of addressing resources for primary

care facilities, in particular improving staffing and medication delivery services. A study in the Free State province of South Africa similarly showed associations between better staffed clinics and improved HIV outcomes; patients attending better staffed clinics were more likely to start ART and had lower mortality while awaiting initiation of ART (Ingle et al. 2010).

To explore the findings described in Paper 3, further analyses were conducted using structural equation and mediation models to examine the complex causal pathways linking socioeconomic factors and depression (Elwell-Sutton et al. unpublished). The results support the findings reported in Paper 3 of a bidirectional link between depression symptoms and socioeconomic adversity, and also suggest a number of direct and indirect pathways linking the two with mediating factors including education, income and employment.

Of interest, 73 percent of participants were women. Studies have demonstrated that women seek healthcare to a greater extent than men for both physical and mental health concerns (Thompson et al. 2016) (Galdas, Cheater, and Marshall 2005). It is therefore expected for more women to be recruited in the study. One might expect that the inclusion criterion to be planning to reside in the area for the study period excluded migrant men but, in fact, only 41 patients out of 4904 screened were excluded on the basis of this requirement.

## 4.4 Addressing NCDs: The PC101 programme

The increasing burden of NCDs and multimorbidity described in this thesis necessitates a comprehensive and integrated approach to chronic disease care, including equipping

primary health care providers to manage NCDs, communicable diseases, mental illness and the complexities of multimorbidity.

The PC101 programme was aimed at addressing the burden of multimorbidity, and the low levels of control and treatment for NCDs in particular. It does this by providing on-site training in the use of a clinical management tool that provides an integrated approach to the primary care management of adults and allows enhanced prescribing provisions for first-line NCD treatments for nurses trained in the use of the tool. It builds on predecessor programmes which had focused largely on communicable diseases, demonstrating consistent, wide-ranging and reproducible outcomes (Fairall et al. 2005) (Zwarenstein et al. 2011) (Fairall et al. 2012).

The RCT evaluating the PC101 programme and reported in Paper 4, saw treatment intensification in both control and intervention arms, particularly for the hypertension and diabetes cohorts, but no statistically significant differences in the primary outcome measures between arms. This is in contrast to the RCTs which have evaluated the PC101 programme's predecessors, PALSA , PALSA PLUS, and the introduction of NIMART, which did show statistically significantly greater improvements in care and in health outcomes in the intervention arms, as summarised in Table 2 (Fairall et al. 2005) (Zwarenstein et al. 2011) (Fairall et al. 2012) (Bachmann et al. 2010).

There are a number of possible reasons why the PC101 programme might not have shown significant results for the primary outcome measures, whereas these previous studies did. Firstly, the PALSA and PALSA PLUS programmes focussed on a limited number of diseases,

predominantly respiratory disease (PALSA) and HIV (PALSA PLUS). Expanding the PALSA PLUS clinical management tool to encompass the most common symptoms and chronic diseases presenting in primary care may have been overwhelming for nurses. In addition, it takes time to change clinician behaviour, perhaps more so for NCDs where ineffective practices can become entrenched and ritualised, and frequency of contact with health services, and thus opportunity to improve care, is much reduced compared with HIV, and perhaps we would have seen more impressive results with a longer follow-up period.

Secondly, a 'Chronic Disease Season' was introduced in the Eden district during the study period, which focused on the management of hypertension and diabetes. This was in part triggered by the PC101 trial itself, which sparked a renewed interest in NCDs, hypertension and diabetes in particular, in the district. This acted as a co-intervention and was rolled out across 17 intervention and 16 control clinics during the follow-up period. Resulting from this, a dilution effect for our trial is suggested by the high rates of treatment intensification in our control as well as intervention arms, particularly for hypertension and diabetes. Further, this was higher compared to previous studies that selected treatment intensification as a primary outcome - about 30% compared to our 40-50% treatment intensification for hypertension and diabetes (Selby et al. 2012) (Billue et al. 2012).

Thirdly, it might be that treatment intensification was too broad an outcome measure. Treatment intensification was not associated with better disease control at follow-up for hypertension and diabetes, as would have been expected. This might be due to patients having their treatment intensified, but not adhering to their treatment regimens. We are unable to investigate this as adherence assessments are complex and were beyond the

scope of this study. Further, in keeping with the pragmatic orientation of the trial, inclusion criteria were broad. This meant that all patients with the conditions of interest were enrolled, including those not adherent to their treatment regimens, for whom adherence counselling rather than treatment intensification may have been more appropriate.

Finally, we cannot exclude that there may have been low levels of uptake of PC101 by clinic staff. Due to financial constraints, we were unable to conduct a detailed process evaluation alongside the trial to explore this. However, limited focus group discussions confirmed a range of uptake of the programme within and between clinics, and increasing uptake over time.

## 4.5 Policy uptake

In 2013 the local Western Cape and National Departments of Health in South Africa elected to commence national implementation of the PC101 programme. This decision was not reversed when the results of the trial were known, in large part because the PC101 programme is perceived to be a highly feasible and acceptable approach to expansion of skills necessary to address rises in multimorbidity. It was instead influenced by high demand expressed by frontline clinicians and managers in the Western Cape province. The National Department were also likely to have been influenced by the generally positive (unpublished) findings of a non-randomised evaluation of PC101 performed in 42 primary care clinics in three other health districts, by an independent researcher commissioned by the National Department (Mahomed et al. 2015).

PC101 is now called Adult Primary Care (APC) nationally, and Practical Approach to Care Kit (PACK) in the Western Cape province. It is a key element of the Integrated Clinical Services Management (ICSM) programme and is included in the checklist of audit criteria for the Ideal Clinic and ICSM compliant package of clinical guidelines (Department of Health 2016).

The Knowledge Translation Unit has, nevertheless, introduced several measures to improve effectiveness of the programme. The PC101 content has been broken down into four training modules (communicable diseases, NCDs, mental health and women's health) to allow staff to become familiar with one area at a time and embed changes into their clinical practice before moving to the next. PC101 workshops are also now provided for doctors, District Implementation Workshops are provided for facility and middle managers, and appointment of clinical governance teams within sub-districts has been implemented, allowing local trouble-shooting of barriers to implementation, and inclusion of non-clinicians in the day-to-day running of the programme.

A community health worker module has been introduced, focusing on condition and medication literacy, and pamphlets are available in local languages. However, there may need to be more emphasis on providing counselling for lifestyle and pharmacological management of NCDs. Although the programme aims to provide an integrated approach to primary care, with limited time and resources in the public sector primary care setting, it might be necessary to prioritise care, adopting risk stratification approaches. The high proportion (10%) of hypertensive participants in the PC101 trial with a blood pressure greater than or equal to 180/110 mmHg, putting them at markedly increased and

immediate risk of complications such as heart attack and stroke, suggests this group of patients warrants particular attention.

The results of the PC101 trial suggest that training in depression diagnosis and management alone is insufficient in improving the care of this condition in primary care. There is a paucity of counselling and mental health referral services in the public sector and antidepressant prescribing is, at present, restricted to doctors. In collaboration with the PRogramme for Improving Mental health carE (PRIME) in South Africa, an intervention has been developed building on PC101 and supplementing it with the introduction of lay counsellors to provide individual and group on-site depression counselling (Petersen et al. 2016). We are currently conducting a pair of randomised controlled trials in the North West province, evaluating this PC101 programme with enhanced mental health provisions. The first trial is evaluating the effect on depressed adults receiving ART (ClinicalTrials.gov NCT02407691); the second trial the effect on depressed patients on antihypertensive medication (ClinicalTrials.gov NCT02425124). To date, 2747 patients across the two trials have been enrolled and are being followed-up. Results are expected in mid-2018.

## 4.6 Further developments arising from this work

PC101 has been further developed into the Practical Approach to Care Kit (PACK) (pack.bmj.com) as one of a suite of integrated, coherent clinical management tools addressing the primary care needs of adults, children, adolescents and community health workers.

In 2015, a partnership was established with the British Medical Journal (BMJ) Publishing Group to enable the development of a global template of the 'PACK Adult' programme. This template is now complete and includes a mentorship programme for countries interested in localising the programme for their local contexts as well as yearly updates. It also includes a database, linking each of the 2372 recommendations in the guide to the BMJ's equivalent evidence product, *Best Practice* (http://bestpractice.bmj.com/best-practice/marketing/about-best-practice.html?button=site-nav), and other sources such as World Health Organization recommendations.

Localisations of PACK Adult for Brazil and Nigeria have been completed, with a randomised controlled trial underway to evaluate its effectiveness on respiratory and cardiovascular endpoints in the city of Florianópolis, Brazil (ClinicalTrials.gov NCT02786030). Discussions are underway for localisation of the programme in a number of other countries.

PACK Child, a clinical management tool similar in layout to PACK Adult, aimed at equipping nurses and doctors to manage common childhood conditions from ages 0 to 13 years at primary care level, is in the final stages of development, and a randomised controlled trial to evaluate it is in the planning stages. A tool for the primary care management of adolescents, 'PACK Adolescent', is also scheduled to be developed, starting in April 2017.

The Knowledge Translation Unit has also been involved in the adaptation of the PC101 and PACK programmes for undergraduate medical students at the Universities of Stellenbosch and Cape Town.

## 4.7 Limitations and strengths

Limitations and strengths are outlined in detail in each of the four papers. Key limitations and strengths of the thesis are summarised below.

Case definition: We relied on self-report of disease for inclusion in the four cohorts, which may have resulted in potential misclassification in that some participants reported conditions that were not confirmed, while others were found to be receiving medications for a disease that they had not reported. For example, 5% of participants in the hypertension cohort, and 7% of participants in the diabetes cohort had no evidence of being on medication for hypertension and diabetes respectively. Including patients who reported a disease, but were not being treated for it, may have contributed to dilution of treatment effects.

Pragmatic study design: While a pragmatic study design is useful for policy makers, it is subject to weaknesses that influence the outcomes, chief of which is unforeseen co-interventions; in our study the 'Chronic Disease Season', introduced by the health authority, was intended to improve NCD care in all clinics and appeared to contribute to higher than expected treatment intensification rates in both the intervention and control groups, particularly for hypertension and diabetes.

Limited health process evaluation: Due to limited funds, a systematic evaluation of uptake of PC101 by intended users, including barriers to and facilitators of uptake, was not performed.

Evaluation of risk factors: Although the randomised controlled trial provides rigorous evidence of causation, observational evidence is not as strong and does not prove that associations are causal. This said, the longitudinal design strengthened the observational analyses, allowing inference of direction of causation which is ambiguous with cross-sectional studies.

The methods of the reported studies have a number of strengths. First, the pragmatic orientation of the trial, observing 'real-world' implementation of the PC101 programme, appears to have given relevant policy makers sufficient confidence to make a decision on the suitability of the intervention for their health system. The work provides both experimental evidence from a rigorously conducted randomised controlled trial and findings from observational studies conducted alongside the RCT in the primary care setting. The sample size was large: a total of 4393 participants across 38 clinics in the RCT, with exceptionally high follow-up rates and data of assured quality. The longitudinal study design enabled analysis of change in control and treatment, and allowed conclusions on the direction of causation, for example, the bidirectional link between socioeconomic factors and depression. A range of socioeconomic and modifiable predictors of hypertension and depression care were investigated. Further, health outcomes as well as process outcomes were included, such as blood pressure, HbA1c levels in blood, and validated health questionnaires including the CESD-10 and St Georges Respiratory Questionnaire.

## 4.8 Conclusions

This thesis provides new and original evidence for high levels of multimorbidity and unmet treatment needs for NCDs in the South African public primary care sector. It confirms associations between socioeconomic and clinic characteristics, and hypertension control and treatment, and depression symptoms and treatment. It identifies potentially modifiable clinic-level factors that could improve care for these diseases. It provides new evidence from South Africa in support of the bidirectional relationship between poverty and depression. Finally, it reports evidence of the effectiveness of a novel programme aimed at improving NCD management by supporting and expanding nurses' role in NCD care.

The work points to the need for improved strategies for diagnosing and managing NCDs and for better integrated NCD care, including equipping primary health care providers to manage NCDs and the complexities of multimorbidity.

Health services need to be sensitive to the impact of socioeconomic factors, in particular lower levels of education. Clinic factors that may be addressed to improve NCD care include adequate staffing of clinics, having pharmacists on site, and provision for community-based collection of chronic medications. The latter is likely to be relevant to the care of all chronic diseases, and points to the need for expansion of convenient medication delivery services in South Africa. Together, these measures should be viewed as achievable opportunities for improving the management of NCDs in primary care in South Africa.

PC101 offers a practical and acceptable tool to help expand the scope of practice of non-physician clinicians to include NCD care. The programme, with several subsequent

adjustments aimed at increasing its impact, has been rolled out nationally in South Africa and is included in the National Department of Health's checklist criteria for the Ideal Clinic and Integrated Clinical Services Management (ICSM) compliant package of clinical guidelines.

PC101 forms the basis for the Practical Approach to Care Kit (PACK) (pack.bmj.com) which now extends to children, adolescents and community health workers. In partnership with the British Medical Journal (BMJ), global templates of the 'PACK Adult' programme have been developed. Localisations of PACK Adult for Brazil and Nigeria have been completed, and a randomised controlled trial is underway to evaluate the programme in the city of Florianópolis, Brazil. Ongoing development and evaluation of these programmes is required to ensure continued improvements in the management of NCDs in primary care.

In summary, this thesis, including the four publications, addresses the public health challenge of providing integrated chronic disease management in South African primary care. It identifies needs and potential solutions to the needs of patients with NCDs in the public primary care setting.

# Funding

This project was funded in part by the United States National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN268200900030C. Funding was also received from United Health, USA; the Department of Health of the Provincial Government of the Western Cape; the Department of Medicine, University of Cape Town, South Africa; the United Kingdom Department for International Development; and the University of Cape Town Lung Institute, South Africa. The study funders did not contribute to the design of the study, the collection, analysis and interpretation of data, or to the writing of manuscripts or decisions to submit them for publication. The researchers were independent from funders and sponsors.

# References


Andresen, E M, J A Malmgren, W B Carter, and D L Patrick
1994 Screening for Depression in Well Older Adults: Evaluation of a Short Form of the CES-D (Center for Epidemiologic Studies Depression Scale). American Journal of Preventive Medicine 10(2): 77–84.

Araya, R, G Lewis, G Rojas, and R Fritsch
2003 Education and Income: Which Is More Important for Mental Health? Journal of Epidemiology and Community Health 57(7): 501–505.

Ataguba, John E, James Akazili, and Di McIntyre
2011 Socioeconomic-Related Health Inequality in South Africa: Evidence from General Household Surveys. International Journal for Equity in Health 10(1): 48.

Bachmann, M. O., L. R. Fairall, C. Lombard, et al.
2010 Effect on Tuberculosis Outcomes of Educational Outreach to South African Clinics during Two Randomised Trials. The International Journal of Tuberculosis and Lung Disease 14(3): 311–317.

Barlinn, Kristian, Jessica Kepplinger, Volker Puetz, et al.
2014 Exploring the Risk-Factor Association between Depression and Incident Stroke: A Systematic Review and Meta-Analysis. Neuropsychiatric Disease and Treatment 11: 1–14.

Barnett, Karen, Stewart W. Mercer, Michael Norbury, et al.
2012 Epidemiology of Multimorbidity and Implications for Health Care, Research, and Medical Education: A Cross-Sectional Study. Lancet 380(9836): 37–43.

Benatar, S R
2013 The Challenges of Health Disparities in South Africa. South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde 103(3): 154–155.

Beran, David
2015 The Impact of Health Systems on Diabetes Care in Low and Lower Middle Income Countries. Current Diabetes Reports 15(4): 20.

Beran, David, Heather J. Zar, Christophe Perrin, et al.
2015 Burden of Asthma and Chronic Obstructive Pulmonary Disease and Access to Essential Medicines in Low-Income and Middle-Income Countries. The Lancet. Respiratory Medicine 3(2): 159–170.

Berlowitz, D. R., A. S. Ash, E. C. Hickey, et al.
1998 Inadequate Management of Blood Pressure in a Hypertensive Population. The New England Journal of Medicine 339(27): 1957–1963.

Berlowitz, Dan R., Arlene S. Ash, Mark Glickman, et al.
2005 Developing a Quality Measure for Clinical Inertia in Diabetes Care. Health Services Research 40(6 Pt 1): 1836–1853.

Billue, Katherine L, Monika M Safford, Amanda H Salanitro, et al.
2012 Medication Intensification in Diabetes in Rural Primary Care: A Cluster-Randomised Effectiveness Trial. BMJ Open 2(5).

van Bruggen, Rykel, Kees Gorter, Ronald Stolk, Olaf Klungel, and Guy Rutten
2009 Clinical Inertia in General Practice: Widespread and Related to the Outcome of Diabetes Care. Family Practice 26(6): 428–436.

Buist, A Sonia, Mary Ann McBurnie, William M Vollmer, et al.
2007 International Variation in the Prevalence of COPD (the BOLD Study): A Population-Based Prevalence Study. Lancet 370(9589): 741–750.

Campaign for Tobacco-Free Kids
2016 Tobacco Control Laws: Country Details for South Africa. http://www.tobaccocontrollaws.org/legislation/country/south-africa/summary, accessed December 5, 2016.

Carter, Barry L., George R. Bergus, Jeffrey D. Dawson, et al.
2008 A Cluster Randomized Trial to Evaluate Physician/Pharmacist Collaboration to Improve Blood Pressure Control. Journal of Clinical Hypertension (Greenwich, Conn.) 10(4): 260–271.

Chan, Juliana C. N., Edward W. Gregg, Jennifer Sargent, and Richard Horton
2016 Reducing Global Diabetes Burden by Implementing Solutions and Identifying Gaps: A Lancet Commission. Lancet (London, England) 387(10027): 1494–1495.

Chen, Wenjia, Jamie Thomas, Mohsen Sadatsafavi, and J. Mark FitzGerald
2015 Risk of Cardiovascular Comorbidity in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. The Lancet. Respiratory Medicine 3(8): 631–639.

Cois, Annibale, and Rodney Ehrlich
2014 Analysing the Socioeconomic Determinants of Hypertension in South Africa: A Structural Equation Modelling Approach. BMC Public Health 14: 414.

Coleman, R, G Gill, and D Wilkinson
1998 Noncommunicable Disease Management in Resource-Poor Settings: A Primary Care Model from Rural South Africa. Bulletin of the World Health Organization 76(6): 633–640.

Department of Health
2013a Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2013-17. http://www.hsrc.ac.za/uploads/pageContent/3893/NCDs%20STRAT%20PLAN%20%20CONTENT%208%20april%20proof.pdf, accessed May 26, 2016.
2013b Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act 54 of 1972) Regulations Relating to the Reduction of Sodium in Certain Foodstuffs and Related Matters. http://www.heartfoundation.co.za/sites/default/files/articles/South%20Africa%20salt%20legislation.pdf, accessed December 5, 2016.
2015 National Health Insurance for South Africa. https://www.health-e.org.za/wp-content/uploads/2015/12/National-Health-Insurance-for-South-Africa-White-Paper.pdf, accessed February 23, 2017.
2016 Ideal Clinic Manual. https://www.idealclinic.org.za/docs/2016/Ideal%20Clinic%20Manual%20v16%20-%2023Jun16.pdf, accessed December 22, 2016.

Elwell-Sutton, Tim, Naomi Folb, Allan Clark, et al.
unpublished Socioeconomic Position and Depression in South African Adults with Long Term Health Conditions: A Longitudinal Study of Causal Pathways.

Fairall, Lara, Max O Bachmann, Carl Lombard, et al.
2012 Task Shifting of Antiretroviral Treatment from Doctors to Primary-Care Nurses in South Africa (STRETCH): A Pragmatic, Parallel, Cluster-Randomised Trial. Lancet 380(9845): 889–898.

Fairall, Lara, Max O. Bachmann, Merrick Zwarenstein, et al.
2010 Cost-Effectiveness of Educational Outreach to Primary Care Nurses to Increase Tuberculosis Case Detection and Improve Respiratory Care: Economic Evaluation alongside a Randomised Trial. Tropical Medicine & International Health: TM & IH 15(3): 277–286.

Fairall, Lara, Eric Bateman, Ruth Cornick, et al.
2015 Innovating to Improve Primary Care in Less Developed Countries: Towards a Global Model. BMJ Innovations 1(4): 196–203.

Fairall, Lara R., Naomi Folb, Venessa Timmerman, et al.
2016 Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-Communicable Chronic Disease Management in Primary Care in South Africa: A Pragmatic Cluster Randomised Controlled Trial. PLoS Medicine 13(11): e1002178.

Fairall, Lara R, Merrick Zwarenstein, Eric D Bateman, et al.
2005 Effect of Educational Outreach to Nurses on Tuberculosis Case Detection and Primary Care of Respiratory Illness: Pragmatic Cluster Randomised Controlled Trial. BMJ (Clinical Research Ed.) 331(7519): 750–754.

Fan, Amy Z., Sheryl M. Strasser, Xingyou Zhang, Jing Fang, and Carol G. Crawford
2015 State Socioeconomic Indicators and Self-Reported Hypertension among US Adults, 2011 Behavioral Risk Factor Surveillance System. Preventing Chronic Disease 12: E27.

Ferrari, Alize J, Fiona J Charlson, Rosana E Norman, et al.
2013 Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. PLoS Medicine 10(11): e1001547.

GACD
2016 Global Alliance for Chronic DIseases Annual Report 2015/16. http://www.gacd.org/about/strategy/GACD-annual-reports/annual-reports-files/annual-report-2015-16, accessed December 20, 2016.

Galdas, Paul M., Francine Cheater, and Paul Marshall
2005 Men and Health Help-Seeking Behaviour: Literature Review. Journal of Advanced Nursing 49(6): 616–623.

GBD 2015 DALYs and HALE Collaborators
2016 Global, Regional, and National Disability-Adjusted Life-Years (DALYs) for 315 Diseases and Injuries and Healthy Life Expectancy (HALE), 1990-2015: A Systematic Analysis for the Global Burden of Disease Study 2015. Lancet (London, England) 388(10053): 1603–1658.

GBD 2015 Disease and Injury Incidence and Prevalence Collaborators
2016 Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 310 Diseases and Injuries, 1990-2015: A Systematic Analysis for the Global Burden of Disease Study 2015. Lancet (London, England) 388(10053): 1545–1602.

GBD 2015 Mortality and Causes of Death Collaborators
2016 Global, Regional, and National Life Expectancy, All-Cause Mortality, and Cause-Specific Mortality for 249 Causes of Death, 1980-2015: A Systematic Analysis for the Global Burden of Disease Study 2015. Lancet (London, England) 388(10053): 1459–1544.

Gill, G V, C Price, D Shandu, M Dedicoat, and D Wilkinson
2008 An Effective System of Nurse-Led Diabetes Care in Rural Africa. Diabetic Medicine 25(5): 606–611.

Global Asthma Network
2014 The Global Asthma Report 2014. http://www.globalasthmareport.org/, accessed December 20, 2016.

Global Burden of Disease Study 2013 Collaborators
2015 Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 301 Acute and Chronic Diseases and Injuries in 188 Countries, 1990-2013: A Systematic Analysis for the Global Burden of Disease Study 2013. Lancet (London, England) 386(9995): 743–800.

Gorman, Bridget K., and Ahilan Sivaganesan
2007 The Role of Social Support and Integration for Understanding Socioeconomic Disparities in Self-Rated Health and Hypertension. Social Science & Medicine (1982) 65(5): 958–975.

Grotto, Itamar, Michael Huerta, and Yehonatan Sharabi
2008 Hypertension and Socioeconomic Status. Current Opinion in Cardiology 23(4): 335–339.

Gunn, Jane M., Darshini R. Ayton, Konstancja Densley, et al.
2012 The Association between Chronic Illness, Multimorbidity and Depressive Symptoms in an Australian Primary Care Cohort. Social Psychiatry and Psychiatric Epidemiology 47(2): 175–184.

Horrocks, Sue, Elizabeth Anderson, and Chris Salisbury
2002 Systematic Review of Whether Nurse Practitioners Working in Primary Care Can Provide Equivalent Care to Doctors. BMJ 324(7341): 819–823.

IDF
2015 International Diabetes Federation Diabetes Atlas Seventh Edition. http://www.diabetesatlas.org/#tab0, accessed May 20, 2016.

Ingle, Suzanne M., Margaret May, Kerry Uebel, et al.
2010 Outcomes in Patients Waiting for Antiretroviral Treatment in the Free State Province, South Africa: Prospective Linkage Study. AIDS 24(17): 2717–2725.

Jamison, Dean T., Lawrence H. Summers, George Alleyne, et al.
2013 Global Health 2035: A World Converging within a Generation. Lancet (London, England) 382(9908): 1898–1955.

Kasprowicz, Victoria O., Jacqueline M. Achkar, and Douglas Wilson
2011 The Tuberculosis and HIV Epidemic in South Africa and the KwaZulu-Natal Research Institute for Tuberculosis and HIV. Journal of Infectious Diseases 204(suppl 4): S1099–S1101.

Kautzky-Willer, Alexandra, Thomas Dorner, Ann Jensby, and Anita Rieder
2012 Women Show a Closer Association between Educational Level and Hypertension or Diabetes Mellitus than Males: A Secondary Analysis from the Austrian HIS. BMC Public Health 12: 392.

Kengne, Andre P, Paschal K Awah, Leopold L Fezeu, Eugene Sobngwi, and Jean-Claude Mbanya
2009 Primary Health Care for Hypertension by Nurses in Rural and Urban Sub-Saharan Africa. Journal of Clinical Hypertension (Greenwich, Conn.) 11(10): 564–572.

Kyrou, Ioannis, Natasa Kollia, Demosthenes Panagiotakos, et al.
2016 Association of Depression and Anxiety Status with 10-Year Cardiovascular Disease Incidence among Apparently Healthy Greek Adults: The ATTICA Study. European Journal of Preventive Cardiology.

Labhardt, Niklaus D, Jean-Richard Balo, Mama Ndam, Jean-Jacques Grimm, and Engelbert Manga
2010 Task Shifting to Non-Physician Clinicians for Integrated Management of Hypertension and Diabetes in Rural Cameroon: A Programme Assessment at Two Years. BMC Health Services Research 10: 339.

Lalkhen, Hoosain, and Robert Mash
2015 Multimorbidity in Non-Communicable Diseases in South African Primary Healthcare. South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde 105(2): 134–138.

Laurant, M., M. Harmsen, H. Wollersheim, et al.
2009 The Impact of Nonphysician Clinicians: Do They Improve the Quality and Cost-Effectiveness of Health Care Services? Med Care Res Rev. 2009 Dec;66(6 Suppl):36S-89S.

Leng, Bing, Yana Jin, Ge Li, Ling Chen, and Nan Jin
2015 Socioeconomic Status and Hypertension: A Meta-Analysis. Journal of Hypertension 33(2): 221–229.

Lim, Stephen S, Theo Vos, Abraham D Flaxman, et al.
2012 A Comparative Risk Assessment of Burden of Disease and Injury Attributable to 67 Risk Factors and Risk Factor Clusters in 21 Regions, 1990–2010: A Systematic Analysis for the Global Burden of Disease Study 2010. The Lancet 380(9859): 2224–2260.

Lönnroth, Knut, Gojka Roglic, and Anthony D. Harries
2014 Improving Tuberculosis Prevention and Care through Addressing the Global Diabetes Epidemic: From Evidence to Policy and Practice. The Lancet. Diabetes & Endocrinology 2(9): 730–739.

Lozano, Rafael, Mohsen Naghavi, Kyle Foreman, et al.
2012 Global and Regional Mortality from 235 Causes of Death for 20 Age Groups in 1990 and 2010: A Systematic Analysis for the Global Burden of Disease Study 2010. The Lancet 380(9859): 2095–2128.

Lund, Crick, Alison Breen, Alan J Flisher, et al.
2010 Poverty and Common Mental Disorders in Low and Middle Income Countries: A Systematic Review. Social Science & Medicine (1982) 71(3): 517–528.

Maepe, L M, and K Outhoff
2012 Hypertension in Goldminers. South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde 102(1): 30–33.

Mahomed, OH, Naidoo S, Asmall S, and Taylor M
2015 Evaluation of PC 101 Training for Professional Nurses in 3 Districts in South Africa. Pretoria: National Department of Health.

Mahomed, Ozayr Haroon, and Shaidah Asmall
2015 Development and Implementation of an Integrated Chronic Disease Model in South Africa: Lessons in the Management of Change through Improving the Quality of Clinical Practice. International Journal of Integrated Care 15: e038.

Mahomed, Ozayr Haroon, Shaidah Asmall, and Melvyn Freeman
2014 An Integrated Chronic Disease Management Model: A Diagonal Approach to Health System Strengthening in South Africa. Journal of Health Care for the Poor and Underserved 25(4): 1723–1729.

Mash, Bob, Lara Fairall, Olubunmi Adejayan, et al.
2012 A Morbidity Survey of South African Primary Care. PloS One 7(3): e32358.

Masoli, Matthew, Denise Fabian, Shaun Holt, Richard Beasley, and Global Initiative for Asthma (GINA) Program
2004 The Global Burden of Asthma: Executive Summary of the GINA Dissemination Committee Report. Allergy 59(5): 469–478.

Mayosi, Bongani M, Alan J Flisher, Umesh G Lalloo, et al.
2009 The Burden of Non-Communicable Diseases in South Africa. Lancet 374(9693): 934–947.

Mendenhall, Emily, Linda M Richter, Alan Stein, and Shane A Norris
2013 Psychological and Physical Co-Morbidity among Urban South African Women. PloS One 8(10): e78803.

Mercer, Stewart W., Jane Gunn, Peter Bower, Sally Wyke, and Bruce Guthrie
2012 Managing Patients with Mental and Physical Multimorbidity. BMJ (Clinical Research Ed.) 345: e5559.

Moffat, Keith, and Stewart W. Mercer
2015 Challenges of Managing People with Multimorbidity in Today's Healthcare Systems. BMC Family Practice 16(1): 129.

Morrison, Deborah, Karolina Agur, Stewart Mercer, et al.
2016 Managing Multimorbidity in Primary Care in Patients with Chronic Respiratory Conditions. NPJ Primary Care Respiratory Medicine 26: 16043.

Murray, Christopher J. L., and Alan D. Lopez
2013 Measuring the Global Burden of Disease. The New England Journal of Medicine 369(5): 448–457.

Murray, John F., Antonio Pio, and Salah Ottmani
2006 PAL: A New and Practical Approach to Lung Health. The International Journal of Tuberculosis and Lung Disease: The Official Journal of the International Union Against Tuberculosis and Lung Disease 10(11): 1188–1191.

National Treasury
2016 Taxation of Sugar Sweetened Beverages. http://www.treasury.gov.za/public%20comments/Sugar%20sweetened%20beverages/POLICY%20PAPER%20AND%20PROPOSALS%20ON%20THE%20TAXATION%20OF%20SUGAR%20SWEETENED%20BEVERAGES-8%20JULY%202016.pdf, accessed February 23, 2017.

Nojilana, Beatrice, Debbie Bradshaw, Victoria Pillay-van Wyk, et al.
2016 Emerging Trends in Non-Communicable Disease Mortality in South Africa, 1997 - 2010. S Afr Med J 106(5): 58.

Pan, An, Qi Sun, Olivia I Okereke, Kathryn M Rexrode, and Frank B Hu
2011 Depression and Risk of Stroke Morbidity and Mortality: A Meta-Analysis and Systematic Review. JAMA 306(11): 1241–1249.

Patel, V, R Araya, M de Lima, A Ludermir, and C Todd
1999 Women, Poverty and Common Mental Disorders in Four Restructuring Societies. Social Science & Medicine (1982) 49(11): 1461–1471.

Patel, Vikram, and Somnath Chatterji
2015 Integrating Mental Health In Care For Noncommunicable Diseases: An Imperative For Person-Centered Care. Health Affairs (Project Hope) 34(9): 1498–1505.

Patel, Vikram, and Arthur Kleinman
2003 Poverty and Common Mental Disorders in Developing Countries. Bulletin of the World Health Organization 81(8): 609–615.

Payne, Rupert A., Gary A. Abel, Bruce Guthrie, and Stewart W. Mercer
2013 The Effect of Physical Multimorbidity, Mental Health Conditions and Socioeconomic Deprivation on Unplanned Admissions to Hospital: A Retrospective Cohort Study. CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne 185(5): E221-228.

Peer, Nasheeta, Krisela Steyn, Cheryl R. Dennison, et al.
2008 Determinants of Target Organ Damage in Black Hypertensive Patients Attending Primary Health Care Services in Cape Town: The Hi-Hi Study. American Journal of Hypertension 21(8): 896–902.

Peer, Nasheeta, Krisela Steyn, Carl Lombard, Nomonde Gwebushe, and Naomi Levitt
2013 A High Burden of Hypertension in the Urban Black Population of Cape Town: The Cardiovascular Risk in Black South Africans (CRIBSA) Study. PLoS ONE 8(11): e78567.

Petersen, Inge, Lara Fairall, Arvin Bhana, et al.
2016 Integrating Mental Health into Chronic Care in South Africa: The Development of a District Mental Healthcare Plan. The British Journal of Psychiatry: The Journal of Mental Science 208 Suppl 56: s29-39.

Poyser, M A, H Nelson, R I Ehrlich, et al.
2002 Socioeconomic Deprivation and Asthma Prevalence and Severity in Young Adolescents. The European Respiratory Journal 19(5): 892–898.

Prince, Martin, Vikram Patel, Shekhar Saxena, et al.
2007 No Health without Mental Health. Lancet 370(9590): 859–877.

Public Health Association of South Africa
2011 The Implementation of PHC Re-Engineering in South Africa. https://www.phasa.org.za/the-implementation-of-phc-re-engineering-in-south-africa/, accessed February 23, 2017.

Rabkin, Miriam, and Wafaa M. El-Sadr
2011 Why Reinvent the Wheel? Leveraging the Lessons of HIV Scale-up to Confront Non-Communicable Diseases. Global Public Health 6(3): 247–256.

Rahman, Iffat, Keith Humphreys, Anna Michaela Bennet, et al.
2013 Clinical Depression, Antidepressant Use and Risk of Future Cardiovascular Disease. European Journal of Epidemiology.

Rayner, Brian
2010 Hypertension: Detection and Management in South Africa. Nephron. Clinical Practice 116(4): c269-273.

Reddy, K. Srinath
2002 Cardiovascular Diseases in the Developing Countries: Dimensions, Determinants, Dynamics and Directions for Public Health Action. Public Health Nutrition 5(1A): 231–237.

van Rensburg, Hendrik CJ
2014 South Africa's Protracted Struggle for Equal Distribution and Equitable Access – Still Not There. Human Resources for Health 12: 26.

Sackett, David L.
2011 Explanatory and Pragmatic Clinical Trials: A Primer and Application to a Recent Asthma Trial. Polskie Archiwum Medycyny Wewnętrznej 121(7–8): 259–263.

Sanne, Ian, Catherine Orrell, Matthew P. Fox, et al.
2010 Nurse versus Doctor Management of HIV-Infected Patients Receiving Antiretroviral Therapy (CIPRA-SA): A Randomised Non-Inferiority Trial. Lancet (London, England) 376(9734): 33–40.

Schmittdiel, Julie A, Connie S Uratsu, Andrew J Karter, et al.
2008 Why Don't Diabetes Patients Achieve Recommended Risk Factor Targets? Poor Adherence versus Lack of Treatment Intensification. Journal of General Internal Medicine 23(5): 588–594.

Seedat, Soraya, D J Stein, A Herman, et al.
2008 Twelve-Month Treatment of Psychiatric Disorders in the South African Stress and Health Study (World Mental Health Survey Initiative). Social Psychiatry and Psychiatric Epidemiology 43(11): 889–897.

Selby, Joe V, Julie A Schmittdiel, Bruce Fireman, et al.
2012 Improving Treatment Intensification to Reduce Cardiovascular Disease Risk: A Cluster Randomized Trial. BMC Health Services Research 12: 183.

Statistics South Africa
2014 Poverty Trends in SA. http://www.statssa.gov.za/?p=2591.

Steyn K, Fourie J, and Temple N
2006 Chronic Diseases of Lifestyle in South Africa: 1995-2005. Technical Report. Cape Town: South African Medical Research Council.

Steyn, K, T A Gaziano, D Bradshaw, et al.
2001 Hypertension in South African Adults: Results from the Demographic and Health Survey, 1998. Journal of Hypertension 19(10): 1717–1725.

Steyn, Krisela, Naomi S Levitt, Maya Patel, et al.
2008 Hypertension and Diabetes: Poor Care for Patients at Community Health Centres. South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde 98(8): 618–622.

Thompson, Ashley E., Yvonne Anisimowicz, Baukje Miedema, et al.
2016 The Influence of Gender and Other Patient Characteristics on Health Care-Seeking Behaviour: A QUALICOPC Study. BMC Family Practice 17: 38.

Thorpe, Kevin E., Merrick Zwarenstein, Andrew D. Oxman, et al.
2009 A Pragmatic-Explanatory Continuum Indicator Summary (PRECIS): A Tool to Help Trial Designers. Journal of Clinical Epidemiology 62(5): 464–475.

Tomlinson, Mark, Anna T Grimsrud, Dan J Stein, David R Williams, and Landon Myer
2009 The Epidemiology of Major Depression in South Africa: Results from the South African Stress and Health Study. South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde 99(5 Pt 2): 367–373.

Tracey, Marsha L., Sheena M. McHugh, Anthony P. Fitzgerald, et al.
2016 Risk Factors for Macro- and Microvascular Complications among Older Adults with Diagnosed Type 2 Diabetes: Findings from The Irish Longitudinal Study on Ageing. Journal of Diabetes Research 2016: 1–9.

Tregenna, Fiona, and Mfanafuthi Tsela
2012 Inequality in South Africa: The Distribution of Income, Expenditure and Earnings. Development Southern Africa 29(1): 35–61.

UNAIDS
2015 UNAIDS AIDSinfo Country Factsheets South Africa 2015. http://aidsinfo.unaids.org/, accessed September 22, 2016.

UNGA
2011 United Nations General Assembly. Political Declaration of the High-Level Meeting of the General Assembly on the Prevention and Control of Non-Communicable Diseases. New York: United Nations, 2011. Http://Www.un.org/Ga/Search/view_doc.asp?symbol=A/66/L.1 (Accessed 1 April 2016).

Vos, Theo, Abraham D Flaxman, Mohsen Naghavi, et al.
2012 Years Lived with Disability (YLDs) for 1160 Sequelae of 289 Diseases and Injuries 1990–2010: A Systematic Analysis for the Global Burden of Disease Study 2010. The Lancet 380(9859): 2163–2196.

WHO
2005 A Primary Health Care Strategy for the Integrated Management of Respiratory Conditions in People of Five Years of Age and Over. http://www.who.int/tb/health_systems/pal/en/, accessed December 9, 2016.
2008a Integrated Health Services.
http://www.who.int/healthsystems/service_delivery_techbrief1.pdf, accessed September 29, 2016.
2008b Evaluation of the Practical Approach to Lung Health.
http://apps.who.int/iris/bitstream/10665/69730/1/WHO_HTM_TB_2008.396_eng.pdf, accessed February 23, 2017.
2010 Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings.
http://www.who.int/nmh/publications/essential_ncd_interventions_lr_settings.pdf?ua=1, accessed February 23, 2017.
2011a Global Status Report on Non-Communicable Diseases 2010. Geneva.
2011b From Burden to “Best Buys”: Reducing the Economic Impact of Non-Communicable Diseases in Low- and Middle-Income Countries.
http://www.who.int/nmh/publications/best_buys_summary.pdf?ua=1, accessed March 8, 2017.
2013a A Global Brief on Hypertension: Silent Killer, Global Public Health Crisis.
http://apps.who.int/iris/bitstream/10665/79059/1/WHO_DCO_WHD_2013.2_eng.pdf?ua=1., accessed October 17, 2016.
2013b Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020. http://www.who.int/nmh/events/ncd_action_plan/en/, accessed May 20, 2016.
2013c Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings.
http://www.who.int/cardiovascular_diseases/publications/implementation_tools_WHO_PEN/en/, accessed January 3, 2017.
2015 Tuberculosis Country Profiles: South Africa.
https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=ZA&LAN=EN&outtype=html, accessed December 5, 2016.
2017 WHO Guidelines Approved by the Guidelines Review Committee.
http://www.who.int/publications/guidelines/en/, accessed January 3, 2017.

Williams, D R, A Herman, D J Stein, et al.
2008 Twelve-Month Mental Disorders in South Africa: Prevalence, Service Use and Demographic Correlates in the Population-Based South African Stress and Health Study. Psychological Medicine 38(2): 211–220.

Zwarenstein, Merrick, Lara R Fairall, Carl Lombard, et al.
2011 Outreach Education for Integration of HIV/AIDS Care, Antiretroviral Treatment, and Tuberculosis Care in Primary Care Clinics in South Africa: PALSA PLUS Pragmatic Cluster Randomised Trial. BMJ (Clinical Research Ed.) 342: d2022.