Burden of Multimorbidity in South Africa: Implications for health policy and service delivery

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KEYWORDS

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Co-morbidity

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ABSTRACT

Background. South Africa is challenged to manage the quadruple burden of disease experienced by its population. Furthermore, the burden of multimorbidity – that is, people living with more than one disease condition – is increasing. Multimorbidity challenges the way the health system is organised as it traverses different health programmes. However, little research has investigated the phenomenon in South Africa.

Aim. The study describes the epidemiology – prevalence, patterns and risk factors - of multimorbidity in South Africa, and makes recommendations for health policy and service delivery.

Methodology. This study employed a multi-phased research design. The first phase involves a systematic review of multimorbidity studies in South Africa to analyse the prevalence of multimorbidity, and to identify disease clusters (patterns of multimorbidity) and factors associated with multimorbidity. In the second phase a consistent method to analyse multimorbidity in national surveys was developed and applied. The three most recent national health surveys were selected (South African Demographic and Health Survey 2016 [SADHS 2016], South African Behaviour and Communication Survey 2017 [SABSSM 2017], and the National Income Dynamics Survey 2017 [NIDS 2017]). All analyses included people aged 15 years and older. Each dataset was appropriately weighted to determine the prevalence of multimorbidity by age and sex. Latent class analyses were conducted to identify disease clustering within the multimorbid population. Multivariate logistic regression was used to identify sociodemographic and behavioural factors associated with multimorbidity. The results from the different surveys were compared, contrasted and discussed in the context of policy developments in South Africa.

Results. The systematic review identified ten studies related to multimorbidity in South Africa. One of the major findings was a lack of consistency in the methods used, as well as an absence of disaggregated reporting by age groups and sex. The analysis of national survey datasets revealed that multimorbidity increased in older age groups and the prevalence was often higher among women compared to men. Hypertension frequently co-occurred with other diseases such as HIV and diabetes. The factors associated with multimorbidity varied between the surveys but older age was the most consistent factor associated with increased multimorbidity in all three surveys. Other

sociodemographic factors that indicated an increased risk for multimorbidity were being female and living in an urban environment, and belonging to the wealthiest quintile. Lifestyle factors associated with an increased risk of multimorbidity were being a smoker and having a high body mass index.

Conclusions. As the South African population ages, multimorbidity is expected to increase. This highlights the need for person-centred, integrated care, and possibly, a gerontological care package. The burden of multimorbidity in older adults and in women, needs to be urgently addressed through further policy development and regulation to deliver universal healthcare and promote healthy ageing.

DECLARATION

I, Rifqah Abeeda Roomaney, declare that this thesis '*Burden of Multimorbidity in South Africa: Implications for health policy and service delivery'* is my own work, that it has not been submitted for any degree or examination to any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

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Date: 18 November 2022

Signed: 

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CONTENTS

Chapter 1. Introduction and Overview of Study

OVERVIEW OF CHAPTER

This chapter situates this doctoral research project within the broader context of multimorbidity research. It provides a high-level overview of the disease burden in South Africa and important policy directives in the country. The chapter describes the varying definitions of multimorbidity, the negative impacts borne by those with multimorbidity and the state of multimorbidity research globally. Chapter 2 provides information on the state of local multimorbidity literature through a systematic review. The chapter then concludes by stating the aims and objectives of the thesis and providing an overview of how the thesis is structured, including the nine articles comprising this thesis.

1.1. BACKGROUND

Burden of disease in South Africa

The *Theory of Epidemiologic Transition* [1] refers to shifting mortality and disease patterns over time, whereby, infectious diseases are gradually displaced by degenerative, lifestyle diseases; influenced by ecobiologic factors, socioeconomic, political and cultural factors, and public-health interventions.[2] South Africa is an upper middle-income country[3, 4] and can be described as being in a *'protracted epidemiologic transition,'* with dual burdens of infectious diseases and non-communicable diseases (NCDs).[5]

South Africa is described as having a quadruple burden of disease.[6, 7] The disease burden consists of high levels of: (a) HIV/AIDS and tuberculosis; (b) other communicable diseases, perinatal conditions, maternal causes, and nutritional deficiencies; (c) NCDs; and, (d) injuries.[8] The second National Burden of Disease estimated that in 2012, NCDs were responsible for 43% of deaths in South Africa.[8] This was followed by HIV and TB (34%), other communicable diseases, perinatal conditions, maternal causes, and nutritional deficiencies (14%) and injuries (10%).[8]

In the following sections, NCDs and HIV - due to their large burdens in South Africa - are discussed in more detail.

Non-communicable diseases

The prevalence of NCDs is increasing globally. Through globalisation, urbanisation, population growth, ageing, and trends towards unhealthy lifestyles, a growing NCD crisis is occurring worldwide.[9] NCDs such as cardiovascular disease (CVD), diabetes, chronic respiratory diseases and cancer share common risk factors such as physical inactivity, unhealthy diets, tobacco use and excessive alcohol use.[9] While NCDs have traditionally been viewed as health problems of the rich, current data show NCDs are rising in developing countries.[10] Worryingly, 77% of deaths due to NCDs occur in low- and middle-income countries (LMICs).[11] In developing countries, a shift towards 'westernised diets' and a lack of physical activity are seen as key risk factors for the rise in NCDs.

In South Africa, increased deaths from NCDs are attributed to population growth and an ageing population.[12] While there is a high burden of NCDs in poor urban areas, the prevalence of NCDs appears to be rising in rural communities.[6]. Risk factors for NCDs, particularly for CVD, are high, even in rural areas.[13] Despite this, the routine health-information systems to monitor NCDs are rudimentary.[14] Hence national health surveys and systematic reviews that harmonise results from smaller studies have been used to indicate the prevalence of this group of diseases. In terms of diabetes type-2, a systematic review assessed the prevalence in people aged 25 years and older to be 15%.[15] A comparative analysis between two national surveys found hypertension prevalence to range between 38% and 48%.[16] Another systematic review found that the overall prevalence in South African of CVD was low (e.g. coronary heart disease 1.3%, stroke 4.3%).[17] However, the authors noted that the low prevalence may be due to a lack of reliable and nationally representative data.[17] While this brief review of NCD estimates in South Africa is far from comprehensive, it shows that NCDs are prevalent among the adult population.

HIV/AIDS

Infectious diseases remain a major contributor to mortality and morbidity in South Africa. South Africa has a large population of people living with HIV and is one of the 15 countries that account for nearly 75% of people living with HIV globally.[18] South Africa has a generalised HIV epidemic and in 2020, it was estimated that 7.8 million adults and children were living with

HIV.[19] For the same year, the HIV prevalence among people aged 15 to 49 years was estimated to be 19%.[19]

On a positive note, the country also has the largest antiretroviral therapy (ART) programme in the world.[20] Improved access to and availability of ART as well as advances in antiretroviral drugs have reduced morbidity and mortality related to HIV,[21] and transformed HIV into a chronic disease. People living with HIV are living longer, ageing [22] and developing other chronic complications.[21, 23]. There is now a growing population of older people with HIV – both due to young people with HIV surviving to older ages, but also due to an increasing number of older people acquiring HIV.[24] These older people are more likely to have multimorbidity compared to younger people with HIV, and have higher levels of multimorbidity compared to people their own age without HIV.[24] The needs of older people with HIV may be considerably different to the needs of younger people, which means the South African health services will need to adjust accordingly.

Ensuring good health for all

The World Health Organization described universal health coverage (UHC) as:

'all people have access to the health services they need, when and where they need them, without financial hardship. It includes the full range of essential health services, from health promotion to prevention, treatment, rehabilitation, and palliative care.'[25]

Achieving UHC is explicitly stated in Sustainable Development Goal (SDG) 3.8.[26] South Africa has championed the cause of the UHC through a National Health Insurance (NHI) scheme proposed in 2011 by the then Health Minister, Aaron Motsoaledi.[27]

The current health system is largely perceived as unequal and inefficient.[27] South Africa's history of discrimination and subjugation has resulted in massive inequalities[28], including in access to healthcare. The existing two-tiered health system consists of 'first-world' healthcare through the private sector and an over-burdened, under-resourced public sector.[27] The vast majority of South Africans (82%) rely on the public healthcare system.[29] The proportion reliant on the public healthcare system may be even higher among the elderly due to the exorbitant costs of private medical aid.

Primary healthcare in developing countries has traditionally focused on acute infectious diseases and increasing chronic conditions means a rethinking of the healthcare system.[30] While the

South African healthcare system has been formulated to implement vertical HIV/TB and disease-specific programmes in the past, the National Department of Health has recognised the need to treat chronic conditions in an integrated manner as set out in the *2016 Adherence Guidelines for HIV, TB and NCDs.*[20] These guidelines acknowledge that one of the biggest problems facing the healthcare system is poor retention in care and non-adherence to chronic medications which lead to poor health outcomes and overall health costs.[20]

The introduction of policy and service-delivery guidelines shows a recognition that an integrated patient-centred health system is important. Whether this is being implemented remains to be seen as recent studies have indicated that policy objectives with regards to integration of care are under-developed.[31]

People with multimorbidity are experiencing siloed service delivery.[32] While estimates are uncertain, many South Africans are thought to be affected by multimorbidity – especially adults over 60 years of age. Multimorbidity may also become the norm in decades to come. Several interrelated factors could lead to an increase in the prevalence of multimorbidity in South Africa, including: an ageing population, disease shifts towards NCDs, lifestyles that promote NCD risk factors, the scaling up of ART and the ageing of the HIV-positive population.

The lack of morbidity data is a serious hindrance to health-service planning and particularly detrimental to the study of multimorbidity. Already, NCD health-information systems have been described as rudimentary. How is it then possible to monitor the number of people with more than one disease condition, especially for people who may have an infectious disease and NCDs?

Problem Statement

Traditionally, health programmes and service delivery are orientated around singular groups of disease. Multimorbidity cuts across different spheres of the health system, and can include services for NCDs, chronic infectious diseases and mental health conditions.[33] As health services are not patient-centred, those with multimorbidity must navigate a fragmented healthcare system [34] and may experience inefficiency in accessing care.

Multimorbidity also has negative consequences for the healthcare system. Multimorbidity drives healthcare utilisation and associated costs.[35] It also alters the resources required for staffing, financing and technological development. Based on patterns identified in other countries, multimorbidity is likely to be a significant contributor to ill health in South Africa therefore

comprehensive information on multimorbidity is needed for health-service delivery planning. A better understanding of the epidemiology of multimorbidity could also allow for interventions to be developed which allow for more effective and efficient treatment of patients.[33, 36]

The current routine health-information system collects aggregated data at health facilities. Consequently, South Africa lacks routine information to monitor and report on multimorbidity on a national scale. In the absence of this information, national survey datasets can provide valuable information about multimorbidity in the general population. However, studies that have attempted to do this have not analysed multimorbidity in a consistent way.

Rationale for the Study

Information on the prevalence and profile of multimorbidity is needed to inform and improve the efficiency of existing programmes and policies on integrated health services in the country. Information is needed on the prevalence of disease clusters, trends and the risk factors associated with disease clusters in order to design interventions to improve service delivery. In addition, this information is needed to target individuals at high risk of developing multimorbidities to prevent them from progressing down the continuum of care. Further, this study contributes to closing the research gap related to multimorbidity in LMICs as more robust studies are needed on multimorbidity in South Africa and sub-Saharan Africa.

A systematic review was used to identify and synthesise existing literature on multimorbidity in South Africa, and reported on critical evidence gaps. The systematic review also contributed to the development of systematic and reproducible methods to analyse multiple surveys; thus improving the validity and reliability of estimates generated. These national burden of disease estimates of multimorbidity are the most reliable current measures available in the country. This study has the potential to provide a baseline for South African estimates of multimorbidity.

National burden of disease studies provide essential information for policymakers in health planning, financing and policy. The current study thus has high potential for influencing health-policy formulation and implementation of comprehensive, integrated primary healthcare in South Africa.

1.2. LITERATURE REVIEW

Definition of multimorbidity

Multimorbidity, in its simplest form, is defined as an individual having multiple diseases.[37] While the term is similar to 'co-morbidity', it differs in that neither disease is considered the index or 'main' disease.[38] Multimorbidity, as a concept, originated in Germany in 1976[39, 40] but only gained some traction internationally in the 1990s.[40]A bibliometric study identified an exponential increase in the number of articles published about multimorbidity in the 2000s, with 80% published after 2010.[41] Therefore, the field is fairly new but growing rapidly.

An aspect that has hindered the study of multimorbidity, is the various definitions used to define multimorbidity and the many ways that it is measured.[37] In 2013, the European General Practice Research network presented a holistic definition whereby they defined multimorbidity as the '*combination of chronic disease with at least one other disease (acute or chronic) or bio-psychosocial factor (associated or not) or somatic risk factor*'.[40] More recently, The Academy of Medical Sciences recommended a simplified definition of multimorbidity whereby it is the *'co-existence of two or more chronic conditions*.'[33] These chronic conditions can include a physical non-communicable disease of long duration (e.g. cardiovascular disease or cancer), a mental health condition of long duration (e.g. mood disorder or dementia) or an infectious disease of long duration (e.g. HIV or hepatitis C).[33] The inclusion of infectious disease of long duration was an important development in the South African context.

Despite efforts and recommendations to standardise the study of multimorbidity, no universally accepted definition exists. These differences make it difficult to compare findings between studies. However, on a positive note, this allows for a focus on locally relevant disease conditions.

Impact of multimorbidity

Multimorbidity results in a wide range of negative consequences. These impacts can be viewed from different perspectives, including those of patients, caregivers, healthcare professionals and the broader economy.[33] The impacts from different perspectives are discussed below.

Individual and community-level impacts

Multimorbidity is associated with higher mortality rates, a lower quality of life, increased treatment burden and economic consequences for those affected and those caring for people with multimorbidity.

At the individual level, multimorbidity is associated with higher mortality rates.[42, 43] A meta-analysis found that having two and three diseases were associated with a double and triple increased risk of death, respectively.[42] A study in an older, rural South African cohort found that multimorbidity was associated with a greater risk of death in men and women, and there was a greater odds of dying within two years.[44] These studies highlight the increased mortality risk associated with multimorbidity. However, living with multimorbidity is also linked to reduced wellbeing and a decreased quality of life. Several systematic reviews have shown negative correlations between multiple disease conditions and quality of life or health-related quality of life.[35, 45-48] A meta-analysis found a mean decrease of -2% to -4% in health-related quality of life for each added disease condition.[48] Although quality of life measures can be influenced by location, the association between multimorbidity and quality of life has been noted in a variety of settings and countries, from high-income countries [48] to countries such as India,[49] China,[50] and South Africa.[51] Hence, multimorbidity may result in a shortened life and also a worsened quality of life.

Patients with multimorbidity face a great treatment burden. These patients have to self-manage complex treatment plans with multiple drugs.[52-55] Some suffer from adverse drug reactions due to polypharmacy.[56] Also, when treatment burden is high, patients may feel overwhelmed and less likely to adhere to treatment which may worsen outcomes.[33, 57] Patients are also impacted as their time and energy are affected by accessing care from multiple providers. A qualitative study based in The Netherlands and Belgium found that multimorbidity impacted organisation of care for patients and their daily life.[58] For example, Dutch participants found gaps in communication between general practitioners and specialists resulting in conflicting advice.[58] Treatment burden is only one part of the problem as these patients also face higher out-of-pocket expenditure (OOPE) due to the treatment burden.

Multimorbidity is known to impact OOPE, as a systematic review showed that NCD multimorbidity was linked to higher OOPE on medicines.[59] The annual OOPE on medicines

increased five-fold when an individual had two diseases, and ten-fold when a patient had three or more diseases.[59] Having two or more diseases was associated with a OOPE median spending of 2.42% of the mean annual household net adjusted disposable income per capita. The review also found that the elderly and those in lower-income quintiles suffered an even greater OOPE burden ratio.[59] Of great concern, the review found that non-adherence was seen as a coping mechanism to manage high OOPE costs and polypharmacy. A study in Brazil focused on catastrophic health expenditure associated with multimorbidity.[60] Catastrophic health expenditure refers to instances where OOPE exceeds the family's ability to pay (i.e. it is a large proportion of income). The study found significant associations between catastrophic health expenditure and multimorbidity; and these were higher among people in lower income groups.[60] In this way, multimorbidity could lead to constrained financial situations.

Multimorbidity also negatively impacts on work productivity and security among those who are employed. A systematic review of longitudinal studies found that workers with multimorbidity had missed days of work due to health-related issues, reductions in work productivity, presenteeism, higher indices of dismissal and increased incidence of early retirement.[61] Even among young people, multimorbidity is associated with absenteeism. For example, a study of young workers in Australia found productivity loss (i.e. absenteeism) increased as the number of health conditions increased.[62]

Caregivers can also find themselves burdened by having to care for family members with multimorbidity. A systematic review found that caregivers experienced problems relating to understanding the condition, monitoring and adjusting treatments, and financial and time constraints.[63] A study in Singapore found that caregivers (who were mainly women) experienced an increase in caregiving time per week.[64] Consequently, reinforcing gender roles and impeding the ability of women to earn an income.

Health systems and the broader economy

Multimorbidity has been described as a ‘defining challenge for health systems’.[36] Most healthcare systems, clinical teams and clinical guidelines are organised around single diseases or single organ lines.[65] While medical specialisation has improved the ability to treat single diseases, it may disadvantage the growing number of patients with multiple diseases.[65] These patients may end up seeing several specialists to treat subcomponents of their overall health

problem in isolation.[65] Treatment guidelines are often also created along single disease or organ lines. For one, patients with multimorbidity are usually excluded from drug trials [66], which can create uncertainty in treatment guidelines. This also impacts on healthcare professionals as they may need to follow numerous guidelines which ultimately may create challenges in delivering patient-centred care to the person with multimorbidity.[33, 67].

Multimorbidity also leads to increased healthcare utilisation and costs.[68, 69] An analysis of 16 European countries found that the number of medical doctor visits increased by the number of disease conditions present.[68] Also, hospitalisation in the previous year was higher among those with multimorbidity.[68] A systematic review based on studies in the United Kingdom found that multimorbidity increases healthcare utilisation and costs at primary and secondary level; as well as dental care.[70] Multimorbidity was associated with costs throughout the medical sphere – for example, it was associated not only with increased total costs but also with hospital costs, primary care use, dental care use, emergency department use and hospitalisations.[70]

Multimorbidity is also a large cost to economies. A study in the United States estimated that multimorbidity-related absenteeism wage loss among working adults amounted to USD$9 billion.[71] Another systematic review of cost of illness studies related to multimorbidity estimated that the average annual cost of multimorbidity per capita ranged from USD$49 to USD$252 313.[72] While the review noted large variability in studies, the authors concluded that multimorbidity was associated with considerable economic burden.

Summary

This section has established the large individual and societal burden caused by multimorbidity. For the individual, living with multimorbidity impacts their ability to work, increases their costs, reduces their quality of life and intensifies the need for regular contact with healthcare services. Family members or caregivers are also affected in various ways. Household income may be used to absorb medical costs. Also, family members may need to accompany their loved ones to health facilities, manage medication or physically care for those with multimorbidity. This increased caregiving and responsibility may impact caregivers in terms of stress and also compromise their work productivity.

The healthcare system has not been designed around individuals having multiple disease conditions which may result in time wasted for the patient and confusing and contrary advice

received. Healthcare workers may not be well equipped or sufficiently trained to manage the complexity presented by patients with multimorbidity. Increasing prevalence of multimorbidity has the potential to increase healthcare utilisation and associated costs, and affect the economy on a macro-scale through loss of productivity from the working population.

The state of multimorbidity research globally

Despite multimorbidity having documented large direct and indirect costs at the individual, healthcare and even macroeconomic level, the problem remains overlooked, particularly in LMICs. Even with similar prevalences of multimorbidity among high-income countries and LMICs, most research has occurred in high-income countries. The next section describes the prevalence of multimorbidity, and trends documented in the literature.

Prevalence of multimorbidity

A significant proportion of the population lives with multimorbidity. A recent systematic review found that the pooled prevalence of multimorbidity globally was 42%.[73] The analysis showed no statistically significant difference between the prevalence of multimorbidity in LMICs and high-income countries (37% versus 44%, respectively).[73] Another systematic review focused on studies in community settings, found that the global pooled prevalence of multimorbidity was 33%. In contrast to the previously mentioned review, the authors found a 'considerable difference' in pooled estimates between LMICs and high-income countries (30% versus 38%, respectively). Despite the differences in these two meta-analyses, both indicate that multimorbidity is 30% or higher in LMICs. Yet research on multimorbidity in LMICs only comprises 5% of the total research conducted in this area,[41] signalling a huge gap in the literature.

Multimorbidity is expected to increase

Although it is challenging to find reliable estimates on multimorbidity, it is theorised that the prevalence of multimorbidity is increasing globally.[74] This increase is largely attributed to population ageing.[74] Ageing is an established risk factor for multimorbidity,[75, 76] as the chances for disease accumulation increases with time and over the life-course.

Population ageing is recognised as a 'megatrend'- with every country on Earth experiencing growth in the proportion of older persons in their population.[77] All regions have experienced an

increase in life expectancy, with the largest gains evident in sub-Saharan Africa.[77] Since women tend to outlive men, a predominantly female older population is emerging.[77] This is an important consideration in terms of multimorbidity, as both ageing and being female, are associated with having multiple diseases.[78] Other factors that impact the prevalence of multimorbidity include the growing prevalence of NCDs, particularly in LMICs. Rapid shifts in the disease profile are taking place in many LMICs, as the prevalence of key modifiable risk factors rise (e.g. unhealthy diets, tobacco use).[79] In addition, the prevalence of chronic infectious diseases such as HIV remains high in LMICs.[80, 81]

1.3. AIM AND OBJECTIVES

Study Aim

The study aimed to determine the prevalence and trends of disease clusters (multimorbidity) in South Africa, and describe health policy and system responses to addressing multimorbidities in service delivery.

Study Objectives

The study was comprised of three main objectives with sub-objectives, as described below:

To review multimorbidity disease clusters among adults in South Africa

A systematic review of prevalence studies focused on South African adults was conducted to:

i. assess the prevalence of multimorbidity.
ii. identify multimorbidity disease clusters; and,
iii. describe trends and/or patterns in multimorbidity disease clusters.

To determine multimorbidity disease clustering in South African national survey datasets

Data from South African nationally representative surveys were analysed. The sub-objectives included, to:

i. develop suitable methodologies to analyse large, complex datasets;
ii. adapt the methodology in *(i)* to identify disease clusters in each survey;

iii. estimate the prevalence of multimorbidity in each survey; and,

iv. characterise the risk profile of adults reporting multimorbidity.

To identify health policies and service-delivery implementation to address multimorbidity at primary healthcare level

This component of the study consisted of a desktop review to identify policies related to multimorbidity. The sub-objectives were to:

i. assess the adequacy of current national health policies in relation to multimorbidity; and,

ii. identify gaps in health policies and service delivery to address multimorbidity.

1.4. OUTLINE OF RESEARCH PROJECT

Figure 1-1 shows the information flow across the study phases. Phase 1 consists of a literature review (systematic review), which helped to inform Phase 2 (analysis of national datasets).

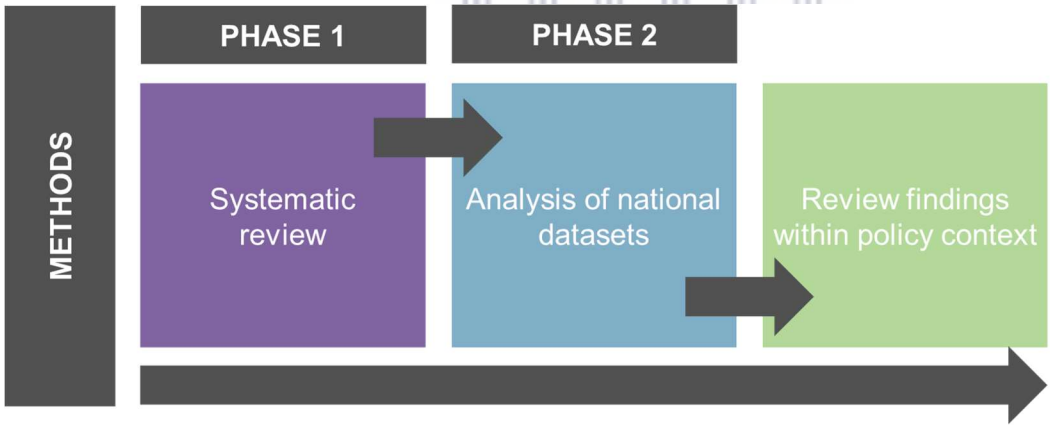

Figure 1-1. Information flow across phases

Ethics considerations

Ethics clearance was granted by the Biomedical Research Ethics Committee of the University of the Western Cape (BM20/5/8). The first and third objectives involve published studies – therefore no ethics concerns were to be addressed. The second objective involved the secondary data

analysis of national survey datasets. All datasets were anonymised, curated and publicly available. Data- use agreements were followed as stipulated.

1.5. OVERVIEW OF THESIS CHAPTERS AND ARTICLES

This thesis consists of eight chapters. Chapters 2 and 3 describe the literature and conceptualisation of multimorbidity in South Africa and LMIC, respectively. Chapter 4 is a description of the methodology (the systematic method in selecting and analysing appropriate surveys), as well as the main findings from each survey. Chapters 5, 6 and 7 present the in-depth analyses and results from the national surveys. Each chapter is discussed in more detail below. To date, eight articles have been published in peer-reviewed journals, and one is in review.

Chapter 2 is titled '*A systematic review of existing multimorbidity prevalence studies in South Africa.'* The chapter aimed to determine the prevalence of multimorbidity based on published South African literature. A systematic review was conducted to identify studies with prevalence estimates, common disease clusters and factors associated with multimorbidity. Two peer-reviewed journal articles are included in this chapter:

- **Roomaney RA**, van Wyk B, Turawa EB, Pillay-van Wyk V. Prevalence of multimorbidity in South Africa: a systematic review protocol. *BMJ Open.* 2020;10(12):e042889. DOI: https://doi.org/10.1136/bmjopen-2020-042889
- **Roomaney RA,** van Wyk B, Turawa EB, Pillay-van Wyk V. Multimorbidity in South Africa: a systematic review of prevalence studies. *BMJ Open.* 2021;11(10):e048676. DOI: https://doi.org/10.1136/bmjopen-2021-048676

Chapter 3 is titled '*Research gaps in low- and middle-income countries.'* The chapter draws on the findings of the previous chapter to highlight gaps in the international literature on multimorbidity. One peer-reviewed journal article is included in this chapter:

- **Roomaney RA**, Van Wyk B, Pillay-van Wyk V. Decolonising multimorbidity? Research gaps in low and middle-income countries. *Pan Afr Med J.* 2022;41(140). DOI: https://doi.org/10.11604/pamj.2022.41.140.32104

Chapter 4 is titled *'Systematic method for calculating multimorbidity in national surveys and overview of results.'* This chapter describes the methods developed to analyse national surveys and

presents an overview of the results from each survey. This chapter includes one peer-reviewed article.

- **Roomaney RA,** Van Wyk B, Pillay-van Wyk V. A systematic method for comparing multimorbidity in national surveys. *BMC Research Notes.* 15; 280 (2022). DOI: https://doi.org/10.1186/s13104-022-06164-3

Chapter 5 is titled '*Analysis of the 2016 Demographic and Health Survey'*. The chapter presents the findings from two articles based on the 2016 South African Demographic and Health Survey. The first explores the prevalence in the survey and risk factors associated with multimorbidity and was published in a peer-reviewed journal. The second is an analysis of disease clustering in those with multimorbidity and has been submitted to a peer-reviewed journal.

- **Roomaney RA**, van Wyk B, Cois A, Pillay-van Wyk V. One in five South Africans are multimorbid: An analysis of the 2016 demographic and health survey. *PLoS One.* 2022; 17(5): e0269081. https://doi.org/10.1371/journal.pone.0269081
- **Roomaney RA**, van Wyk B, Cois A, Pillay-van Wyk V. Multimorbidity disease patterns in South Africa: A Latent Class Analysis of the 2016 Demographic and Health Survey. (*Submitted to Chronic Illness)*

Chapter 6 is titled '*Analysis of the 2017 South African National HIV Prevalence, Incidence, Behaviour and Communication Survey'*. This chapter presents the findings from two articles based on the 2017 South African National HIV Prevalence, Incidence, Behaviour and Communication Survey. The first shows the prevalence and patterns of multimorbidity; while the second is focused on ageing in people with HIV. Both articles have been published in peer-reviewed journals.

- **Roomaney RA**, van Wyk B, Cois A, Pillay-van Wyk V. Multimorbidity Patterns in a National HIV Survey of South African Youth and Adults. *Frontiers in Public Health.* 2022;10 (1): 862993. DOI: https://doi.org/10.3389/fpubh.2022.862993
- **Roomaney RA,** van Wyk B, Pillay-van Wyk V. Aging with HIV: Increased Risk of HIV Comorbidities in Older Adults. *Int J Environ Res Public Health.* 2022;19(4):2359. DOI: https://doi.org/10.3390/ijerph19042359

Chapter 7 is titled an 'Analysis of the 2017 National Income Dynamics Study'. This chapter presents the findings from one article based on the 2017 National Income Dynamics Study. It also

analyses multimorbidity by wealth quintile. The article has been published in a peer-reviewed journal.

- **Roomaney RA**, Van Wyk B, Cois A, Pillay-van Wyk V. Inequity in the distribution of non-communicable disease multimorbidity in adults in South Africa: An analysis of prevalence and patterns. *International Journal of Public Health.* 2022; 67. DOI: https://doi.org/10.3389/ijph.2022.1605072

Chapter 8 is the concluding chapter and consists of a summary of the main findings, discussion and recommendations in the context of the current policy environment.

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Chapter 2. A systematic review of existing multimorbidity prevalence studies in South Africa

OVERVIEW OF CHAPTER

The aim of this chapter is to determine the prevalence of multimorbidity based on published South African literature. A systematic review was conducted to identify studies with prevalence estimates, common disease clusters and factors associated with multimorbidity. Article 1 is the protocol that guided the systematic review. Article 2 presents the findings and results of the systematic review. The systematic review revealed a dearth of research (n=10 published articles) on multimorbidity in South Africa. Studies were also difficult to compare as the methods used to assess multimorbidity differed. The prevalence of multimorbidity ranged from low to moderate (3 – 23%) for those studies that included younger age groups (e.g. 15 years and older); and moderate to high (30 – 87%) prevalence rates of multimorbidity were reported in studies with a more narrow group of selected age groups (e.g. 40 years and older). Half the studies reported on disease clustering and four of the five studies reported 'hypertension and diabetes' as a disease cluster. The results of the systematic review informed the methodology used in subsequent chapters.

Articles

- **Roomaney RA**, van Wyk B, Turawa EB, Pillay-van Wyk V. Prevalence of multimorbidity in South Africa: a systematic review protocol. *BMJ Open.* 2020;10 (12):e042889. DOI: https://doi.org/10.1136/bmjopen-2020-042889
- **Roomaney RA**, van Wyk B, Turawa EB, Pillay-van Wyk V. Multimorbidity in South Africa: a systematic review of prevalence studies. *BMJ Open*. 2021;11(10):e048676. DOI: https://doi.org/10.1136/bmjopen-2021-048676

2A. Article: Prevalence of multimorbidity in South Africa: A systematic review protocol

Abstract

Introduction. Multimorbidity has increased globally over the past two decades, due to ageing populations and increased burden of non- communicable diseases (NCDs). In a country like South Africa, with a growing burden of NCDs and a high prevalence of HIV, information on multimorbidity can improve planning for healthcare delivery and utilisation, and reduce costs in the context of constrained health resources. This review aims to synthesise prevalence studies on multimorbidity, and identify dominant clusters and trends of multimorbidity in South Africa.

Methods and analysis. We will search electronic bibliographic databases (PubMed, Scopus, JSTOR, POPLINE, PsycINFO, ScienceDirect, Web of Science and CINAHL), and the reference lists of included articles. Two researchers will independently screen title and abstracts, and then full text to identify studies published before and in 2020 that report on prevalence of multimorbidity in South Africa. Risk of bias assessments will be done for each study. Information on the prevalence of multimorbidity and disease clusters will be extracted from each study. Where possible, prevalence of specific clusters of multimorbidity will be pooled using a random effects meta- analysis to account for variability between studies. The I2 statistic will be used to establish the extent of heterogeneity due to variation in prevalence estimates rather than due to chance. The systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta- Analyses.

Ethics and dissemination. Only published journal articles will be included in the systematic review. This review received ethics approval as part of a larger project by the University of the Western Cape Biomedical Science Research Ethics Committee (BM20/5/8). The findings from this research will be used to estimate the prevalence of multimorbidity in South Africa and will contribute to the design of future research projects. The findings will be disseminated in a peer-reviewed journal article.

PROSPERO registration number. CRD42020196895

Strengths and limitations of this study:

To our knowledge, this will be the first systematic review to estimate the prevalence of multimorbidity in South Africa.

- This systematic review will include articles conducted in community/general and health-facility settings.
- This protocol follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols 2015 guidelines.
- The findings will be used to inform future research projects and can guide health policy and planning for service delivery in South Africa.
- The study may be limited by the way in which source articles define multimorbidity.

Introduction

Multimorbidity, defined as the co-existence of two or more chronic conditions, has increased globally in the past two decades.[1, 2] Although a gold standard definition of multimorbidity has not been established, it has been recommended that the operationalization of multimorbidity can include a combination of non-communicable diseases (NCDs), mental health conditions and infectious diseases.[1] The increase in multimorbidity is attributed to ageing populations [3] and the growing burden of NCDs.[1] Whereas the increase in NCDs was initially predominantly observed in high-income countries; recently this increase was also reported in low and middle-income countries (LMICs).[4]

The prevalence of multimorbidity places additional stress on already severely strained health systems in LMICs [5] by driving up healthcare utilization and costs.[6-9] Furthermore, multimorbidity alters the patterns of individual health behaviours and access of health services; which in turn, has further implications for health systems responsiveness and pressing the urgency for further health reforms away from a programmatic approach to comprehensive, integrated services delivery. The need for reforms to integrate the treatment of various chronic conditions have been acknowledged.[10, 11] Researchers have since highlighted the need to incorporate elements specific to people living with multimorbidity. These include the need for: multimorbid patients to have access to coordinated and multidisciplinary teams of health professionals; support

for patients to self-manage their workload, and evidence-based guidelines applicable to multimorbid conditions.[12-15] It is essential to grasp the magnitude and clustering of multimorbidity to inform health policy and regulations at a national level.

South Africa has a quadruple burden of disease of HIV/AIDS, NCDs, injuries and other communicable diseases with perinatal conditions, maternal causes, and nutritional deficiencies.[16, 17] As HIV treatment has improved, people living with HIV in South Africa can expect a near-normal life expectancy.[18] However, ageing adults living with HIV are at a higher risk of developing chronic conditions such as NCDs compared to those not infected, and at an earlier age.[19] An emerging pattern of HIV and NCD multimorbidity was described in the country.[13] The burden of mental health conditions in people living with HIV has also been recognised;[20-23] with an estimated 40% of people living with HIV also afflicted by a diagnosable mental disorder.[24, 25] This demonstrates the complex burden of disease in the country.

Systematic reviews on multimorbidity that were conducted to date were mostly on older adults and in high-income countries.[26-30] These reviews reported pooled prevalences of multimorbidity between 38% and 66%.[26, 28, 31] In contrast, only two reviews included or were conducted on multimorbidity in LMICs.[32] The 'global' systematic review included LMICs but limited the included studies to community settings; and did not include health care settings [31]. Although the systematic review of multimorbidity in India and Bangladesh included primary health care settings, none were selected.[33] The authors acknowledged that this was due to a gap in the multimorbidity literature in primary health care settings.

While community-based studies on multimorbidity are important, it is also essential for reviews on multimorbidity to include studies conducted in health care settings, because these studies can give a good indication of the number of people accessing healthcare for chronic conditions.[29] Both community-based and health facility-based studies provide insight into the scale of the problem. To our knowledge, no study has been done to assess the prevalence of multimorbidity in South Africa that included studies in primary care settings. There is a need for research into multimorbidity in LMICs on the African continent as their disease burden differs from high income countries; that is, overlapping burdens of NCDs and infectious diseases which lead to new multimorbidity disease combinations.[19] The proposed systematic review aims to synthesize

existing literature on the prevalence of multimorbidity in South Africa, and identify common disease clusters and trends in the country.

Research questions

This systematic review aims to address the following review questions:

(1) What is the prevalence of multimorbidity in persons over the age of 18 years in South Africa in studies reported up to and including 2020?
(2) What is the prevalence of multimorbidity in adult males and females stratified by age group in South Africa in studies reported up to and including 2020?
(3) What are common multimorbidity disease clusters in South Africa in studies reported up to and including 2020?
(4) What are the trends in the prevalence of multimorbidity disease clusters in South Africa over time?

Methods and analysis

Protocol and registration

The methods for this systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[34] and the PRISMA Protocols (PRISMA-P) statement (Supplementary material 1).[35, 36] The systematic review will be registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Eligibility criteria

The **C**o**C**o**Pop** (**C**ondition, **C**ontext and **P**opulation) mnemonic for prevalence systematic reviews [37] will be used to define the inclusion criteria (Table 2A-1).

Condition. Articles about the prevalence of multimorbidity in South Africa will be included. Case definitions for multimorbidity may be defined in various ways. Ideally, articles will need to provide a clear description and definition of how they have conceptualised multimorbidity. For articles where multimorbidity has not been clearly defined, this article will adopt an operational definition of multimorbidity, similar to Pati *et al* [33]. Their operational definition states 'studies documenting two or more chronic conditions, even though not mentioning the term

multimorbidity'.[33, p.4] The article will also need to be explicit about which diseases have been included in their definition of multimorbidity.

Table 2A-1. Summary of eligibility criteria

Condition	Context	Population
Primary studies reporting the prevalence of multimorbidity in South Africa, using acceptable case definitions. Studies focused on 'multiple chronic diseases', 'co-existing conditions' and 'multiple diseases' will also be assessed to determine if they fit the definition of multimorbidity.	South African observational studies up to and including 2020. Study types include population-based studies and cross-sectional studies. Study settings include ambulatory, community-based, general practice, primary healthcare and other healthcare settings.	Males and females, aged 18 years and above that reside in South Africa.

The way in which multimorbidity was measured will need to be clearly defined. For example, whether a count of conditions was done. Also, the way in which diseases were diagnosed must be clear (e.g. self-report, clinical assessment, laboratory test).

Context. Articles must report on studies conducted in South Africa. The setting of the study can be community-based, or health facility-based (e.g., inpatient, outpatient).

Population / types of participants. This systematic review will be restricted to people who reside in South Africa and are over the age of 18 years old. Ideally, articles should report on the prevalence of multimorbidity by age group and sex.

Outcomes. The primary outcome will be the prevalence of multimorbidity in South Africa.

Types of studies

Observational, cross-sectional study designs are the most appropriate for determining the prevalence of a health condition, particularly common conditions of long duration.[37] Thus, included articles will be cross-sectional or population-based study designs.

Articles must document the prevalence of multimorbidities, or their data must allow for the calculation of multimorbidity prevalence. Articles will need to define multimorbidity as the co-

existence of at least two disease conditions or an operational definition will be applied. Articles with a sample size of less than 100 participants will be excluded as these studies may be susceptible to the influence of extreme observations.[38] All articles before and including 2020 will be included. Additionally, in order to be included in this study, articles must be original and peer reviewed.

Inclusion and exclusion criteria are described in Table 2A-2. The following types of documents or studies will be excluded:

- Reviews, opinion pieces, conference presentations, letters, editorials, dissertations, abstracts, grey literature.
- Studies not conducted in South Africa within the specified period.
- Studies that do not allow for the calculation of multimorbidity prevalence.
- Experimental studies.
- Studies not published in English.

Table 2A-2. Summary of inclusion and exclusion criteria

Inclusion Criteria	Exclusion criteria
Peer-reviewed articles.	Non peer-reviewed articles and grey literature.
Articles with more than 100 participants.	Articles with smaller sample sizes (<100 participants).
Articles about multimorbidity in adults in South Africa.	Articles not about multimorbidity, not about adults or not conducted in South Africa.
Observational studies.	Experimental studies.
Articles where it is possible to calculate the prevalence of multimorbidity.	Articles where it is not possible to calculate the prevalence of multimorbidity or to only calculate multimorbidity in a subset of people with a disease.

Search strategy

A comprehensive search strategy was formulated by reviewing search terms used in other systematic reviews of multimorbidity.[26-31, 33, 39-42] The search strategy will be modified, where necessary, according to the database or search engine used (Table 2A-3). Reference lists of included articles will be screened for relevant articles. The following electronic databases will be

searched: PubMed, Scopus, JSTOR, POPLINE, PsycINFO, ScienceDirect, Web of Science and CINAHL.

Search terms will include 'multimorbidity' and linguistic variations such as 'multi-morbidity', 'multimorbidities', 'multi-morbidities', 'multi morbidity', 'multi morbidities', multiple morbidities', 'multiple-morbidities'. Terms such as 'multiple conditions', 'multiple diseases', 'multiple chronic diseases', 'multiple chronic conditions', 'multiple illnesses', 'multiple diagnoses', 'multi-pathology', 'chronic condition', 'chronic diseases' [33] will also be included. These terms will be further restricted by location 'South Africa' and by method and study design 'prevalence, epidemiology, pattern'. This will be done by using the 'AND' and 'OR' Boolean operators where appropriate.

The term 'comorbidity' is now accepted to be distinct from multimorbidity.[41] This study will exclude the search term 'comorbidity' as was done by another multimorbidity systematic review.[31] However, if the search results include comorbidity studies that examine the prevalence of multimorbidity, the eligibility of these studies will be considered.

Table 2A-3. **Example search strategy for PubMed**

Search	Query
#4	Search ((#3 NOT (animals[mh] NOT humans[mh])))
#3	Search (#1 AND #2)
#2	Search (South Africa[mh] OR South Africa*[tiab] OR RSA [tiab] OR Africa, Southern[mh:noexp] OR Southern Africa[tiab])
#1	Search (Multimorbidity OR multi-morbidity OR multimorbidity[tiab] OR "multi morbidities" OR multimorbidity[mh] OR multimorbidit* OR multimorbid OR multimorbidities OR multi-morbidit* OR "multiple morbidities" OR "multiple-morbidit*" OR "multiple morbidities" OR multidisease* OR multi-disease* OR "multiple disorder" OR "multiple illness"

Study selection and eligibility criteria

One reviewer will conduct the literature search. Once the search is run, citations will be downloaded into a reference management system such as EndNote (EndNote X8, Thomson Reuters). Duplicates will be excluded using the EndNote deduplication function. Citations will be exported from EndNote into Rayyan.[43]

Selection process

Two reviewers (RAR and EBT) will independently screen the titles and abstracts of the search output to select potentially eligible studies using pre-specified eligibility criteria. The web-based system, Rayyan, will be used to manage the screening process. Rayyan was designed by the Qatar Foundation to expedite systematic reviews by semi-automating the initial screening of titles and abstracts.[43] The full-text of potentially relevant articles will be retrieved and independently reviewed by two review authors (RAR and EBT) for eligibility.

Eligible citations will be uploaded into a web-based electronic system, the Burden of Disease Review Manager (BODRevMAN). This system was designed by the Burden of Disease Research Unit of the South African Medical Research Council to facilitate, systemize and manage the process of systematic review, the risk-of-bias assessment and provide a summary of data extracted.[38] BODRevMAN is tailored to the systematic review of observational studies. It facilitates the independent quality assessment and extraction of information from included full-text articles. Any disagreements will be resolved through discussion or another review author (VPvW or BvW) will add input to enable a consensus. A PRISMA flow diagram will detail the study selection decisions made.

The researchers will not be blinded to the authors, titles and institutions of potentially eligible studies. Where there are multiple studies from the same dataset, the most appropriate data will be included. Where additional information is needed, the authors of the study will be contacted. One reviewer will email the corresponding author and a maximum of two attempts will be made, separated by one week.

Quality assessment

Two reviewers will independently assess study characteristics and the risk of bias of each study. The reviewers will use a modified checklist[44] based on the Hoy *et al*[45] risk of bias tool for population-based prevalence studies and the Newcastle-Ottawa Scale[46] for assessing the quality of non-randomised studies (Supplementary material 2 [47]). The tool has been described previously.[38, 48] Results from the two researchers will be compared and differences will be discussed between them. Where consensus is not reached, a third reviewer (VPvW) will be called on to arbitrate. Studies with a high risk of bias will be excluded and the reasons for their exclusion will be noted.

Data extraction

Two reviewers will independently extract data using BODRevMAN. The data extraction facilitated by BODRevMAN is in accordance with recommendations by Munn *et al.* [37] for prevalence systematic reviews. The following data will be extracted:

- Citation details: authors, title, journal and year.
- Study details: study design, study setting (community or health facility), timeframe for data collection, geographical location and sample size.
- Case definition: how multimorbidity was defined and how disease conditions were measured.
- Participant characteristics: age, sex, urban/rural, socioeconomic characteristics.
- Description of main results: percentage prevalence of multimorbidity (n/N) and 95% CIs. Prevalence of conditions stratified by age and sex. Information on the most common disease clusters in the study sample.

In addition, the aims of the study, the method of data analysis used and any points of difference that may affect the interpretation of findings [37] will be noted.

Data synthesis

The results will be presented in accordance with the PRISMA statement. Studies that are deemed to have a moderate or low risk of bias will be included in the analysis. Where appropriate, graphs will be used to display the information from included articles. The quantitative results will be summarized for individual studies and will include point estimates and interval estimates (e.g. 95% CIs). The prevalence data will be broken down by age, sex and disease clusters if the information is available. Differences and similarities between studies will be documented. Possible trends will also be noted.

If articles are amenable to meta-analysis, this will be done using Stata V.15 (College Station, Texas). A random effects meta-analysis will be used. Estimates will be pooled to obtain a summary estimate and 95% CI. A χ^2 test will be used to assess statistical heterogeneity and the I^2 statistic will be used to assess the degree of homogeneity.[49, 50] Where there are more than ten studies, publication bias will be assessed with a funnel plot and an egger test.[51]

Where sufficient data exist, subgroup analysis will be conducted based on multimorbidity case definition used, study setting (e.g., community or health facility), age groups, sex and time periods. Ideally, multimorbidity prevalence will be estimated by age group and sex.

If it is not possible to do a meta-analysis, the findings from included articles will be presented in summary tables that will include the year of data collection, the study type and setting (community of health facility-based), location of study, the definition of multimorbidity used in each study, the diseases and number of diseases included in the study and how they were ascertained (e.g., measured or self-reported).

Patient and public involvement

No patients will be involved directly in this study.

Ethics and dissemination

This systematic review will be the first to review all available studies reporting on the prevalence of multimorbidity in South Africa. This study will provide estimates that will be valuable to health services planning. It will also provide much needed information on multimorbidity on the African continent and in LMICs in general.

The findings from this systematic review will be written up using the PRISMA guidelines. It will be disseminated through publication in a peer-reviewed journal article and/or conference proceedings.

This study is a secondary analysis of published studies. The data from published studies cannot be linked to individuals. This review received ethics approval as part of a larger project by the University of the Western Cape Biomedical Science Research Ethics Committee (BM20/5/8).

Supplementary material

Supplementary material 1 [36]: https://bmjopen.bmj.com/content/bmjopen/suppl/2020/12/15/bmjopen-2020-042889.DC1/bmjopen-2020-042889supp001_data_supplement.pdf

Supplementary material 2 [47]: https://bmjopen.bmj.com/content/bmjopen/suppl/2020/12/15/bmjopen-2020-042889.DC1/bmjopen-2020-042889supp002_data_supplement.pdf

2B. Article: Multimorbidity in South Africa: A systematic review of prevalence studies

Abstract

Objectives. To review prevalence studies of multimorbidity in South Africa to identify prevalence estimates, common disease clusters and factors associated with multimorbidity.

Design. Systematic review.

Setting. South Africa (general community and healthcare facilities).

Data sources. Articles were retrieved from electronic databases (PubMed, Web of Science, Scopus, CINAHL, Science Direct and JSTOR).

Eligibility criteria. Studies addressing the prevalence of multimorbidity in South Africa were eligible for inclusion. A systematic search was done in various databases up to December 2020. A risk of bias assessment was conducted for each article using a modified checklist.

Study selection. Two researchers independently screened titles and abstracts; assessed the risk of bias of each study and extracted data. Included studies were described using a narrative synthesis.

Results. In total, 1 407 titles were retrieved; of which 10 articles were included in the narrative synthesis. Six studies had a low risk of bias and three had a moderate risk of bias. One study was not assessed for risk of bias, because there was no criteria that apply to routine health information system. Three of the included studies were population-based surveys, four were community-based cohorts, and three cross-sectional studies of health facility data. The prevalence of multimorbidity was low to moderate (3 – 23%) in studies that included younger people or had a wide range of selected age groups; and moderate to high (30 – 87%) in studies of older adults. The common disease clusters were hypertension and diabetes, hypertension and HIV, and TB and HIV

Conclusion. All studies indicated that multimorbidity is a norm in South Africa, especially amongst older adults. Hypertension is the main driver of multimorbidity. Research on multimorbidity in South Africa needs to be strengthened with high-quality study designs.

Registration. PROSPERO (CRD42020196895).

Strengths and limitations of this study

- To our knowledge, this is the first systematic review of multimorbidity prevalence studies in South Africa, and of an African country.
- This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.
- This review includes studies conducted in general community and healthcare settings.
- A limitation of this study was that it excludes studies conducted in subpopulations with one specific disease (e.g., multimorbidity in cancer patients).
- Grey literature (non-academic literature) was excluded.

Introduction

One-third of adults residing in low-income and middle-income countries (LMICs) are thought to be afflicted by two or more coexisting health conditions; also known as multimorbidity.[31] The last two decades have seen an exponential growth in the number of studies about multimorbidity.[32] This can be attributed to more research into ageing populations,[32] and the recognition that multimorbidity impacts patient care and healthcare systems.[2] Other consequences of multimorbidity include increased mortality levels,[52] lowered quality of life,[53] the risk of polypharmacy [54] and intensified utilisation of health services and associated costs.[7, 8] More recently, multimorbidity was implicated as a risk factor for COVID-19 mortality.[55, 56] Most research to date has been conducted in high-income countries; sparking calls for similar research in LMICs.[1, 32, 57] Research is needed into multimorbidity in LMICs, like South Africa, where disease burdens differ to those in high-income countries. South Africa has a unique disease burden – it has the largest number of people living with HIV in the world.[58] With the availability of antiretrovirals, people with HIV are living longer and developing age-related non-communicable diseases (NCDs).[59] At the same time, the burden of disease due to NCDs is increasing in the country; giving rise to a disease pattern of coexisting infectious diseases and NCDs.[60, 61]

In resource-constrained health settings, it is imperative that we estimate the magnitude of multimorbidity as well as the nature and type of disease clusters to more efficiently manage patients and organise health service delivery. South Africa lacks a robust national routine health information system to inform its morbidity profile. Countries with less robust routine health information systems need to rely on smaller-scale studies and surveys to better understand the scale and impact of the problem of multimorbidity. This has led to numerous studies focused on quantifying the prevalence of multimorbidity and studies focused on integrated care in South Africa.[13, 62-65] However, many of these studies suffer from the methodological problems that tend to plague multimorbidity studies elsewhere, which is a lack of standardisation.[29] This makes it difficult to compare and interpret studies, given their varying estimates and methodologies. This study set out to systematically assess multimorbidity prevalence studies in South Africa, to report on common disease clusters and factors associated with multimorbidity in South Africa.

Methods

Search strategy and database search

The protocol for this study was published elsewhere.[36] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34] guided this study (Supplementary material [66]). One researcher experienced in systematic review methodology (EBT), performed a systematic literature search in PubMed, Web of Science, Scopus, CINAHL, Science Direct and JSTOR to identify articles reporting epidemiological data on multimorbidity in the adult population of South Africa. The search strategy was reviewed by an expert librarian (Supplementary material [66]). The time frame of the search was not restricted and covered a period up to December 2020.

Study selection and data extraction

The search output citations were downloaded and saved to EndNote V.X8.[67] The EndNote deduplication function was employed, and remaining citations were uploaded into an electronic screening website, Rayyan.[43] Two researchers (RAR, EBT) independently screened the titles and abstracts and studies deemed irrelevant were discarded. A third researcher (BvW) assisted with conflicts. Case reports, reviews, editorials, letters, studies among children, studies not

conducted in South Africa, study designs that were not cross-sectional or cohorts, studies where it was not possible to calculate the prevalence of multimorbidity in the general population (e.g., studies only examining multimorbidity in cancer patients) were excluded. Where multiple studies reported on the same source of data (e.g., one national survey), only the most relevant study was included.

The full texts were independently assessed by two researchers (RAR, EBT) using the electronic data capture system, the Burden of Disease Review Manager (BODREVMAN).[38] BODREVMAN facilitates the independent data collection of study characteristics (study design, sample size, geographical location, whether a study is community-based or facility-based). Also, data on the definition of multimorbidity used, the disease conditions included in the study and the prevalence of multimorbidity (by age and sex where possible) were extracted. Disagreements were discussed and resolved. The reference lists of included articles were screened for additional studies.

Quality assessment

Two researchers (RAR, EBT) independently assessed and appraised each article. BODREVMAN contains a modified checklist based on the Newcastle Ottawa[46] and Hoy checklist.[45] The tool has been described elsewhere.[48] Each article was independently scored and categorised as either having a high, moderate or low risk of bias. Studies based on routine health information systems (RHIS) did not undergo a risk of bias assessment due to a lack of assessment criteria for this study type.

Data extraction and analysis

Information on multimorbidity definitions, disease conditions included and the proportion of the sample with more than one condition, were extracted. Authors were contacted for data by age and sex breakdowns. Studies were categorised by study type (cohort or cross-sectional), and study setting (community or facility-based). It was noted whether disease conditions included were self-reported or biologically assessed.

The mean and SD, or the absolute number and the percentage were recorded, as appropriate. The age range and sex for each category were recorded. Where data appeared in graphical formats, authors were contacted for the original data or WebPlotDigitizer V.4.3 (California)[68] was used

to extract data. STATA V.15 (StataCorp, TX) was used to calculate standard errors using the sample size and prevalence estimates where possible.

Patient and public involvement

Patients and the public were not involved in this study.

Results

Search results

In total, 1 407 titles were retrieved, and 1 081 records were screened after deduplication (Figure 2B-1). By screening titles and abstracts, 1 040 articles were excluded. Forty-one full-text articles were assessed for eligibility, of which ten were included in a narrative synthesis.[69-78] In the title and abstract screening phase, reviewers conflicted on 2.9% of the articles. In the full-text phase, the reviewers had conflicts in 2 of the 41 articles. All conflicts were resolved.

Study characteristics

The sample sizes of included studies ranged from 422[72] to 47 334 participants[75] (Table 2B-1). All included studies were published after 2015 but the period of data collected ranged from 2003[69] to 2015.[74, 75, 77] Three studies conducted a secondary data analysis of population-based surveys.[69-71] The surveys analysed were the 2003 World Health Survey (WHS),[69] 2007 and 2010 WHO Study on global AGEing and adult health (SAGE),[70, 72] and the 2008 and 2012 South African National Income Dynamics Survey (NIDS).[71] Three studies were cross-sectional analyses of community-based cohorts and surveys.[73-75] The remaining three studies were of a cross-sectional nature and based in health facilities.[76-78]

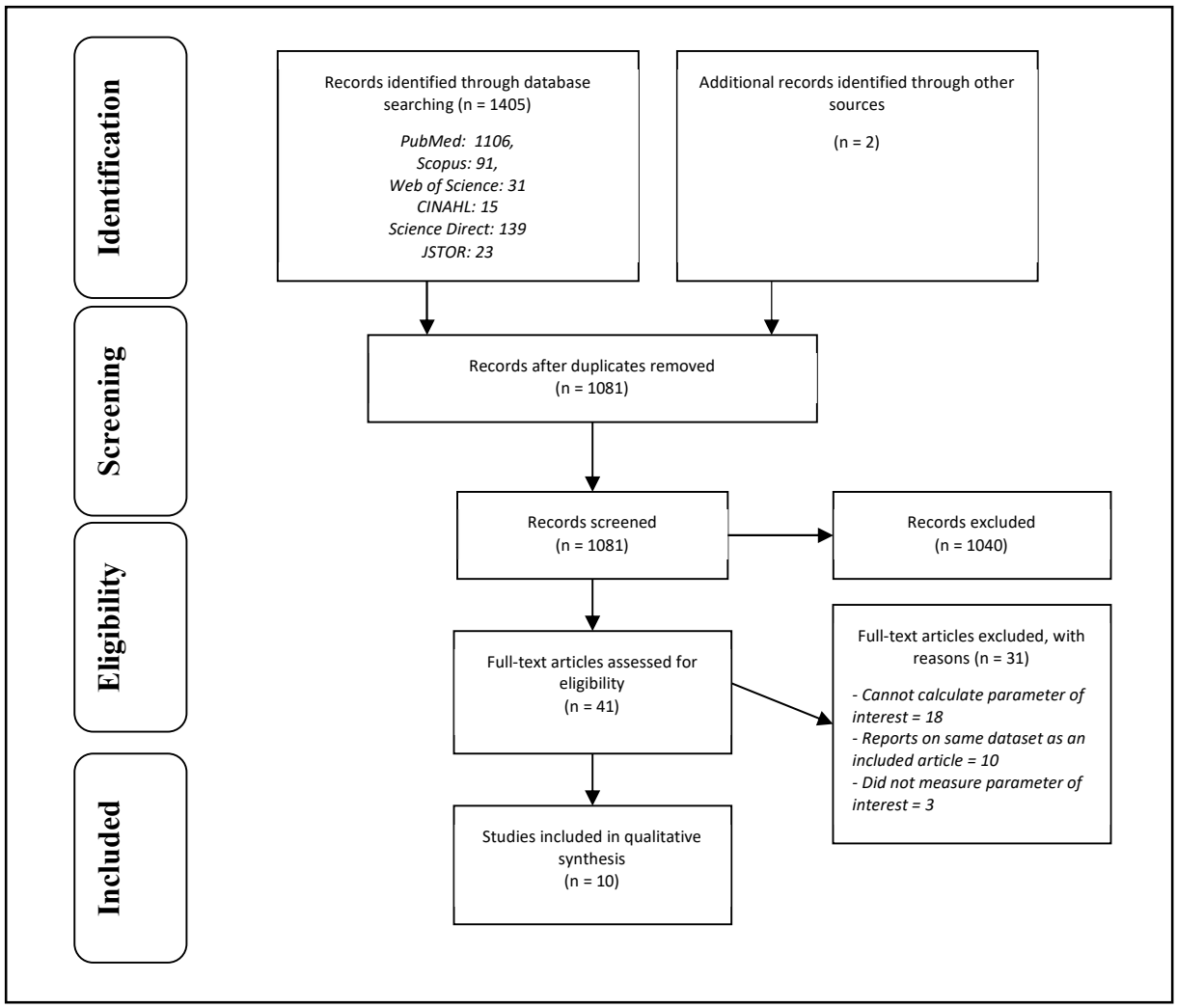

Figure 2B-1. PRISMA flow diagram

Three studies were conducted nationally[69-71] with others conducted in Kwa-Zulu Natal province (n=3),[72, 73, 75] the Western Cape province (n=2) [77, 78] and Mpumalanga province (n=1).[74] One study was conducted in primary healthcare facilities in the Western Cape, North West, Northern Cape and Limpopo provinces.[76] Four studies were conducted in rural areas [72-75], two studies were conducted in urban areas[77, 78] and the remaining studies were conducted in both urban and rural areas.[69, 70, 76] Six studies had a low risk of bias,[69-71, 74-76] three had a moderate risk of bias[72, 73, 77] and one based on a RHIS was not assessed for risk of bias due to a lack of assessment criteria for this study type.

Table 2B-1. Characteristics of included studies

Study type	Study	Study population and size	Year	Location	Risk of bias (score)
Population-based survey	Afshar, Roderick, Kowal *et al* (2015). [69]	N= 2629. Adults 18 years and older in the 2003 World Health Survey.	2003	South Africa (Urban and rural areas included)	Low (14)
	Garin, Koyanagi, Chatterji *et al* (2016). [70]	N = 3836. Adults 50 years and older in the 2007 WHO Study on global AGEing and adult health.	2007-2008	South Africa (Urban and rural areas included)	Low (15)
	Weimann, Dai, Oni (2016). [71]	N=18526 in 2008. N=20015 in 2012. Participants 15 years and older in the National Income Dynamic Survey Wave 1 (2008) and Wave 3 (2012).	2008, 2012	South Africa (Urban and rural areas included)	Low (17)
Cross-sectional study (Community-based)	Ghose, Razak (2017). [72]	N=422. Adults 50 years and older infected and/or affected by HIV in the SAGE Well-being of Older People Study (WOPS) 2010.	2010	Hlabisa subdistrict, KwaZulu-Natal (Rural)	Moderate (12)
	van Heerden, Barnabas, Norris *et al* (2017). [73]	N=570. Adults older than 18 years enrolled in a cohort study to increase engagement in HIV care and testing.	Nov 2011 - Jun 2012	KwaZulu-Natal (Rural)	Moderate (13)
	Chang, Gómez-Olivé, Payne *et al* (2019). [74]	N = 3889. Adults enrolled in the Health and Ageing in Africa: A longitudinal study of an INDEPTH Community in South Africa Programme.	2014-2015	Agincourt Health and Demographic Surveillance System, Bushbuckridge subdistrict, Mpumalanga (Rural)	Low (17)
	Sharman, Bachmann (2019). [75]	N= 47 334. Participants 15 years and older enrolled in the population-based HIV and health surveillance study, conducted by the Africa Health Research Institute.	2009-2015	Umkhanyakude district, KwaZulu-Natal (Rural)	Low (14)

Study type	Study	Study population and size	Year	Location	Risk of bias (score)
Cross-sectional study (Health facility-based)	Lalkhen, Mash (2015). [76]	N=5793 Primary healthcare (PHC) users where all participants had at least one NCD (Hypertension, Diabetes, Asthma, Epilepsy, COPD, Osteoarthritis).	2010	Primary healthcare facilities in the Western Cape, North West, Northern Cape and Limpopo (Urban and rural areas included)	Low (16)
	Roche, de Vries (2017). [77]	N= 491. Consecutive admissions to an internal medicine department of a large district hospital.	2015	District hospital, Cape Town, Western Cape (Urban)	Moderate (13)
Routine Health Information Systems	Oni, Youngblood, Boulle *et al* (2015). [78]	N=14 364. Chronic disease patients (adults) with at least one disease (HIV, TB, diabetes, and hypertension) identified using the Western Cape Department of Health Data Repository and the Electronic prescription system.	Sep 2012 - May 2013	Michael Mapongwana clinic, Khayelitsha, Cape Town, Western Cape (Peri-urban)	NA

Disease conditions assessed

Study findings on the prevalence of multimorbidity can be influenced by 1) the definition of multimorbidity used, 2) the number of disease conditions included in the study, 3) the actual disease conditions included and 4) how the disease conditions were measured.

All included studies used a 'count' of the number of diseases to define multimorbidity, that is, multimorbidity was defined by having two or more diseases (Supplementary material). Half of these studies specified they were only focused on chronic conditions.[69-71, 74, 78] Two health facility-based studies included acute conditions such as lower respiratory infections.[76, 77] The inclusion of acute disease conditions could inflate the prevalence of multimorbidity. The full list of disease conditions included can be found in Supplementary material.[66]

One study included two definitions of multimorbidity – a 'count' definition (as described above) and another more detailed definition. The detailed definition specified multimorbidity as the presence of conditions from more than one of the following categories of disease: cardiometabolic conditions, mental disorders, or HIV and anaemia.[74] When using this definition, the prevalence of multimorbidity was lowered as it only includes discordant diseases (i.e., excludes diseases that

belong to the same category such as hypertension and diabetes). For this review, we used their results from the 'count' definition, unless otherwise stated.

The number of disease conditions included in each study ranged from 4 [78] to 24.[77] (Table 2B-2). Diabetes was included as a disease condition in all 10 studies. Most studies included hypertension (n=9) in their assessment of multimorbidity. HIV (n=5), asthma (n=5) and heart disease (n=5) were also commonly included disease conditions.

The study design and setting influenced how disease conditions were measured (Supplementary material [66]). Population-based surveys tended to use self-reported data, although some included measurements of blood pressure and obesity. Studies based on cohorts tended to use a mix of measured (biomarkers) and self-reported disease conditions. Facility-based studies tended to use medical records and biomarkers to determine the disease burden in their samples.

Table 2B-2. Ten common disease conditions reported in articles

Disease conditions included	Studies										Total articles included in
	Afshar, Roderick, Kowal et al (2015)	Garin, Koyanagi, Chatterji et al (2016)	Weimann, Dai, Oni (2016)	Ghose, Razak (2017)	van Heerden, Barnabas, Norris et al (2017)	Chang, Gómez-Olivé, Payne et al (2019)	Sharman, Bachmann (2019)	Lalkhen, Mash (2015)	Roche, de Vries (2017)	Oni, Youngblood, Boulle et al (2015)	
Diabetes	x	x	x	x	x+	x	x	x	x	x	**10**
Hypertension		x	x	x	x	x	x	x	x	x	**9**
HIV			x	x	x±	x	x		x	x	**5**
Asthma	x	x		x				x	x		**5**
IHD / Heart disease/ Angina	x	x		x		x			x		**5**
Depression	x^	x		x±	x	x*					**4**
COPD		x		x'				x	x		**4**
Arthritis/ osteoarthritis	x	x		x				x			**4**
TB / Current TB			x				x		x	x	**4**
Lipid disorder					x	x			x		**3**

*Depression, post-traumatic stress disorder, alcohol dependence, + Hyperglycaemia, 'Chronic lung disease, ^ Depression, schizophrenia or psychosis
± Assessed condition but was not able to incorporate into multimorbidity calculation based on the way study reported it
IHD=Ischaemic Heart Disease, COPD=Chronic Obstructive Pulmonary Disease; TB= Tuberculosis

Patterns of disease clusters observed

The studies reported on common disease clusters using bubble charts of pair-wise co-morbid conditions,[70, 74] reporting each disease with their most common comorbid condition,[75, 76] or schematics detailing double and triple morbidities.[71, 74, 78] The results of the studies were difficult to compare due to how the data were reported. Four studies did not describe common disease clusters found in their study populations.[69, 72, 73, 77]

While it was not possible to ascertain the largest disease cluster in one study, Garin *et al.* [70] found hypertension featured strongly with diabetes, stroke, angina, cataract, cognitive impairment and all other conditions examined in their analysis. Arthritis and obesity were also commonly listed as comorbid conditions for all other disease conditions.

Table 2B-3 summarises the top five disease clusters from the five remaining studies. The number of disease combinations varied in each study with some studies reporting less than 10 disease clusters[71, 78] and others reporting more than 20 disease clusters[74-76] (Supplementary material [66]).

Hypertension was frequently comorbid with other diseases (Table 2B-3). Weimann *et al.* [71] and Oni *et al.* [78] showed similar patterns of disease – with hypertension and diabetes being the most common disease cluster. In these studies, the disease cluster hypertension and HIV ranked highly, followed by TB and HIV. In terms of having three co-occurring diseases, both ranked the combination of TB, diabetes and hypertension highest; followed by the combination of hypertension, HIV and TB. Lalkhen and Mash [76] also found hypertension and diabetes to be the largest disease cluster in their study. While Chang *et al.* [74] found the largest disease cluster was hypertension and dyslipidaemia, followed by hypertension and anaemia; and the combination of hypertension, dyslipidaemia and anaemia. Anaemia and HIV also commonly co-occurred.

Age and sex tend to influence the susceptibility of an individual to certain diseases. However, studies generally did not report disease clusters by these breakdowns. Two studies reported that HIV was more prevalent in their younger participants;[74, 75] while hypertension affected those over the age of 40 years, and diabetes and angina affected people above the age of 60 years. One study also noted that hypertension and diabetes were more common in females compared to males, and TB was more common in males.[75] One study noted that multimorbidity was lower in patients

with HIV that were on ART (compared to patients not on ART or with unknown ART status) but the association did not hold when broken down by age group.[78]

These results must be interpreted with caution as each study included different disease conditions; and even when the same disease conditions were included, these could differ in the way they were measured for example, self-reported or biologically measured.

Table 2B-3. Top five disease clusters in each study

Disease combinations / clusters			Total studies reported (n=5)	Study citation
Disease 1	**Disease 2**	**Disease 3**		
Hypertension	Diabetes		**4**	[71, 75, 76, 78]
Hypertension	HIV		**3**	[71, 75, 78]
TB	HIV		**3**	[71, 75, 78]
Hypertension	TB		**2**	[71, 78]
Diabetes	HIV		**2**	[75, 78]
TB	Diabetes		**1**	[71]
Hypertension	Osteoarthritis		**1**	[76]
Asthma	Hypertension		**1**	[76]
Hypertension	COPD		**1**	[76]
Hypertension	IHD		**1**	[76]
Hypertension	Dyslipidaemia		**1**	[74]
Hypertension	Anaemia		**1**	[74]
Hypertension	Dyslipidaemia	Anaemia	**1**	[74]
Anaemia	HIV		**1**	[74]
Hypertension	Anaemia	HIV	**1**	[74]

Multimorbidity prevalence

Due to study heterogeneity, it was not possible to do a meta-analysis. Studies reported multimorbidity prevalence by varying age breakdowns making direct comparison difficult. Several studies reported multimorbidity by age group and/or sex (Supplementary material [66]). Two studies reported the median/mean age of participants but the age range of participants was not included[76, 77] and one did not report an overall multimorbidity prevalence for their study[73]. From the remaining studies, multimorbidity prevalence tended to be low to moderate in studies which included younger people or had a wide range of age groups (3% – 23%) (Figure 2B-2); and moderate to high in studies reporting on adults aged 50 years and older (30% – 71%) (Figure 2B-3).

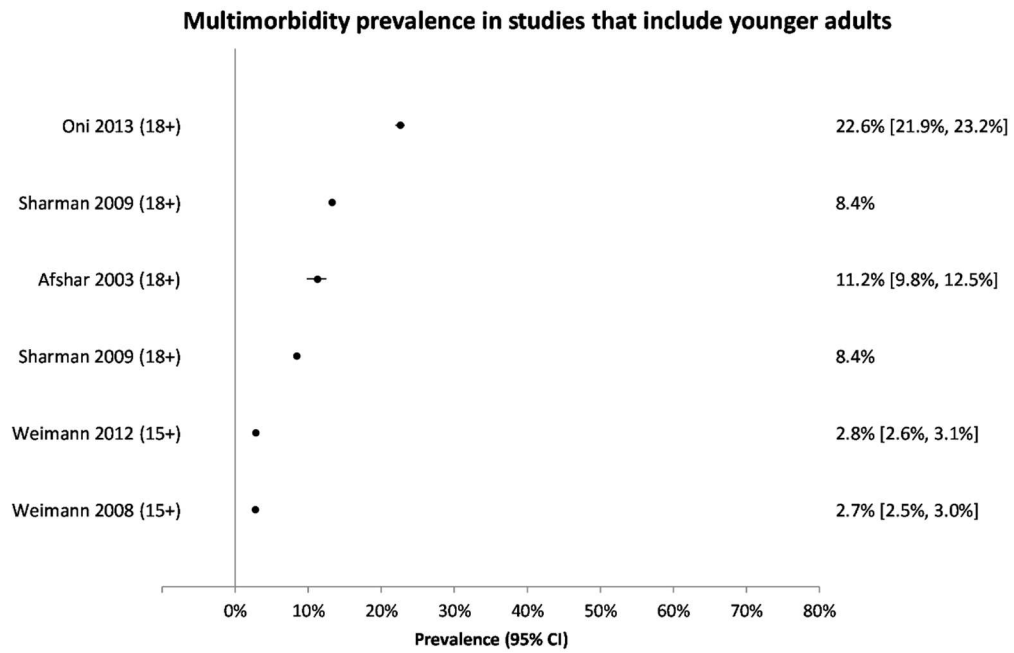

Figure 2B-2. Graph of multimorbidity prevalence estimates for studies that include younger age groups

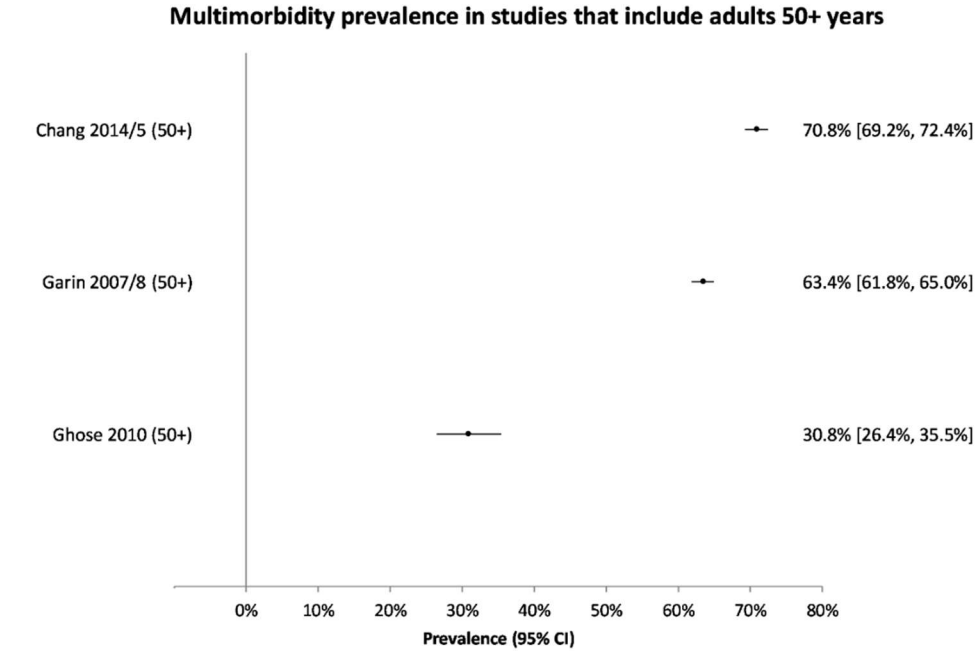

Figure 2B-3. Graph of multimorbidity prevalence in studies including persons aged 50 years and older

In population-based surveys, each study reported a different age group (Table 2B-4). In those 18 years and above, Afshar *et al.* [69] reported an overall prevalence of 11%, however, this was age-standardised against the WHO Standard Population which means it uses a standardised age structure rather than the one found in South Africa. Another study reported the results of a panel survey in 2008 and 2012 and showed a rather low prevalence of multimorbidity (2.7%) for those aged over 15 years old.[71] The study showed a negligible increase (0.1%) during a four year period. A study that only reported on those aged above 50 years of age, showed a very high overall prevalence of multimorbidity (63.4%).[70]

Among community-based cross-sectional studies, the prevalence among older adults ranged from 18%[75] to 69%.[74] However, Chang *et al.* [74] used two definitions of multimorbidity and when applying the second definition (categories of discordant disease groups), they estimated a lower prevalence of 54%. One study that included younger people noted a 5% increase in multimorbidity prevalence between the period 2009 to 2015.[74]

In health facilities, two studies found moderate levels of multimorbidity (14.4% and 22.6%).[76, 78] One study based in a health facility found an extremely high prevalence of multimorbidity (87.0%), however, this study included both chronic and acute health conditions.[77]

Table 2B-4. Multimorbidity prevalence by age group

	Study	Year	Age band (years)	Prevalence of multimorbidity	
				n/N	% (95% CI)[α]
Population-based surveys	**Afshar (2015)'**	2003	Overall (18+)	-	11.2 (9.8 - 12.5)
	Garin (2016)	2007/8	Overall (50+)	2376 / 3747*	63.4
	Weimann (2016)	2008	Overall (15+)	-	2.7 (2.5 – 3.0)
		2012	Overall (15+)	-	2.8 (2.6 – 3.1)
Cross-sectional study (Community-based)	**Ghose (2017)**	2010	Overall (50+)	130 / 422	30.8
	Chang (2019)	2014/15	Overall (40+)	2700 / 3889	69.4
	Sharman (2019)	2009	Overall (18+)	-	8.4

	Study	Year	Age band (years)	Prevalence of multimorbidity	
				n/N	% (95% CI)[α]
		2015	Overall (40+)	-	18.4
		2015	Overall (18+)	-	13.2
Cross-sectional study (Health facility-based)	**Lalkhen (2015)**	2010	Overall (Mean age[±])	2806 / 5793	48.4
	Roche (2017)	2015	Overall (Mean age 49 years)	371 / 427	87.0
Routine health information systems	**Oni (2015)**	2012/13	Overall (18+)	3246 / 14364	22.6

α Not all studies reported a 95% CI and there was insufficient information to calculate this.
* Estimated from available information.
ʿ Reports a standardised multimorbidity prevalence.
± Mean age of patients with osteoarthritis (56.9 years), COPD (56.8 years), diabetes (56.6 years), hypertension (56.4 years), asthma (45.5 years), epilepsy (37.9 years).

Factors associated with multimorbidity

Most of the included studies reported on factors they found to be associated with multimorbidity (Supplementary material [66]). Multimorbidity was frequently associated with increasing age. [69-71, 74, 75, 78] However, Garin *et al.* [70] noted a decrease in the prevalence of multimorbidity in the age group 60+ years and Chang *et al.* [74] noted a decrease from the age group 69+ years.

Being female was inconsistently linked to a high prevalence of multimorbidity. The pattern was noted in two studies;[70, 71] although another study reported it was not statistically significant;[74] while one found no distinction between males and females.[78] One study found that living in urban areas was a risk factor for multimorbidity[71] while another found that living in rural areas was associated with multimorbidity.[70] Other factors found to be associated with multimorbidity were: a lower level of education;[69, 70] being separated, divorced or widowed;[70, 74] living in KwaZulu-Natal or the Eastern Cape provinces, being Indian/Asian or being obese.[71] Socioeconomic deprivation was found to be associated with multimorbidity in one study,[71] but another found no association between wealth and multimorbidity.[74]

Other studies identified the effects of multimorbidity such as having memory complaints (in women), suffering from depression,[72] decreased well-being and self-reported health.[74, 75] One study found that length of stay in hospital was not related to multimorbidity and also did not link lifestyle risk factors to multimorbidity.[77]

Discussion

This study set out to assess the prevalence of multimorbidity in adults in South Africa using systematic review methodology. This study found considerable heterogeneity among included articles, which stemmed from differences in study design, disease conditions assessed and how study results were reported. Despite this, we found a low to moderate multimorbidity prevalence in studies including younger people and a moderate to high prevalence in studies including older adults. Due to study heterogeneity, it is difficult to compare these results to the findings of a recent systematic review which estimated a pooled multimorbidity prevalence of 30% for LMICs.[31]

Three of our included studies reported fairly low levels of multimorbidity prevalence.[69, 71, 75] One study standardised the prevalence to the world population which may have resulted in a lower prevalence estimate (11.2%).[69] The other study reported an overall prevalence of less than 3% among people 15 years and older; and in people over the age of 65 years, they estimated a prevalence of only 10%.[71] The same 2008 dataset from a population-based survey was used in another study and found a similar prevalence of multimorbidity, despite using different methods (4.0%).[79] The low prevalence found in this survey could be attributed to a healthier population being sampled or as the authors suggested, underreporting of self-reported data due to stigma around HIV and TB.[71] The study also included only four disease conditions which may have resulted in a lower prevalence. In contrast, a study that included many acute and chronic conditions resulted in a very high prevalence estimate.[77] This highlights the significant impact of study design on the estimates produced. The third study had a large sample size but may have underestimated the burden of multimorbidity due to the use of self-reported data.[75] Also, they had missing data on HIV due to additional consent being required.

Age is accepted to be an important predictor of multimorbidity.[77] Most studies showed that the prevalence of multimorbidity increased with age, however, two studies observed decreases in the oldest age groups. This needs further investigation. What also remains unclear is whether multimorbidity does in fact affect people at younger ages in LMICs.[1] Based on this systematic review, more studies need to interrogate multimorbidity by age group as the lack of reporting makes it difficult to monitor. Age and sex are both important predictors of multimorbidity and multimorbidity should be reported in a disaggregated manner where possible.[80]

The common diseases assessed in our included studies (diabetes and hypertension) have a high prevalence in South Africa. It was surprising that only half of the studies included HIV as a condition of interest; given the high prevalence of HIV in the country. However, many of the studies were based on secondary data analysis and were limited to the conditions that were included. Future primary studies in South Africa should plan to incorporate infectious diseases (HIV and TB) into studies of multimorbidity where possible.

Despite few studies reporting on which disease clusters were largest, hypertension appeared to be the biggest contributor to the burden of multimorbidity, particularly the co-occurrence of hypertension with diabetes. That said, hypertension and diabetes were also among the most widely included conditions in studies of multimorbidity. Hence, these findings may be biased to conditions that are included in studies and not necessarily the reality of the situation. Given that the prevalence of hypertension is high in South Africa (44% of men and 46% of women aged 15 years and older, as high as 84% in people aged above 65 years),[81] it does hold weight that it would be a common co-morbid condition. A recent study on COVID-19 mortality in South Africa found the combination of hypertension and diabetes was a common disease cluster in people who had succumbed to the disease.[82] This cluster of disease was more prevalent than having hypertension or diabetes only. Information on the prevalence of comorbidities and multimorbidities may prove very important in light of the COVID-19 pandemic.

We mainly included three types of studies in our analysis; studies based on the secondary data analysis of national surveys, studies based on community cohorts and studies based in health facilities. All three types of studies have strengths. National survey data can provide an overall picture of what is happening in the general population. However, they tend to use self-reported data which may result in an underestimation of the burden of disease; as a large percentage of NCDs are underdiagnosed. Nevertheless, there are many more national surveys that could be analysed to provide an overview of multimorbidity from these sources. Studies based on cohorts generated rich information, tended to have large sample sizes and had a mixture of self-report data and measure biological samples. These studies were mostly limited to rural areas. Whether multimorbidity is more common in rural or urban areas in South Africa remains unclear. Existing cohorts will continue to provide a good source of information on multimorbidity and we can expect more data to come out of planned urban cohorts.[83] Studies based in health facilities tended to include more health conditions (both acute and chronic diseases) and tended to report higher levels

of multimorbidity. This may be due to people who require health care (ill individuals) accessing these facilities. However, these studies provide an important source of information that is highly relevant to the management and planning for multimorbidities. For example, a recent study by Mannie and Kharazi [84] assessed the geographical distribution of comorbidities among 2.6 million commercially insured individuals in South Africa using a comorbidity index that highlighted healthcare utilization. Using this score, they were able to identify areas of high utilization and underserved individuals; although they did not provide detail on the types of services needed. Multimorbidity is known to increase the costs to healthcare systems.[85]

Prevalence estimates from systematic reviews can provide an important source of information that is used for evidence-based health decision making - especially in LMICs that have constrained health information systems. A multimorbidity prevalence systematic review conducted for South Asia highlighted the insufficient work conducted in the area of multimorbidity and called for greater methodological rigour to better build scientific evidence in this domain.[33] In a similar vein, we also advocate for more studies to be conducted and with rigorous study designs. A recent report by the Academy of Science of South Africa,[86] highlighted the problematic nature of multimorbidity research in sub-Saharan Africa as: funding provided for only specific diseases; lack of health system preparedness; and low prioritisation of multimorbidity due to a lack of political commitment to implement concomitant heath reforms. Research into multimorbidity is crucial for better understanding of the nature of the problem in the sub-Saharan African region, and to identify ways to introduce comprehensive health service delivery.[86]

This systematic review was limited in that it excluded studies conducted with sub-populations that had one specific disease (e.g. multimorbidity in cancer patients). While these studies are very important, their inclusion would require different search strategies. This study differed from the protocol in that it includes age groups of 15 years plus as the age 15 years is commonly reported as adults in population-based surveys.

Conclusion

To our knowledge, this is the first systematic review of multimorbidity prevalence for an African country and one of the few focused on an LMIC. This systematic review set out to determine the prevalence of multimorbidity of adults in South Africa, ideally stratified by age and sex. We found that there was a low number of studies focused on multimorbidity in South Africa. Studies with data available indicated many people aged 50 years and older are afflicted with more than one

long-term disease condition. These findings are significant as they support the notion that multimorbidity is the norm and not an exception; which has strong implications for how healthcare is organised and utilised. These findings may also be reflective of the situation in other LMICs.

Our study indicated that a large component of multimorbidity was attributed to hypertension. While HIV did contribute to multimorbidity, NCDs were the most common source, even in environments with a high HIV prevalence. However, these results should be interpreted with caution as many studies focused only on older adults and did not give disease clusters using age breakdowns. Heterogeneity in studies also made it difficult to detect trends.

More studies are needed in the general population to determine which disease clusters are most prevalent and could potentially be targeted for intervention. Sources of secondary data could be further explored to answer this question. Studies at health facilities would help to provide information regarding multimorbidity's effect on quality of life indicators, to assess whether people are receiving optimal treatment; and to identify the ways that multimorbidity might be impacting healthcare utilisation.

Supplementary material

Supplementary material [66]: https://bmjopen.bmj.com/content/bmjopen/suppl/2021/10/06/bmjopen-2021-048676.DC1/bmjopen-2021-048676supp001_data_supplement.pdf

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Chapter 3. Research gaps in low- and middle-income countries

OVERVIEW OF CHAPTER 3

This chapter draws on the findings of Chapter 2 to highlight gaps in the international literature on multimorbidity. The article was published as a commentary focusing on how the conceptualisation of multimorbidity has been informed by high-income countries. It also proposes reasons why multimorbidity research has been neglected in low- and middle-income countries (LMICs). For example, historically, definitions of multimorbidity were derived from studies in high-income countries, and resulted in the current research focus on non-communicable diseases (NCDs). Infectious diseases need to be considered in studies of multimorbidity as these disease conditions can also be long-term in nature (e.g. HIV, long-COVID, etc.). The Academy of Science has explicitly included HIV in their definition of multimorbidity, making multimorbidity more relevant to countries with high HIV burdens. LMICs have an important role to play, and the knowledge generated through research in LMICs can contribute to the global understanding of multimorbidity and how to efficiently manage it. Researchers in LMICs also need to be empowered to do research that is locally relevant and needed, rather than research prioritised through a top-down approach by international donors. The nature of donor funding in South Africa has led to the concentration of research on health-systems strengthening for delivery of care for infectious diseases such as HIV and TB. This resulted in the development of robust health-information systems for the monitoring and evaluation of HIV, while neglecting NCDs and other diseases conditions, and creating siloed information systems. Therefore, it is difficult to monitor multimorbidity using existing health-information systems.

Article

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3. Article: Decolonising multimorbidity? Research gaps in low and middle-income countries

Abstract

Multimorbidity is defined as the co-existence of multiple health conditions in one person. However, its use in research has been predominantly applied to non-communicable diseases, because research was conducted almost exclusively in developed countries. More recently, infectious diseases of long duration such as HIV, have also been included in the conceptualisation of multimorbidity. While multimorbidity is a growing area of research globally; much less is known about the phenomenon in low and middle income countries (LMICs) where disease burdens are heavily impacted by HIV. Health systems and services tend to be constrained in LMICs and information on disease patterns are important to better prioritize services. This commentary aims to describe the changing conceptualization of multimorbidity, the dearth of research into multimorbidity in LMICs and how the knowledge generated by research in LMICs can contribute to the global understanding of multimorbidity. LMICs can play a key role in the implementation of integration research.

Introduction

Multimorbidity refers to the co-existence of multiple health conditions in an individual. Living with more than one disease condition impacts how affected individuals receive and manage their medical treatment and also how health services are structured.[1] At the individual level, multimorbidity is associated with reduced wellbeing, a decreased quality of life and higher mortality rates. People with multimorbidity face a great 'treatment burden' as their time and energy are impacted through accessing care from multiple providers. Those with multimorbidity have to self-manage complex treatment plans with multiple drugs, are less likely to adhere to treatment due to being overwhelmed, and some suffer from adverse drug reactions due to polypharmacy. Multimorbidity can be challenging for healthcare professionals to treat, due to the complexity of following numerous guidelines and challenges in delivering patient-centred care. In addition, patients with multimorbidity are usually excluded from drug trials, which can create uncertainty in treatment guidelines. From a health systems perspective, multimorbidity leads to increased

healthcare utilization and healthcare costs. Most healthcare systems, clinical teams and clinical guidelines are organised around single diseases or single organ lines, further hindering patients' access to integrated care. In this commentary we argue that there is a dearth of research into multimorbidity in low and middle income countries (LMICs) and that the knowledge generated from LMICs can contribute to a more nuanced and globally relevant understanding of multimorbidity.

Defining the problem

What 'health conditions' are included in the conceptualisation of multimorbidity has been subject to debate from as early as the year 2001.The definition of multimorbidity has been notoriously heterogeneous, and numerous institutions have attempted to define it. In 2013, the European General Practice Research Network presented a holistic definition whereby they described multimorbidity as the 'combination of chronic disease with at least one other disease (acute or chronic) or bio-psychosocial factor (associated or not) or somatic risk factor'.[2] In 2016, the World Health Organization (WHO) defined it as the 'coexistence of two or more chronic conditions in the same individual' and further elaborated that they are referring to long-term health conditions which require complex and ongoing care.[3] Following a workshop held in South Africa in 2016, the Academy of Medical Sciences and the Academy of Science South Africa proposed a definition in line with the WHO whereby it was defined as the 'co-existence of two or more chronic conditions' and added that these chronic conditions can include physical non-communicable disease of long duration, a mental health condition of long duration or an infectious disease of long duration such as HIV and TB.[1] Their definition clearly includes HIV which is important because there is ambiguity in what is considered a 'chronic disease' and whether it includes infectious diseases of long duration such as HIV or Hepatitis C. The workshop also noted that due to the high burden of disease due to HIV, multimorbidity may affect young people in low and middle income countries.

Why the focus on multimorbidity?

While multimorbidity in its current conceptualisation may be a relatively new concept, there have always been people that have suffered from more than one disease. The term multimorbidity was

first used in Germany in 1976 and became internationally recognised in the 1990s.[4] The area of multimorbidity has seen an exponential rise in the number of articles published in the past two decades.[4] So, why has multimorbidity become such an important area of research?

The attention to this area could be for various reasons. All over the world, but especially in high income countries, the general population is ageing. Many studies have shown that multimorbidity is associated with ageing; the older an individual gets, the higher chances of developing multiple diseases. This, in part, explains the focus on multimorbidity as it is often put in the same category of frailty, geriatrics and of managing diseases in the elderly. Another reason is access to high quality information. Researchers have been able to analyse large administrative datasets or electronic health records to better understand the burden of multimorbidity in their country. These datasets make it easier to track people that have multiple disease conditions or are taking medication for more than one disease.

LMICs have been left behind

The estimated prevalence of multimorbidity in LMICs is not much lower than that of high-income countries (30% versus 38%, respectively).[5] Despite this, there is a dearth of studies on multimorbidity in LMICs. Only 5% of studies on multimorbidity were focused on or were set in LMICs.[4] A recent scoping review of multimorbidity studies in LMICs further revealed that the majority of multimorbidity studies were confined to only six middle income countries (e.g. Brazil, China, South Africa, India, Mexico and Iran).[6] This indicates that there is much to uncover regarding multimorbidity in LMICs, especially in low income countries.

Populations in LMICs are also ageing, the burden of non-communicable diseases is increasing rapidly, and this is coupled with existing burdens of infectious diseases. Infectious disease conditions form a substantial proportion of the burden of disease in LMICs compared to disease burdens in high income countries. The intersecting burden between non-communicable and infectious diseases has been highlighted in parts of the world such as South Africa; where HIV prevalence is high and no longer a death sentence due to the availability of antiretroviral medication. While there has been success in integrating HIV and TB services and surveillance programmes, more work needs to be done to link these to other diseases; especially since many people living with HIV also suffer from other chronic diseases such as hypertension and common

mental disorders. In addition, research has emerged to show that multimorbidity does not only affect the elderly. Due to the high burden of HIV in LMICs, researchers believe that younger people could develop multiple disease conditions because HIV tends to affect younger adults.[1] Some research indicates that people from lower socioeconomic settings may be more vulnerable to multimorbidity, which may also have implications for LMICs.

Health systems in LMICs are arguably more constrained and tend to have less robust routine health information systems making it difficult to even identify whether multimorbidity is an issue. Also, in many LMICs, vertical programme structures often exist due to international donor requirements perpetuated by unequal power relations.[7] International donors have the power to influence monitoring and evaluation processes[7] which could further hinder the identification of multimorbidity as problematic in LMICs dependent on donor funding, if it does not fit the agenda of the donor. For example, in South Africa, it is difficult to monitor NCDs as these diseases received little attention in the past.[8] Systems to monitor HIV and TB are comparatively better developed, in part, due to funding by international donors. While HIV and TB systems have been implemented in most public health facilities,[8] data quality issues persist.

Further research and the potential for innovation

More research is needed into multimorbidity in LMICs as patterns of disease burdens may significantly differ from those in high income countries and could generate hypotheses on lesser known disease combinations. In doing so, we may need to tweak our existing conceptualisation of multimorbidity (for example, the consideration of acute disease) so that the concept of multimorbidity is more meaningful to contexts outside of high income countries. There have been arguments against the inclusion of acute disease conditions for practical reasons or that its inclusion may inflate the prevalence of multimorbidity. Another reason could be that acute disease conditions may also not be of interest to where the majority of multimorbidity studies emanates from.

The definition of multimorbidity is loose and broad enough to include diseases such as HIV, TB and Hepatitis B, etc. However, more guidance is needed around when is the duration of a disease considered ‘long enough’ or disease conditions of an episodic nature. Also, by completely excluding acute disease conditions from the concept of multimorbidity, we may end up limiting

the research on emerging acute infectious diseases, like COVID-19. While mental health services have generally been overlooked in LMICs; in 2020, the WHO highlighted the need for increased effort to tackle the mental health burden of people with neglected tropical diseases.[9] Thus highlighting the intersection of two incredibly neglected areas of research and health service. Another area of concern to LMICs is injuries and disability due to interpersonal violence and road traffic injuries. We conducted a systematic review to identify studies that quantify the prevalence of multimorbidity in South Africa, and identify common disease clusters and identify research gaps.[10]

LMICs need to be a part of the efforts to identify and manage multimorbidities. Countries such as South Africa are recognised as being on the cutting edge of implementation research regarding the integration of care. The South African government has planned to integrate care by capitalizing on existing HIV infrastructure, in an effort towards health systems strengthening. This would help to monitor, manage and integrate services for other important HIV co-morbidities such as diabetes, hypertension and mental disorders. Other examples of interventions in South Africa include the integrated chronic disease management model, the collaborative care model for common mental disorders comorbid with chronic conditions and the Practical Approach to Care Kit to support clinical decision making and also integrates the routine care of common comorbidities.

Conclusion

Studies on multimorbidity are very limited in LMICs - they are limited both in the number of studies that have been conducted but also in the depth of information available due to health information systems which limit data interoperability. These countries tend to lack the resources to show that multimorbidity is a problem (e.g. access to electronic health records) and when they do, they need to ensure that the disease conditions assessed are relevant to their respective settings.

More studies are needed on multimorbidity in LMICs. The findings of these studies could be used to organise health systems more effectively and improve the healthcare experiences for those people living with multimorbidity in LMICs. By identifying disease burdens relevant to LMICs, interventions in one setting could be trialled in others. It could also be used to generate hypotheses and inform interventions to screen, detect and treat people; especially considering the emerging

diabetes epidemic in LMICs. These findings may also be relevant to high income countries, where patterns of multimorbidity in LMICs could be similar to those in immigrant populations.

References to Chapter 3

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Chapter 4. Systematic method for calculating multimorbidity in national surveys

OVERVIEW OF CHAPTER

This chapter describes a systematic method for comparing multimorbidity in national survey datasets. It illustrates a simple and transparent process for estimating multimorbidity in national surveys – one that can easily be adopted in other LMICs. It also describes the prevalence of multimorbidity, the factors associated with it and common disease clusters in three national surveys (2016 South African Demographic and Health Survey [SADHS 2016], 2017 South Africa National HIV Prevalence, Incidence, Behaviour and Communication Survey [SABSSM 2017], and the 2017 National Income Dynamics Study [NIDS 2017]). These surveys were selected because they were the most recent available in South Africa and included information on health data that allowed for the calculation of multimorbidity prevalence, disease patterns and factors associated with multimorbidity. While the overall prevalence of multimorbidity differed between the surveys (20.7% SADHS, 5.9% SABSSM and 2.7% NIDS), results for each survey followed a similar pattern when disaggregated by age group and sex. Namely, the prevalence rose with age and was higher in women compared to men. Also, hypertension was prominent in eight out of the 11 disease clusters identified. Chapters 5 to 7 include in-depth analyses of national surveys.

Article

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4. Article: A systematic method for comparing multimorbidity in national surveys.

Abstract

Objective: Due to gaps in the literature, we developed a systematic method to assess multimorbidity using national surveys. The objectives of this study were thus to identify methods used to define and measure multimorbidity, to create a pre-defined list of disease conditions, to identify potential national surveys to include, to select disease conditions for each survey, and to analyse and compare the survey findings.

Results: We used the count method to define multimorbidity. We created a pre-defined list of disease conditions by examining international literature and using local data on the burden of disease. We assessed national surveys, reporting on more than one disease condition in people 15 years and older, for inclusion. For each survey, the prevalence of multimorbidity was calculated, the disease patterns among the multimorbid population were assessed using a latent class analysis and logistic regression was used to identify sociodemographic and behavioural factors associated with multimorbidity. The prevalence of multimorbidity varied for each survey from 2.7% to 20.7%. We used a systematic and transparent method to interrogate multimorbidity in national surveys. While the prevalence in each survey differs, they collectively indicate that multimorbidity increases in older age groups and tends to be higher among women.

Introduction

Multimorbidity (the co-existence of a minimum of two long term disease conditions in one individual) is associated with a range of negative impacts, including a reduced quality of life,[1] problems with medication adherence[2] and premature death.[3] There is a dearth of studies on multimorbidity in low and middle income countries (LMIC).[4] While there is a growing research interest on multimorbidity in South Africa, the variability in survey methods led to disparate estimates on the prevalence of multimorbidity.[5-7]

Several South African nationally representative surveys (e.g. South African Demographic and Health Survey [SAHDS], South Africa National HIV Prevalence, Incidence, Behaviour and Communication Survey [SABSSM], and the National Income Dynamics Study [NIDS]) provide important information about health conditions in the general population, particularly adults, and

can be used to determine the prevalence and patterns of multimorbidity.[6] Information on the prevalence of disease clusters, trends and the characteristics associated with disease clusters present an opportunity to advocate for improved service delivery and target high-risk individuals. In the current paper, we illustrate a uniform method of analysing multiple national surveys to create a composite overview of multimorbidity disease prevalence and disease clustering and, compare findings of three nationally representative surveys in South Africa.

Methods

The objectives of this study were to: a) identify methods used to define and measure multimorbidity, b) create a pre-defined list of disease conditions to include in the study of multimorbidity, c) identify potential national surveys to include, d) select disease conditions for each survey, and e) analyse and compare survey data (Fig S.1).

Multimorbidity measures and pre-defined disease condition list

The simplest and most common method to measure multimorbidity is to create an index - which is a count of the number of disease conditions in an individual using a predefined list of medical conditions. [8, 9] A multimorbidity variable can then be created by defining the number of people with two or more disease conditions as multimorbid. The type of disease conditions and the number of disease conditions included in studies of multimorbidity differ. A study recommended that disease conditions be included if they are commonly assessed in other multimorbidity studies or are relevant to the population under study.[10] Studies of multimorbidity have commonly included conditions such as hypertension (high blood pressure), chronic obstructive pulmonary disease (COPD), diabetes, malignancy, stroke, dementia, depression, joint disease, anxiety, congestive heart failure, coronary heart disease, asthma, cardiac arrhythmia, thyroid disease, anaemia, hearing problems, dyslipidemia, obesity, prostatic hypertrophy and osteoporosis.[9-14] We also reviewed the list of common disease conditions found in a mortality based study, the second South African National Burden of Disease Study (SANBD2).[15] The SANBD2 list overlaps and differs with various conditions commonly included in other studies of multimorbidity (Fig S2). However, the SANBD2 also includes HIV, TB, diarrhoeal disease, lower respiratory infections and injuries as these are important to the South African burden of disease. We excluded acute conditions

(diarrhoea and lower respiratory infections) and violence due to difficulty with measuring these conditions in a cross-sectional survey.

Survey inclusion

We searched online data repositories (e.g. DataFirst, Human Sciences Research Council, World Health Organization and Statistics South Africa) for potentially eligible surveys. Surveys were considered potentially eligible if they focused on South African adults and youth (people aged 15 years and older), were nationally representative, collected data post-1994 (after apartheid in South Africa) and contained relevant information (i.e. allow for the calculation of multimorbidity prevalence). We also considered the methodological quality of the surveys (e.g. methodological issues specific to each survey such as survey skip patterns, differences in target population and sampling strategies, response rates, and the way in which sampling weights have been calculated and calibrated to population totals).

Potentially eligible datasets were downloaded from data repositories and data user agreements were accepted. Data user agreements were saved to an electronic file. Due to the number of surveys deemed eligible, we focused on the most recent set of surveys.

Survey details and disease conditions

Data were extracted from each survey regarding the survey's study design, sampling and the variables of interest. Disease conditions were assessed against the pre-defined lists of disease conditions. We noted how the disease conditions of interest were measured (i.e. self-reported or physically measured). For example, if blood pressure was physically measured, the instrument used, and the number of repeated measurements were recorded.

Where disease conditions were self-reported, the survey questions were documented in Microsoft Excel. We included self-reported disease conditions that were "current" at the time of the survey. Disease conditions were excluded if the condition could not be assumed to be current due to the way the question was asked. For example, if the participant was asked if they have 'ever had cancer', it could not be assumed that they had cancer at the time of the survey. In certain cases, it was appropriate to include diseases where the participant was asked whether they had 'ever' been diagnosed with the disease, such as in the case with a chronic disease with minimal chances of cure (e.g. HIV).

Other variables of interest

Sociodemographic and behavioural data that could be associated with multimorbidity - such as age, sex, educational attainment, employment status, socioeconomic status, locality, alcohol and tobacco consumption, and information on body mass index - were extracted. These variables were identified based on an overview of five systematic reviews that identified biomedical, socioeconomic, social and environmental, and behaviours associated with multimorbidity. [13]

Data analysis

Data analysis consisted of three main components which was to estimate the prevalence of multimorbidity by age and sex, identify characteristics associated with multimorbidity using a logistic regression and latent class analysis to identify disease clusters or classes within the multimorbid population. The logistic regression and latent class analysis are described in detail in Roomaney *et al*.[6, 7] All survey datasets were weighted to the South African population using Statistics South Africa data for the appropriate year. All results shown are weighted.

Results

Three surveys were selected due to these being the most recent health-related, nationally representative surveys in South Africa. Table S1 describes the various aims and methods employed by each survey (e.g. survey design, sampling methods and data access). SADHS 2016 and SABSSM 2017 used similar survey methods.

Table S2 shows the disease conditions included in each survey. Between four and nine disease conditions were investigated per survey (i.e. SADHS 2016 = 9, SABSSM 2017 = 6 and NIDS 2017 =4). All three surveys included diabetes, heart disease and hypertension; while HIV and TB were assessed in two surveys (SADHS 2016 and SABSSM 2017), and stroke was assessed in SADHS 2016 and NIDS 2017. SADHS 2016 measured HbA1c using dry blood spots to determine diabetes status. Similarly, HIV status was also determined via testing of a dry blood spot in SADHS 2016 and SABSSM 2017. Hypertension was measured using blood pressure monitors in SADHS 2016 and NIDS 2017. Table S3 shows the prevalence of each disease in the surveys.

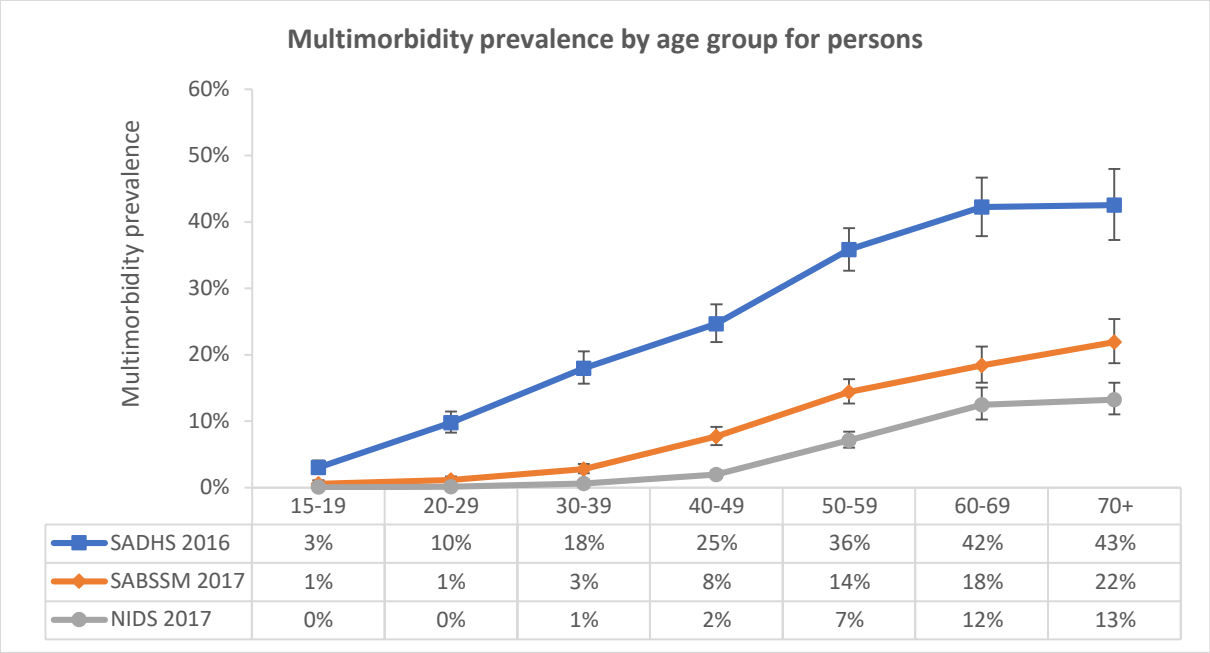
Table 4-1 illustrates the variability in the prevalence(s) of multimorbidity across the surveys. The calculated multimorbidity prevalence was highest in SADHS 2016 (20.7%); while 5.9% and 2.7%

calculated for SABSSM 2017 and NIDS 2017, respectively. In each survey, the prevalence of multimorbidity was almost double in women compared to men. While the prevalence varied between the surveys, the pattern of multimorbidity by age group was similar – starting with a low prevalence and increasing as age increases (Fig. 4-1, Table S4).

Table 4-1. Overall multimorbidity prevalence (weighted)

Number of disease conditions	SADHS 2016 (%, 95% CI)			SABSSM 2017 (%, 95% CI)			NIDS 2017 (%, 95% CI)		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
No disease	48.6 (47.0-50.1)	55.8 (53.5–58.1)	41.8 (40.0–43.4)	71.9 (70.8-73.1)	78.6 (77.3-79.9)	65.9 (64.3-67.4)	74.5 (73.5-75.4)	76.0 (74.5-77.5)	71.7 (73.0-74.2)
1 disease	30.8 (29.5–32.0)	29.4 (27.5–31.2)	32.1 (30.6–33.7)	22.2 (21.2-23.2)	17.3 (16.1-18.5)	26.7 (25.4-28.0)	22.8 (21.8-23.8)	22.1 (20.7-23.6)	22.3 (23.4-24.6)
2 diseases	14.1 (13.2–15.1)	10.5 (9.4 – 11.8)	17.4 (16.2–18.7)	4.9 (4.5-5.4)	3.5 (3.0-4.0)	6.3 (5.7-6.9)	2.3 (2.1-2.6)	1.5 (1.2-1.9)	2.7 (3.1-3.5)
3+ diseases	6.6 (5.9 – 7.3)	4.3 (3.5-5.2)	8.7 (7.8-9.8)	0.9 (0.7-1.2)	0.6 (0.4-0.9)	1.2 (1.0-1.5)	0.4 (0.3-0.5)	0.3 (0.2-0.5)	0.4 (0.5-0.7)
Multimorbidity (≥ 2 diseases)	20.7 (19.5–21.9)	14.8 (13.4–16.3)	26.2 (24.7–27.7)	5.9 (5.4-6.4)	4.1 (3.6-4.7)	7.5 (6.8-8.2)	2.7 (2.4-3.1)	1.8 (1.5-2.3)	3.6 (3.2-4.0)

SADHS 2016: South African Demographic and Health Survey 2016. SABSSM 2017: South African National HIV Prevalence, Incidence, Behaviour and Communication Survey 2017. NIDS 2017: National Income Dynamics Study 2017.



	15-19	20-29	30-39	40-49	50-59	60-69	70+
SADHS 2016	3%	10%	18%	25%	36%	42%	43%
SABSSM 2017	1%	1%	3%	8%	14%	18%	22%
NIDS 2017	0%	0%	1%	2%	7%	12%	13%

Figure 4-1. Prevalence of multimorbidity by age group and survey (weighted)

The surveys described different disease conditions, and therefore direct comparison of disease patterns is limited. However, as indicated in Table 4-2, the combination of Diabetes and Hypertension was prevalent in all three surveys, while heart disease and Hypertension was prevalent in two surveys. Hypertension was prominent in 8 out of 11 disease classes.

Table 4-2. Disease classes per survey

Surveys	SADHS 2016	SABSSM 2017	NIDS2017
HIV, Hypertension and Anaemia	X		
Anaemia and Hypertension	X		
Cardiovascular	X		
Diabetes and Hypertension	X	X	X
HIV and Hypertension		X	
Heart disease and Hypertension		X	X

HIV, Diabetes and Heart disease		X	
TB and HIV		X	
Hypertension, TB and Cancer		X	
All diseases except HIV		X	
Stroke and Hypertension			X

The factors associated with multimorbidity varied between the surveys (Table S5 and S6). Older age was the most consistent factor associated with increased multimorbidity in all three surveys. Other sociodemographic factors that indicated an increased risk for multimorbidity was being female and living in an urban environment (in SABSSM 2017) and belonging to the wealthiest quintile (in NIDS 2017). Lifestyle factors associated with an increased risk of multimorbidity were being a smoker and having a high body mass index (both in NIDS 2017).

Level of education and employment status were associated with decreased odds of multimorbidity e.g., secondary and being employed (in SADHS 2016 and SABSSM 2017) and tertiary education (in NIDS 2017). Alcohol use was associated with decreased odds of multimorbidity in one survey (SADHS 2016) - which is may be linked to the 'sick quitter' hypothesis, i.e. sick people abstain from drinking alcohol due to taking prescribed medication which could lead to negative interactions.[16]

Discussion

In this paper we developed and used a systematic strategy to analyse multimorbidity prevalence and disease patterns in three national surveys. Several studies have highlighted the problematic variation in study design when assessing multimorbidity.[17-20] We followed recommendations of Nguyen *et al*. [17] to determine the prevalence of multimorbidity using a standardised protocol and to report multimorbidity by age and sex. This systematic method offers a way in which other LMIC can determine multimorbidity from available national survey data sets in the absence of robust routine health information. Our developed method allows for transparency in recording the

survey differences and thus produces improved comparison between studies, particularly by reporting prevalence by age and sex using standardised intervals.

Two key findings were that multimorbidity was consistently higher among women compared to men; and that multimorbidity increased in older age groups. Although female sex has inconsistently been linked to higher levels of multimorbidity in South Africa,[5] the findings on age and sex [17] are consistent with much of the international literature.[21] Rising multimorbidity in aging populations has implications for healthcare costs and service utilisation in a country such as South Africa with an ageing population.[22]

Even though the surveys assessed different disease conditions, hypertension and diabetes was a disease combination common to all three surveys. Hypertension was involved with almost all the multimorbid disease patterns, whether it was combined with communicable or NCDs. At a minimum, this indicates the urgent need to regularly screen for hypertension in the adult population; particularly in those already diagnosed with a chronic disease. The management of co-occurring diseases, especially in the elderly, needs to be managed in an integrated manner to ensure optimal care.

Conclusion and recommendations

We provided a systematic and transparent method that can be used to interrogate multimorbidity in national surveys. While the prevalence in each survey differs, they collectively indicate that multimorbidity increases in older age groups and tends to be higher in women. This is an important consideration to ensure equitable and efficient health service delivery in South Africa.

We recommend that future surveys ask self-reported questions in a consistent manner that can be used to analyse multimorbidity. We would also recommend that a consistent and minimum set of diseases are asked about in self-reported health questionnaires. This could be based on international surveys but also diseases that are important locally.

Limitations

There were several limitations, most of which led to an under-estimation in disease prevalence. Firstly, each survey had a different amount of disease conditions available to analyse. In addition,

the same disease conditions were not available in each survey hence this makes comparison of the prevalence of multimorbidity difficult.

We included self-reported disease conditions which may underestimate the prevalence as people may have been unaware that they have the disease. However, a recent systematic review indicated no significant difference in the prevalence of multimorbidity when self-report versus clinic/administrative data were used.[21] Where self-reported disease conditions were included, the way in which the question was asked at times differed. We excluded disease conditions that we could not confirm were current diseases. This would have also underestimated the prevalence of multimorbidity. We also excluded acute disease conditions.

Supplementary material

Supplementary material:

https://ndownloader.figstatic.com/files/36711048

References to Chapter 4

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Chapter 5. Analysis of the 2016 South African Demographic and Health Survey

OVERVIEW OF CHAPTER

This chapter presents the findings from two articles based on the 2016 South African Demographic and Health Survey (SADHS). This survey is of critical importance to health information on adult morbidity in South Africa. Analysis of the SADHS also encourages international comparisons of multimorbidity, as the survey is conducted in many different countries and regions. The survey is unique in that it measured both HIV and HbA1c (diabetes) in participants, allowing for a fairly accurate measure of co-occurrence between these two notable diseases on a national level. The first article aimed to determine the prevalence of multimorbidity in South Africa and found that 20.7% of people were multimorbid. Multimorbidity was highest in older age groups and more common in females. Being employed, possessing tertiary education and consuming alcohol was associated with reduced odds of multimorbidity. The second article was restricted to the sub-group of people with multimorbidity and assessed patterns of disease. Using a latent class analysis, four major classes of disease were identified. The disease classes from largest to smallest were: (1) *HIV, Hypertension and Anaemia,* (2) *Anaemia and Hypertension* (3) *Cardiovascular-related,* and (4) *Diabetes and Hypertension*. Several sociodemographic and behavioural factors predicted membership to disease classes. Almost 40% of multimorbid people belonged to the HIV, Hypertension and Anaemia class. These articles together indicate that integrated care – especially between non-communicable and infectious disease is critical in managing multimorbidity in the country.

Articles

- **Roomaney RA**, van Wyk B, Cois A, Pillay van Wyk V. One in five South Africans are multimorbid: An analysis of the 2016 Demographic and Health Survey. *PLoS One.* 2022; https://doi.org/10.1371/journal.pone.0269081
- **Roomaney RA**, van Wyk B, Cois A, Pillay van Wyk V. Multimorbidity disease patterns in South Africa: A Latent Class Analysis of the 2016 Demographic and Health Survey. (Submitted)

5A. Article: One in five South Africans are multimorbid - An analysis of the 2016 Demographic and Health Survey

Abstract

Multimorbidity is a global research priority, yet relatively little is known about it in low and middle income countries. South Africa has the largest burden of HIV worldwide but also has a growing burden of non-communicable diseases; potentially leading to uncommon disease combinations. Information about the prevalence of multimorbidity and factors associated with it can assist in healthcare planning and targeting groups of people for interventions. This study aimed to determine the prevalence of multimorbidity by age and sex, as well as factors associated with multimorbidity in people 15 years and older. This study analyses the nationally representative 2016 South African Demographic Health Survey. The sample included 10 336 people who participated in the Adult Health questionnaire and approximately 7 961 people who provided biomarkers. Multivariate logistic regression was used to measure the association of multimorbidity with age, sex, living in an urban or rural area, education level, wealth level, employment status, body mass index, current alcohol or tobacco use. All analyses were conducted using STATA 15. Multimorbidity was present in 20.7% (95% CI: 19.5% – 21.9%) of participants; in 14.8% (95% CI: 13.4% - 16.3%) of males and 26.2% (95% CI: 24.7 – 27.7%) of females. Multimorbidity increased with age; with the highest odds in the 55 - 64 years old age group (OR: 24.910, 95% CI: 14.901 - 41.641, $p < 0.001$) compared to those aged 15 – 24 years. The odds of multimorbidity was also higher in young females compared to young males (OR: 2.734, 95% CI: 1.50 – 4.99, p= 0.001). Possessing tertiary education (OR: 0.722, 95% CI: 0.537 - 0.97, p=0.031), being employed (OR: 0.813, 95% CI: 0.675 - 0.979, p=0.029) or currently using alcohol (OR: 0.815, 95% CI: 0.686 – 0.968, p=0.02) was protective against multimorbidity. Multimorbidity is prevalent within the South African population, with females and older adults being most affected. However, multimorbidity is also observed in younger adults and most likely driven by the high prevalence of HIV and hypertension.

Introduction

People living with more than one disease (also known as multimorbidity) have their lives impacted in many ways; including a reduced quality of life,[1-6] an increased risk of dying [7-9] and an intensified need to utilise healthcare.[10-14] Despite these negative impacts, the area of multimorbidity remains under researched when compared to research afforded to single disease conditions.[15] This is particularly acute in low and middle income countries (LMICs) where 5% of multimorbidity research globally has taken place.[15] Little is known about multimorbidity in LMICs where disease burdens are thought to differ from countries with more established multimorbidity profiles.

South Africa is an upper middle-income country [16] with a quadruple burden of disease consisting of: HIV/AIDS and tuberculosis (TB); other communicable diseases, perinatal conditions, maternal causes, and nutritional deficiencies; non-communicable diseases (NCDs); and injuries.[17] South Africa has a very high HIV prevalence and it is not uncommon that people living with HIV also develop other chronic conditions. Given this HIV burden, information is needed on the prevalence of multimorbidity to plan for more responsive healthcare services. This information is valuable for planning purposes as health service delivery could be made more efficient around common disease clusters to the benefit of those living with multimorbidity. Knowing who is most affected by multimorbidity (i.e. determinants or factors that are common in those affected) can also be used to design interventions to target those individuals. While multimorbidity research has been emerging in the country for the past decade, few studies have reported the prevalence of multimorbidity and factors associated with it in a consistent and comparable manner.[18] The authors conducted a systematic review of multimorbidity prevalence studies in South Africa and found significant heterogeneity in the study designs as well as the estimates of prevalence.[18] Of the studies included,[19-27] the prevalence of multimorbidity ranged from 3 to 87%. In addition, the factors associated with multimorbidity were disparate and at times contradictory. Among the factors that were occasionally associated with multimorbidity in South Africa were: age, being female, locality, education level, body mass index (BMI) and marital status.

Prevalence estimates form an important part of the information used for evidence-based health decision-making. Given the lack of studies conducted about multimorbidity in South Africa, we aimed to determine the prevalence of multimorbidity by age group and sex in the country using the 2016 Demographic and Health Surveys (SADHS 2016). In addition, this article reports the

process and results derived from a systematic analysis of the SADHS 2016 to establish factors associated with multimorbidity in the South African population. The SADHS 2016 is unique in South Africa in that it is a nationally representative survey which includes biomarkers for the measurement of HIV, HbA1c (diabetes), blood pressure and anaemia status.

Materials and methods

Sample and data source

National survey data is an important source of information about multimorbidity. National surveys represent a largely untapped resource that could shed light on multimorbidity in the general population. This is especially true for LMICs such as South Africa where limited information exists about multimorbidity. The DHS project, primarily funded by the United States Agency for International Development has conducted more than 230 nationally representative comparable household surveys in more than 80 countries since 1984.[28] The DHS collects data on a range of topics such as fertility, contraception, maternal and child health, HIV, malaria and domestic violence.[28] For many countries, the DHS is an important source of information for policy making, monitoring and evaluation and as the country's public health evidence base.[28] In terms of multimorbidity, the DHS collects information on self-reported health conditions and biological markers.

This article presents a secondary analysis of national survey data from the SADHS 2016. The survey is nationally representative with the aim of providing up-to-date estimates of demographic and health indicators such as information on fertility levels, marriage, sexual activity, contraceptive use, nutrition, child mortality, aspects of child health, exposure to the risk of HIV infection, behaviour and health indicators.[29] The SADHS 2016 also collected information on anthropometry, anaemia, hypertension, HbA1c levels and HIV among adults 15 years and older.

The SADHS 2016 followed a stratified two-stage sample design and a total of 750 primary sampling units (PSUs) were selected and stratified by urban, traditional and farm areas. A fixed number of twenty dwelling units were randomly selected in each PSU. Of these dwelling units, sub-sampling occurred whereby half of the households were eligible for a South African-specific module on Adult Health that included the collection of biomarkers.[29]

All participants signed consent forms to participate in the study SADHS 2016. For this secondary data analysis, the anonymised dataset with necessary permissions was obtained from the DHS programme. In addition, ethics clearance was granted by the Biomedical Research Ethics Committee of the University of the Western Cape (BM20/5/8) as part of the lead author's PhD project.

Description of included variables

Multimorbidity is frequently measured by counting the number of co-existing conditions, using a predefined list of medical conditions.[30, 31] Various studies have used this technique when doing secondary data analysis.[32] Estimation of multimorbidity included: self-reported diseases (e.g. bronchitis/ COPD, heart disease, high blood cholesterol, stroke, TB in the last 12 months), biomarker disease (e.g. HIV, anaemia, high blood pressure) and a combination of the two (i.e. diabetes). Disease variables were coded as binary (disease absent '0' or disease present '1'). An index variable was created where for each individual, the number of disease conditions present was counted. If there was information about a disease condition missing, this was counted as "no disease present". The disease index variable was further categorised to create another variable, the Multimorbidity Index. This variable categorised individuals into either having "no multimorbidity" (no disease or only one disease present) or "multimorbidity present" (two diseases or more present).

Self-reported diseases

The study sample consisted of 10 336 youth and adults who completed the Adult Health module and were asked about the presence of several diseases (Table 6-1) e.g. "Has a doctor, nurse or health worker told you that you have or have had any of the following conditions". The response to the questions were "No", "Yes" or "Don't know", with the "Don't know" response recorded as missing values. TB in the last 12 months was constructed from two other variables: whether a participant had ever had the disease and whether they had the disease in the last 12 months or more than 12 months ago.

The analysis included data where the variables were deemed to be "current" conditions. Disease conditions were excluded for the following reasons: (i) disease conditions that could not be assumed to be current at the time of the survey due to the way that the question was asked (ii) disease conditions that were considered to be acute or of short duration (iii) disabilities or injuries.

Two clinicians assisted where the information was unclear. Further details are available in Supplementary material - Table S1.[33]

Table 5A-1. Survey questions on self-reported diseases.

Variable	Survey Question
Diabetes	Has a doctor, nurse or health worker told you that you have or have had any of the following conditions: diabetes or blood sugar?
Emphysema/ Bronchitis/COPD	Has a doctor, nurse or health worker told you that you have or have had any of the following conditions: chronic bronchitis, emphysema, or COPD?
Heart disease	Has a doctor, nurse or health worker told you that you have or have had any of the following conditions: Heart attack or angina/chest pains?
High blood cholesterol	Has a doctor, nurse or health worker told you that you have or have had any of the following conditions: high blood cholesterol or fats in the blood?
Stroke	Has a doctor, nurse or health worker told you that you have or have had any of the following conditions: stroke?
TB in the last 12 months	Has a doctor, nurse or health worker ever told you that you have TB?
	When was the last time you had TB?

Physically measured diseases (biomarkers)

Of the people included, approximately 74.4% (n= 7 961) of people also had information on physically measured diseases. The following information was of interest to the analysis: diabetes (HbA1c), HIV status (dry blood spot), blood pressure measurements, anaemia (Hb), anthropometry (height and weight). Nurses collected blood specimens from finger pricks.

For diabetes, dry blood spots were analysed using a blood chemistry analyser which measures total haemoglobin concentrations.[29] A participant was assigned diabetic status if their HbA1c $\geq$ 6.5 mmol.[34, 35] Participants with normal HbA1c values but on medication to manage diabetes were also assigned diabetic status. For participants without HbA1c data, their disease status was based on their self-assessment of whether they had diabetes or not.

For HIV, dry blood spots were tested with an enzyme-linked immunosorbent assay (ELISA) and a second ELISA was done for confirmation.[29] The results of the first ELISA was included in this study.

For anaemia, nurses collected blood samples in a microcuvette and the analysis of haemoglobin was conducted on site. The SADHS 2016 anaemia results were adjusted for smoking status and altitude.[29] Anaemia levels below 7.0 g/dl were considered as severe anaemia. Moderate anaemia

was considered levels between 7.0g/dl and 9.9g/dl. For pregnant women, mild anaemia were levels between 10.0 g/dl and 10.9 g/dl and between 10.0 g/dl and 11.9 g/dl for all other adult women. [36] Participants were then categorized either having no anaemia or having anaemia. The degree of anaemia was characterized as mild, moderate or severe.

Three blood pressure measurements were taken from participants using digital blood pressure monitors.[29] For this study, the first measurement was excluded and the average of the remaining repeated measurements were taken. The values were categorised as: hypertension absent (Systolic < 120 mmHg & diastolic < 80 mmHg), Pre-hypertension (Systolic: 120–139 *mmHg* or diastolic: 80-89 *mmHg*), Stage 1 Hypertension: (Systolic: 140–159 *mmHg* or diastolic: 90–99 *mmHg*), Stage 2 hypertension (Systolic ≥160 *mmHg* or diastolic ≥100 *mmHg*).[37] Hypertension was coded as being absent (normal or pre-hypertension) or present (Stage 1 or Stage 2 hypertension). People on medication to manage hypertension were included in those that had hypertension. Data cleaning for diabetes [38] and hypertension [39] followed the procedures used in the Second South African Comparative Risk Assessment. Further details of data collection, cleaning and coding is listed in Supplementary material -Table S2 [33].

Other variables of interest

Systematic reviews identified the following characteristics (among others) as being related to multimorbidity: (i) Biomedical and individual: ageing, female, (ii) Socioeconomic: lower socioeconomic status, high-income group (in low and middle-income countries), lower education, (iii) Social and environmental: living in urban environments (iv) Behavioural: tobacco, overweight and obese.[40] For this study, the following variables were investigated as predictor variables: age category, sex, locality, highest education level, wealth index, employment status, BMI category, current smoker status and current alcohol drinker status.

The ages of participants were taken from DHS 2016 dataset. Participants under the age of 15 years were excluded. Where appropriate, age was analysed in 10-year age bands. The variable sex was included and participants were coded as male or female. Locality was included and coded as either urban or rural. Educational attainment was also included and described by the 'highest grade or form you completed at that level'. This study divided the responses into three categories: primary school or less, secondary school, and tertiary education. Employment status was coded as employed (currently working) or unemployed.

This study made use of the SADHS 2016 wealth index. The wealth index uses principal component analysis to score households according to the types of goods that are owned and other characteristics.[29] The households were divided into five quintiles, from poorest (Quintile 1) to richest (Quintile 5).

This study also examined current alcohol and tobacco use. For current alcohol use, the responses to the following two questions were combined: *"Have you ever consumed a drink that contains alcohol such as beer, wine, ciders, spirits, or sorghum beer?"* and "*Was this within the last 12 months?*". For tobacco use, the question "*Do you currently smoke tobacco every day, some days, or not at all?*". Both variables were coded as binary (e.g. Yes/No).

The BMI of participants were also examined. Height and weight were measured using a digital scale and stadiometer.[29] BMI was calculated using the *BMI* STATA package. BMI was categorized as follows: underweight (15 .0 - <18.5 kg/m^2), normal weight (18.5 - <25.0 kg/m^2), overweight (25.0 - <30.0 kg/m^2), obesity grade 1 (30.0 - <35.0 kg/m^2), obesity grade 2 (35.0 - <40.0 kg/m^2), obesity grade 3 (40.0 - <60.0 kg/m^2).[41] Data cleaning was done in accordance to another study.[41] Further details are listed in Supplementary material -S2 Table [33].

Analysis

The statistical analysis was done using STATA 15.0 (Stata Corporation, College Station, Texas, USA) software. The STATA survey set ('*svy*') of commands were used to account for the complex survey design. Sampling weights were calibrated against the Statistics South Africa mid-year population estimates.[42]

For unweighted data (sample), frequencies were used to display categorical data. Age was analysed as a continuous variable while gender, locality, province, educational level and wealth index were analysed as categorical variables. Bivariate associations between locality, province, highest education level and wealth index by sex were assessed using Chi-square tests. The prevalence of having single disease conditions by sex was also assessed with Chi-square tests. For weighted data, multimorbidity status was described using histograms and box plots against age.

Regression methods were used to describe the relationship between a dependent variable and other predictor variables.[43] In this case, a multivariate logistic regression was employed because the dependent variable was binary *(Multimorbidity absent = 0, Multimorbidity present =1)*.

Crude odds ratios were estimated by only including the dependent variable and one predictor variable. Three models were constructed for logistic regression with multimorbidity as the dependent variable. Model 1 contained only demographic information (e.g. age and sex), while Model 2 contained sociodemographic information (e.g. age, sex, educational attainment, wealth index and employment status). The final model (Model 3) included all variables in the previous models but also included lifestyle or behavioural factors (e.g. alcohol use, tobacco use and BMI).

Model checking was performed using various statistical tests. The link test [44] was used to determine if there were specification errors. Interaction terms were added where necessary. Influential observations were checked using the Pearson residuals, deviance residuals and Pregibon leverage [45] on the unweighted model as these tests cannot be used on survey weighted data. Influential observations were dropped, and the model was refitted. The crude and adjusted odds ratios were reported with 95% CIs and *p*-values of less than 0.05 were considered as statistically significant.

Results

Sample description

There were 10 336 youth and adults included in the sample; with more females (59.2%) than males (Table 6-2). The median age of participants was 36 years (interquartile range: 24 – 52 years), with females being slightly older than males but this was not statistically significant. More than half of the sample resided in urban areas (55.0%) and most (64.5%) had completed secondary education. The majority of participants were Black African (84.7%), followed by coloured (9.6%), white (4.4%) and Indian/Asian (1.4%). Age, urban location and education did not differ between males and females. There were significant differences between the proportion of males and female participants in the sample, by province ($p < 0.001$) and wealth quintile ($p = 0.018$).

Table 5A-2. Description of sample population (unweighted).

	Total (N=10 336) **% (n)**	**Male** (N=4210) **% (n)**	**Female** (N= 6126) **% (n)**	***p*-value'**
Age* (Median years and IQR)	36 (24 – 52)	33 (22 - 49)	37 (25 – 54)	0.442
Urban location	55.0 (5 685)	55.2 (2 324)	54.86 (3 361)	0.735
Province:				**<0.001**
Western Cape	7.29 (754)	6.65 (280)	7.74 (474)	
Eastern Cape	13.08 (1 352)	13.16 (554)	13.03 (798)	
Northern Cape	8.53 (882)	8.38 (353)	8.64 (529)	
Free State	9.97 (1 031)	9.12 (384)	10.56 (647)	
Kwa-Zulu Natal	15.2 (1 571)	14.32 (603)	15.8 (968)	
North West	10.5 (1 085)	11.97 (504)	9.48 (581)	
Gauteng	9.97 (1 031)	11.16 (470)	9.16 (561)	
Mpumalanga	11.8 (1 220)	12.23 (515)	11.51 (705)	
Limpopo	13.64 (1 410)	12.99 (547)	14.09 (863)	
Education level				0.502
Primary or less	26.26 (2 714)	25.65 (1 080)	26.67 (1 634)	
Secondary complete	64.51 (6 668)	65.11 (2 741)	64.1 (3 927)	
Tertiary	9.23 (954)	9.24 (389)	9.22 (565)	
Wealth index				**0.018**
Quintile 1 (Poorest)	20.3 (2 098)	20.45 (861)	20.19 (1 237)	
Quintile 2 (Poorer)	21.55 (2 227)	22.71 (956)	20.75 (1 271)	
Quintile 3 (Middle)	22.61 (2 337)	23.06 (971)	22.3 (1 366)	
Quintile 4 (Richer)	19.99 (2 066)	18.74 (789)	20.85 (1 277)	
Quintile 5 (Richest)	15.56 (1 608)	15.04 (633)	15.92 (975)	
Employed	33.9 (3 506)	41.6 (1 751)	28.7 (1 755)	**<0.001**

*Age in years. 'Categorical variables were tested using Chi-squared, continuous variables tested using Wilcoxon signed rank test.

All self-reported disease conditions were more common in females compared to males (Table 5A-3). Females had a slightly higher prevalence of TB in the last 12 months compared to males, however, the difference was not statistically significant. Other than hypertension, all physically measured disease conditions were significantly more common in females than males. The prevalence of multimorbidity in the sample population was 22.9% (Supplementary material -Table S3 [33]).

Table 5A-3. Prevalence of single disease conditions by sex and method of measurement in South Africa for 2016 (unweighted data).

Disease condition	Total % (n/N)	Male % (n/N)	Female % (n/N)	*p*-value
SELF-REPORTED				
Diabetes	4.5 (459 /10 292)	3.6 (150 /4 176)	5.1 (309 /6 116)	**<0.005**
Bronchitis / COPD	1.3 (132 /10 290)	1.0 (40 /4 177)	1.5 (92 /6 113)	**<0.005**
Heart disease	3.4 (354 /10 305)	2.4 (101 /4 183)	4.1 (253 /6 122)	**0.015**
Cholesterol	2.9 (296 /10 282)	2.3 (94 /4 167)	3.3 (202 /6115)	**0.002**
Stroke	1.4 (146 /10 309)	1.0 (40 /4 186)	1.7 (106 /6123)	**0.001**
TB in last 12 months	1.3 (138 /10 336)	1.3 (53 /4 210)	1.4 (85/6126)	0.576
PHYSICALLY MEASURED (BIOMARKER)				
HIV	19.9 (1 307 /6 584)	13.8 (346/2 517)	23.6 (961 /4 067)	**<0.005**
Hypertension	46.2 (3 678/ 7 961)	45.1 (1 412 /3 130)	46.9 (2 266 /4 831)	0.117
Anaemia	25.9 (1 862/ 7 200)	17.7 (489/ 2 769)	31.0 (1 373 /4 431)	**<0.001**
Diabetes (HbA1c)	12.4 (839 /6 763)	9.3 (241 /2 591)	14.3 (598 /4 172)	**<0.001**
PHYSICALLY MEASURED (BIOMARKER) AND SELF-REPORTED				
Diabetes (self-report or HbA1c)	10.06 (1 036 / 10 295)	7.35 (307/ 4 178)	11.92 (729 /6 117)	**<0.001**

Prevalence of single diseases and multimorbidity

Table 5A-4 shows the weighted prevalence of each included disease condition by sex. Of the self-reported diseases, diabetes had the highest prevalence (4.4%), followed by high cholesterol (3.5%), heart disease (3.1%), COPD or bronchitis (1.4%), stroke (1.4%) and TB in the last 12 months (1.2%). The prevalence of physically measured diseases was higher than that of self-reported diseases. Of the physically measured diseases, hypertension occurred most frequently (45.0%), followed by anaemia (24.7%), HIV (19.6%) and diabetes (11.7%).

Diabetes was the only disease condition included in this study that was both physically measured and self-reported in the questionnaire. The prevalence of physically measured diabetes was more than double that of self-reported diabetes (11.7% versus 4.4%, respectively). This indicates that self-reported diabetes is most likely underreported. When combining the responses of the

measured and self-reported diabetes, the composite prevalence was 9.1%. All diseases were more prevalent in females compared to males.

Table 5A-4. Prevalence of single disease conditions by sex and method of measurement in South Africa for 2016 (weighted data).

Disease condition	Total % (95% CI)	Male % (95% CI)	Female % (95% CI)
Self-reported			
Diabetes	4.4 (3.9 – 5.0)	3.7 (3.0 – 4.5)	5.1 (4.4 – 5.9)
Bronchitis / COPD	1.4 (1.1 – 1.8)	1.1 (0.8 – 1.6)	1.7 (1.3 – 2.2)
Heart disease	3.1 (2.7 – 3.5)	2.3 (1.8 – 2.9)	3.8 (3.3 – 4.5)
Cholesterol	3.5 (2.9 – 4.2)	3.0 (2.3 – 3.8)	4.1 (3.4 – 4.9)
Stroke	1.4 (1.1 – 1.7)	1.0 (0.7 – 1.5)	1.7 (1.4 – 2.1)
TB in last 12 months	1.2 (0.9 – 1.5)	0.9 (0.6 – 1.3)	1.5 (1.0 – 2.0)
Measured (Biomarker)			
HIV	19.6 (18.2 – 21.1)	13.7 (11.8 – 15.8)	24.5 (22.7 – 26.4)
Hypertension	45.0 (43.1 – 46.9)	44.1 (41.5 – 46.7)	45.8 (43.7 – 48.0)
Anaemia	24.7 (23.2 – 26.3)	16.8 (15.0 – 18.8)	31.3 (29.2 – 33.5)
Diabetes (HbA1c)	11.7 (10.7 – 12.8)	9.1 (7.8 – 10.6)	13.9 (12.6 – 15.4)
Measured (Biomarker) and self-reported			
Diabetes (self-report or HbA1c)	9.1 (8.4 – 9.9)	6.9 (5.9 – 7.9)	11.1 (10.2 – 12.3)

Note: Biomarker prevalence differed slightly from the DHS report due to the different data cleaning methods and cut-offs employed.

The number of diseases present in one individual ranged from zero to six. The difference in the prevalence in the number of diseases by sex was statistically significant ($p<0.001$). About 49% of the participants had none of the diseases included in the study, with more males compared to females being "disease-free" (55.8% versus 41.8%, respectively, $p<0.001$) (Table 5A-5). Less than a third of participants (30.8%) had one disease and there was a difference between males and females (29.4% versus 32.1%, respectively, $p=0.0183$). Multimorbidity was present in 21% of participants. The prevalence of multimorbidity in females was almost double that of males (26.2%

vs 14.8%, respectively) and the difference between the sexes was statistically significant ($p<0.001$).

Table 5A-5. Number of diseases in individuals by sex in South Africa for 2016 (weighted data).

Number of diseases	Total % (95% CI)	Male % (95% CI)	Female % (95% CI)
No disease	48.6 (47.0 – 50.1)	55.8 (53.5 – 58.1)	41.8 (40.0 – 43.4)
1 disease	30.8 (29.5 – 32.0)	29.4 (27.5 – 31.2)	32.1 (30.6 – 33.7)
2 diseases	14.1 (13.2 – 15.1)	10.5 (9.4 – 11.8)	17.4 (16.2 – 18.7)
3 diseases	5.2 (4.7 – 5.9)	3.5 (2.8 – 4.3)	6.8 (6.0 – 7.8)
4 diseases	1.1 (0.8 -1.3)	0.6 (0.4 – 0.9)	1.4 (1.1 – 1.9)
5 diseases	0.2 (0.1 – 0.4)	0.1 (0.1 – 0.3)	0.4 (0.2 – 0.6)
6 diseases	0.07 (0.02 – 0.19)	0.01 (0.01 – 0.04)	0.01 (0.01 – 0.02)
Multimorbidity (≥ 2 diseases)	**20.7 (19.5 – 21.9)**	**14.8 (13.4 – 16.3)**	**26.2 (24.7 – 27.7)**

Multimorbidity prevalence increased with increasing age in both males and females (Figure 5A-1, S3 Table). The prevalence of multimorbidity was consistently higher in females compared to males across the different age groups. Multimorbidity was present at lower levels: 3% for adolescents aged 15 – 19 years and 10% for 20 – 29 years old. In females, multimorbidity peaked at 47% in the 60 – 69 years old; whereas in males, it peaked at 40% in the 70 -79 years old. Multimorbidity prevalence dropped slightly in the age group 80 years and over. However, the observed drop is most likely due to uncertainty introduced by a smaller number of people aged 80+ being included in the sample. People with multimorbidity tended to have an older median age compared to those with no multimorbidity (Figure 5A-2), but this difference was not statistically significant.

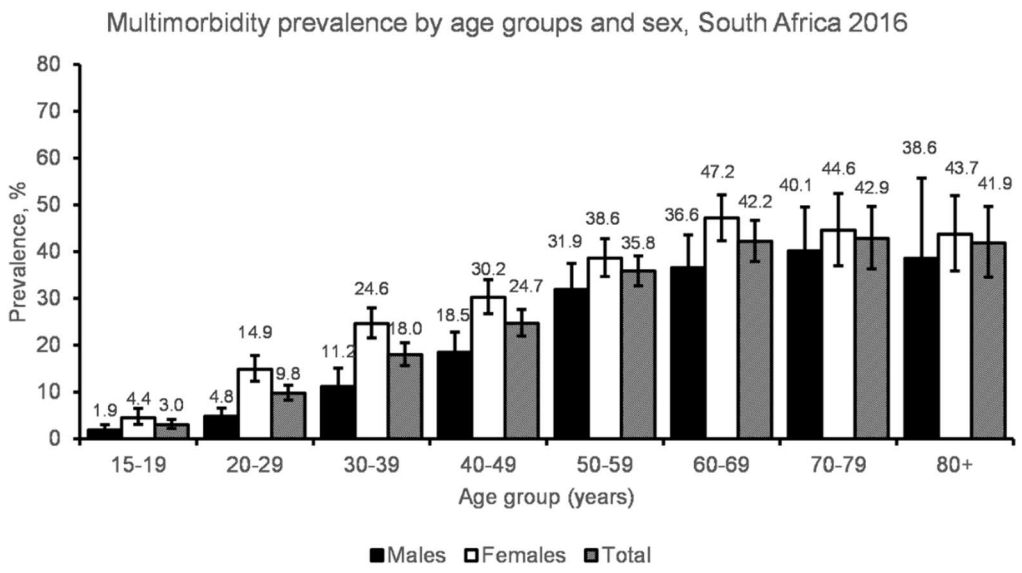

Figure 5A-1. Estimated multimorbidity prevalence by age group and sex in South Africa in 2016.

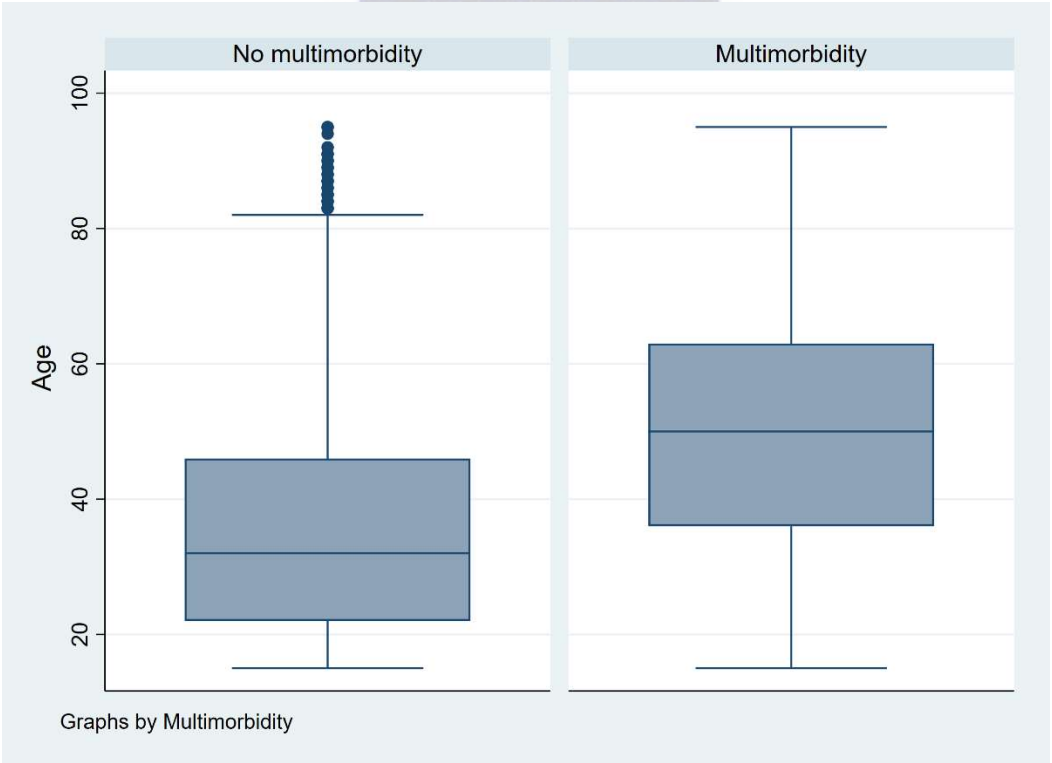

Figure 5A-2. Multimorbidity status by age.

Factors associated with multimorbidity

The factors associated with multimorbidity were investigated through a logistic regression (Table 5A-6). For the final model, outliers were dropped and the model was refitted due to its limited ability in predicting multimorbidity in young women with a low BMI (Supplementary material - Fig S1 [33]). An interaction term between age and sex was added to the model to improve its fitness.

The final model showed that the odds of being multimorbid increased with age, with the highest odds if the participant was in the 55 – 64 years of age group (OR: 24.910, 95% CI: 14.901 - 41.641, p<0.001), compared to 15 – 24 years old. Younger females (15 – 34 years) had larger odds of being multimorbid compared to males in the same age groups.

The odds of being multimorbid were reduced if an individual had tertiary education (OR: 0.722, 95% CI: 0.537 - 0.970, p=0.031) compared to only having completed primary school education. Those that were employed had reduced odds of multimorbidity compared to those that were unemployed (OR: 0.813, 95% CI: 0.675 - 0.979, p=0.029). Those that had used alcohol recently also reported lowered odds compared to those that were not using alcohol (OR: 0.815, 95% CI: 0.686 – 0.968, p=0.02). BMI and current tobacco use were not significant when adjusted for age, sex and other variables. The wealth index was not a predictor of multimorbidity. Additional models can be found in S5 Table.

Table 5A-6. Factors associated with multimorbidity

Variable	Unadjusted Odds ratios (95% CI)	Final model (Model 3) Odds ratio (95% CI)
Age category *(Reference: 15 – 24 year)*		
25 - 34 years	**2.982 (2.407 - 3.695) ***	**3.923 (2.299 - 6.695) ***
35 - 44 years	**4.861 (3.769 - 6.269) ***	**8.417 (5.101 - 13.890) ***
45 – 54 years	**7.527 (5.844 - 9.694) ***	**14.165 (8.654 - 23.185) ***
55 – 64 years	**11.764 (8.837 - 15.662) ***	**24.910 (14.901 - 41.641) ***
65+ years	**14.181 (10.951 – 18.364) ***	**23.062 (13.719 - 38.766) ***
Sex (*Reference: Male)*	**2.038 (1.804 – 2.301) ***	1.135 (0.831 - 1.551)
Age category and sex interaction		
15-24#Female	-	**2.734 (1.498 - 4.988) ***
25-34#Female	-	**1.896 (1.169 - 3.075) ***
35-44#Female	-	1.340 (0.842 - 2.132)
45-54#Female	-	1.089 (0.676 - 1.755)
55-64#Female	-	0.866 (0.558 - 1.345)
65+#Female	-	**1 (omitted)**

Variable	Unadjusted Odds ratios (95% CI)	Final model (Model 3) Odds ratio (95% CI)
Urban *(Reference: Rural)*	**0.817 (0.721 – 0.925) ***	1.107 (0.901 - 1.360)
Education *(Reference: Primary)*		
Secondary	**0.423 (0.372 -0.480) ***	0.966 (0.819 - 1.140)
Tertiary	**0.323 (0.251 – 0.414) ***	**0.722 (0.537 - 0.970)***
Wealth index (Reference: Poorest)		
Poorer	0.995 (0.829 - 1.194)	1.067 (0.864 - 1.317)
Middle	1.076 (0.874 - 1.324)	1.126 (0.867 - 1.464)
Richer	1.036 (0.845 - 1.270)	1.034 (0.778 - 1.374)
Richest	0.901 (0.713 – 1.138)	0.754 (0.545 - 1.044)
Employed *(Reference: Not employed)*	**0.744 (0.643 – 0.861) ***	**0.813 (0.675 - 0.979)***
BMI *(Reference: Underweight)*		
Normal weight	0.961 (0.679 – 1.361)	0.892 (0.609 - 1.309)
Overweight	**1.779 (1.227 – 2.581) ***	1.033 (0.680 - 1.571)
Obesity group 1	**2.536 (1.759 – 3.655) ***	1.213 (0.793 - 1.854)
Obesity group 2	**2.94 (1.965 – 4.397) ***	1.340 (0.840 - 2.137)
Obesity group 3	**3.518 (2.367 – 5.228) ***	1.527 (0.956 - 2.438)
Current alcohol use *(Reference: No current alcohol use)*	**0.571 (0.498 – 0.653) ***	**0.815 (0.686 - 0.968) ***
Current tobacco use *(Reference: No current tobacco use)*	**0.704 (0.592 – 0.838) ***	0.893 (0.710 - 1.122)

Discussion

Using the DHS national survey, it was found that one in five South Africans aged 15 years or above was multimorbid. The prevalence of multimorbidity generally increased with age and reached 42% in the 60 years and older age groups. The prevalence of multimorbidity was higher in females compared to males, but the difference was larger in younger age groups. Our study corroborates other studies that have found high levels of chronic diseases in the sub-Saharan region. For example, an analysis of DHS surveys in 33 sub-Saharan African countries (excluding South Africa), found that there was a high prevalence of hypertension, anaemia, underweight, overweight and obesity in females 15 years or above.[46]

Several other national surveys have been analysed to determine the prevalence of multimorbidity in South Africa.[19-21, 47] The prevalence estimates varied from 2.8%[21] to 63.4%[20], although these studies looked at differing age groups, used varying data collection methods and included different disease conditions. The 2003 World Health Survey which surveyed adults 18 years older found a standardised prevalence of 11.2%.[19] Two waves of the National Income Dynamic Surveys (2008 and 2012) found a low prevalence of 2.7% and 2.8%, respectively.[21] The same 2008 dataset was analysed using different methods but found a similar low prevalence of 4%.[47] Garin *et al*. [20] used the 2007/2008 World Health Organization Study on global AGEing (SAGE)

and adult health and found a prevalence of 63.4% in adults over the age of 50 years. Most of these studies included self-reported diseases and physically measured hypertension. Self-reported diseases are likely to be underreported as people may be unaware that they have a disease. The DHS physically measured more diseases compared to the National Income Dynamic Surveys and World Health Survey (i.e. HIV, diabetes and anaemia) which may explain its ability to detect higher levels of multimorbidity. The number of disease conditions included in each study also varied. The Garin *et al.* [20] study was restricted to adults over the age of 50 years and included a larger number of disease conditions (e.g. depression, cognitive impairment, edentulism and obesity as a disease condition) and therefore reported higher prevalence of multimorbidity. A recent analysis of Wave 2 SAGE (2014/2015) [48] of adults aged 45 years and older, included fewer disease conditions than Garin *et al.* [20] (7 vs. 12); reported a multimorbidity prevalence of 21%. Another discrepancy to note is that the 2016 DHS was more recently conducted than the other national surveys.

In terms of factors associated with multimorbidity, an increasing age was associated with being multimorbid. This follows trends in reporting in international [40] and the South African literature on multimorbidity . Multimorbidity is often associated with older adults, especially in high income countries [49] due to shifting demographic trends whereby people are living longer, ageing and developing chronic diseases of lifestyle. However, our study had an interesting finding in observing that multimorbidity was present in 10% of young adults between the ages of 20 – 29 years. This is most likely attributed to the high prevalence of single disease such as HIV, anaemia and hypertension in South Africa. HIV is known to affect younger adults in South Africa. A South African national HIV prevalence survey indicated that 7.9% of people (4.8% of males, 10.9% of females) aged 15 – 24 years were HIV positive in 2017.[50] Also, the prevalence of hypertension in South Africa is thought to be increasing. In young South Africans, hypertension is frequently associated with having a family history of the disease (suggesting a genetic component) and obesity or metabolic syndrome.[51, 52] In this study, approximately 32% of people with HIV under 30 years of age, also had hypertension (Fig S3 - [33]). This has implications for young people in that they will have to be on lifelong treatment for both diseases.

The present study showed that having tertiary education decreased the odds of multimorbidity, this has been noted both locally and internationally.[19, 20, 53] However, a systematic review of education levels and multimorbidity in Southeast Asia found the association was inconsistent.[54]

This study found that being employed decreased the odds of multimorbidity. Similar results were found in an analysis of social determinants and multimorbidity in South Africa.[47] Yet, this could also be interpreted to mean that healthier people are more likely to be employed. In a systematic review of multimorbidity and its impact on workers, multimorbidity was found to have a negative impact on work, worsening absenteeism and lowering employability.[55] The wealth index was not significantly associated with multimorbidity. The relationship between wealth and multimorbidity in this study may be unclear as the diseases included may have different patterns according to the individual disease. For example, HIV could be associated with being in a lower wealth quintile, while cardiovascular diseases such as diabetes could be associated with being in a higher wealth quintile. The same argument could be used to explain the findings on BMI. This study indicated that having a high BMI could be associated with multimorbidity but the findings were not significant. High BMI has been identified as associated with multimorbidity in other studies.[56] However, the inclusion of HIV and anaemia could mean that people with lower BMIs were also prone to being multimorbid. An interesting finding was that alcohol use was associated with decreased odds of multimorbidity. A study of binge drinking among adults in the United States found that binge drinkers tended to have lower levels of multimorbidity.[57] They related these findings to the 'sick quitter' hypothesis whereby adults stop drinking due to interactions with prescribed medications.[58]

Limitations

The current analysis was limited to the data available and disease conditions asked about in the original survey. Additional disease conditions (e.g. cancer) could have been included in the analysis, but the survey in question only asked if the individual had "ever" had the disease. A strength of this study is that disease conditions were only included if the person could have been considered to have the disease at the time of the survey or at a time close to when the study took place. Many studies of multimorbidity include past and current disease conditions without distinction. Had there been included more disease conditions, the prevalence estimates would have most likely be higher. Also, we did not account for pregnancy status in our calculation of BMI.

The study is limited to a simple count of diseases to determine multimorbidity. Studies done with electronic health records or surveyed people specifically for multimorbidity may have taken the severity of diseases into account. Nonetheless, the DHS provides a robust source of data that could

be analysed in other LMICs to generate information about multimorbidity where little is still known.

The analysis included self-reported and measured (biomarker) diseases. Self-reported diseases may have been underreported due to participants being unaware that they have a disease. In this study, the prevalence of measured (biomarker) diseases was higher than self-reported diseases. In addition, this study was cross-sectional by nature meaning that we cannot confer temporality.

Conclusion

This study showed that one in five South Africans, 15 years or above, are managing more than one disease condition. Multimorbidity started in adolescents and increased with age. Females were more frequently affected than males. It was found that having tertiary education and being employed lowered the odds of multimorbidity.

The high prevalence of multimorbidity needs to be addressed in South Africa. This could be done in a twofold manner: (a) by reducing the high prevalence of single diseases such as hypertension and (b) by simultaneously targeting people with existing diseases to reduce their chances of becoming multimorbid. More studies are needed to identify common disease clusters to assist in the endeavour of targeting high risk people. More studies are also needed to determine whether the trends in multimorbidity are changing in the country. For example, to understand whether policies aimed at diseases such as HIV and hypertension have helped to decrease multimorbidity. Also, information is needed on how emerging diseases such as COVID-19 may affect people with multimorbidity in South Africa.

Supplementary file - https://doi.org/10.1371/journal.pone.0269081.s001

5B. Article: Multimorbidity disease patterns in South Africa: A Latent Class Analysis of the 2016 Demographic and Health Survey *(Submitted)*

Abstract

Objectives. South Africa has the largest burden of HIV worldwide and has a growing burden of non-communicable diseases; the combination of which may lead to diseases clustering in ways that are not seen in other regions. This study sought to identify common disease classes and sociodemographic and lifestyle factors associated with each disease class.

Methods. Data were analysed from the South African Demographic Health Survey 2016. A latent class analysis was conducted using nine disease conditions. Sociodemographic and behavioural factors associated with each disease cluster was explored. All analysis was conducted in Stata 15 and the LCA Stata plugin was used to conduct the latent class and regression analysis.

Results. Multimorbid participants were included (n = 2 368). Four disease classes were identified: *HIV, Hypertension and Anaemia* (comprising 39.4% of the multimorbid population), *Anaemia and Hypertension* (23.7%), *Cardiovascular-related* (19.9%) and *Diabetes and Hypertension* (17.0%).

Discussion. This study affirmed that integrated care is urgently needed, evidenced by the largest disease class being an overlap of chronic infectious diseases and non-communicable diseases. This study also highlighted the need for hypertension to be addressed. Tackling the risk factors associated with hypertension could avert an epidemic of multimorbidity.

Background

Multimorbidity (living with more than one chronic disease) is associated with an increased risk of mortality,[9] poorer self-rated health,[59] reduced quality of life and increased healthcare utilization and associated costs.[10] The prevalence of multimorbidity is likely to increase as populations' age, the burden of non-communicable diseases (NCDs) grows,[60] and chronic complications arise due to infections from COVID-19. Approximately, 30% of people in low and middle income countries (LMICs) are living with multimorbidity.[61] Still, compared to high income countries, much less is known about multimorbidity in LMICs; with LMICs accounting for only 5% of the scientific literature on multimorbidity globally.[15] An increase in the

prevalence of multimorbidity could prove dire to many countries already struggling to cope with the ill health of their populations.

Multimorbidity is thought to start at younger ages in LMICs,[60] likely due to disease burdens affecting younger people such as HIV. With the increased availability of antiretroviral therapy (ART), life expectancies for people living with HIV have increased.[62] HIV is now considered a chronic disease and is commonly co-morbid with chronic diseases such as hypertension, dyslipidaemia, diabetes and cardiovascular disease.[63]

South Africa has one of the highest HIV prevalence in the world, with 7.9 million people living with HIV in 2017.[50] The HIV prevalence reaches 33.3% in females and 19.4% in males between the ages of 25 - 49 years.[50] South Africa boasts the largest ART programme in the world, with 5 599 664 adults and children on ART.[64] Furthermore, South Africa reports high burdens of disease due to tuberculosis (TB), NCDs, injuries, and maternal and child health.[17] A systematic review of multimorbidity in the country[18] found that multimorbidity is prevalent, especially among women and older adults.

While knowing the prevalence of multimorbidity is important, it is also vital to understand how diseases cluster together and what factors are associated with the clustering. This can better enable researchers and clinicians to develop appropriate guidelines for the management of multimorbidity, generate new hypothesis on aetiology underlying associations, facilitate studies to identify risk factors[62] and identify groups of people to target for screening interventions. Latent class analysis (LCA) is a popular method used to identify subgroups or classes.[65] LCA is a cross-sectional latent variable mixture modelling technique which aims to find heterogeneity within the population and probabilistically assigns each individual to a class.[65] LCA is considered advantageous over other clustering techniques as it provides fit statistics and covariates can be included in models.[65]

LCA has been used to identify multimorbidity disease patterns or classes in several other studies. A recent study analysed NCD data to determine latent classes in older South Africans and identified three groups, namely: minimal multimorbidity risk (83%), concordant multimorbidity (11%) and discordant multimorbidity (6%).[48] Similarly, our study aims to determine disease patterns among multimorbid people in South Africa using LCA. Where our study differs is that we limited our analysis to multimorbid people, we used a more inclusive age range (15 years and

older) and we included chronic infectious diseases such as HIV, which is important to the local context. We aimed to determine sociodemographic and lifestyle factors associated with each disease class. To our knowledge, this the first South African LCA study that includes HIV in an analysis of multimorbidity patterns.

Methods

Data, measures of disease and variables of interest

This study used data from a nationally representative survey, the South African Demographic and Health Survey (SADHS) 2016. The survey uses a stratified two-stage sample design and a total of 750 primary sampling units were selected. Twenty dwelling units were randomly selected in each primary sampling unit and these were sub-sampled such that half of the households were eligible for a South African-specific module on adult health that included the collection of biomarkers.[29] Detailed methods can be found elsewhere.[29] This analysis was restricted to persons 15 years and older who had more than one disease condition.

We included disease conditions which could be deemed to be "current." Two clinicians assisted where the information was unclear. Individuals were asked whether they were diagnosed by a health worker with the following conditions: diabetes, heart disease, high blood cholesterol, stroke, TB in the last 12 months and chronic obstructive pulmonary disease (COPD) or bronchitis.

For testing of HbA1c and HIV, nurses collected finger-prick blood specimens on a filter paper card. The dry blood spot for HbA1c were analysed with a blood chemistry analyser measuring total haemoglobin levels.[29] The presence of diabetes was indicated either by the presence of a HbA1c levels greater than 6.5 mmol/l, [34, 35] through self-report, or if a participant was on treatment for diabetes. For HIV, dry blood spots were tested with enzyme-linked immunosorbent assay (ELISA) and confirmed with a second test.[29] We included the results of the first ELISA.

Blood specimens for anaemia testing were collected in a microcuvette and haemoglobin levels were tested on site to detect the presence or absence of anaemia.[29] We considered anaemia to be present whether mild (pregnant women: Hg levels between 10.0 g/dl - 10.9 g/dl, other adults: 10.0 g/dl - 11.9 g/dl), moderate (7.0g/dl - 9.9g/dl) or severe (< 7.0 g/dl).[36] Participants had their blood pressure measured three times and we averaged the second and third measurement.[39]

Hypertension was defined as having blood pressure outside the health range (Stage 1 Hypertension: systolic: 140–159 mmHg or diastolic: 90–99 mmHg; Stage 2 Hypertension: Systolic ≥160 mmHg or diastolic ≥100 mmHg) or being on antihypertensive medication [37]. Further details on data cleaning are provided in Table S1.

Self-reported demographic variables included age, sex and years of schooling (primary completed, secondary completed and tertiary education).[29] Behavioural and lifestyle variables were also included based on factors commonly associated with multimorbidity.[15] We determined current alcohol use (in the past 12 months) by combining the responses of two questions ('Have you ever consumed a drink that contains alcohol such as beer, wine, ciders, spirits, or sorghum beer?" and "Was this within the last 12 months?'). For tobacco use, those that smoked either every day or some days were considered to be current smokers. Body Mass Index (BMI) was also considered. Participants had their height and weight measurements taken. BMI was categorised as underweight, normal weight, and overweight/obese.

Ethics

Participants gave their consent to take part in the survey, take measurements of heights, weights and blood pressure and collect blood specimens. This study was a secondary data analysis of an anonymised dataset which was obtained from the DHS programme. Ethics clearance to conduct this study was granted by the Biomedical Research Ethics Committee of the University of the Western Cape (BM20/5/8) as part of the author's PhD project.

Statistical analysis

Data cleaning was conducted in Stata 15 (College Station, TX: StataCorp LLC). The LCA Stata Plugin[66, 67] was used as it accommodates clustering and weighting common to surveys with complex sampling designs.

Nine disease outcomes were included as indicator variables and were coded as binary variables (i.e. disease present or disease absent). The model selection was done without covariates.[68] We first estimated a one class model and then added additional classes to compare the relative fit of each model using fit statistics.[68] We compared the Bayesian information criterion (BIC),[69] the Akaike information criterion (AIC)[70] and the adjusted BIC (aBIC).[71] We determined which model had the lowest AIC, BIC and aBIC values (with lower values indicate a better

relative fit). The substantive meaning of the classes were also considered i.e. whether the classes are what would be expected from theory, whether they are easy to interpret and also whether classes are large enough.[65] Once the appropriate LCA model was selected, each individual was assigned to a class based on their posterior class membership probabilities. We then performed a multivariate regression with class membership as the outcome. Covariates were investigated based on factors that are commonly associated with multimorbidity.[40] We also explored employment status and wealth index but these were later removed due to the sparse design matrix. A reference class was specified by the researchers, and was based on which class was the largest. We chose to exclude participants that were not multimorbid as the large number of 'healthy' individuals would present problems in detecting multimorbid classes.

Results

Sample description

Of the 2 368 multimorbid participants, the majority were female (71.5%) (Table 5B-1). The median age was 50 years. Generally, males and females were similar in most aspects, but males were significantly more likely to be employed and were more likely to belong to wealthier quintiles.

Table 5B-1. Description of the multimorbid population by sex (unweighted).

	Total (N=2 368) **% (n)**	**Male** (N=674) **% (n)**	**Female** (N= 1694) **% (n)**	**P-value'**
Age* (Median years and IQR)	50 (37 – 63)	52 (39 -64)	50 (36 – 63)	0.527
Urban location	53.7 (1 271)	55.6 (375)	52.9 (896)	0.227
Province				0.532
Western Cape	6.9 (163)	7.3 (49)	6.7 (114)	
Eastern Cape	15.9 (376)	15.1 (102)	16.2 (274)	
Northern Cape	7.3 (172)	8.9 (60)	6.6 (112)	
Free State	13.6 (323)	13.2 (89)	13.8 (234)	
Kwa-Zulu Natal	16.4 (389)	16.6 (112)	16.4 (277)	
North West	10.5 (249)	11.1 (75)	10.3 (174)	
Gauteng	7.1 (169)	7.7 (52)	6.9 (117)	
Mpumalanga	13.2 (313)	11.9 (80)	13.8 (233)	
Limpopo	9.0 (214)	8.2 (55)	9.4 (159)	
Education level				0.132
Primary or less	40.2 (953)	40.1 (270)	40.3 (683)	

Secondary complete	53.5 (1266)	52.1 (351)	54.0 (915)	
Tertiary	6.3 (149)	7.9 (53)	5.7 (96)	
Employed	30.7 (727)	38.9 (262)	27.4 (465)	**<0.001**
Wealth index				**0.002**
Quintile 1 (Poorest)	20.3 (481)	20.9 (141)	20.1 (340)	
Quintile 2 (Poorer)	21.2 (503)	21.5 (145)	21.1 (358)	
Quintile 3 (Middle)	23.8 (563)	21.2 (143)	24.8 (420)	
Quintile 4 (Richer)	20.9 (494)	18.4 (124)	21.8 (370)	
Quintile 5 (Richest)	13.8 (327)	18.0 (121)	12.2 (206)	

*Age in years. 'Categorical variables tested using Chi-squared, continuous various tested using Wilcoxon rank sum test.

Distribution of diseases in the multimorbid population

Among the population with multimorbidity, the majority were estimated to have hypertension (Figure 5B-1). Anaemia, HIV and diabetes were also prevalent. When taking age into account, hypertension, diabetes, heart disease, high cholesterol, bronchitis/COPD and stroke increased in older age groups (Supplementary material -Fig S1). Most of the disease conditions were more prevalent among females compared to males (Supplementary material -Table S2).

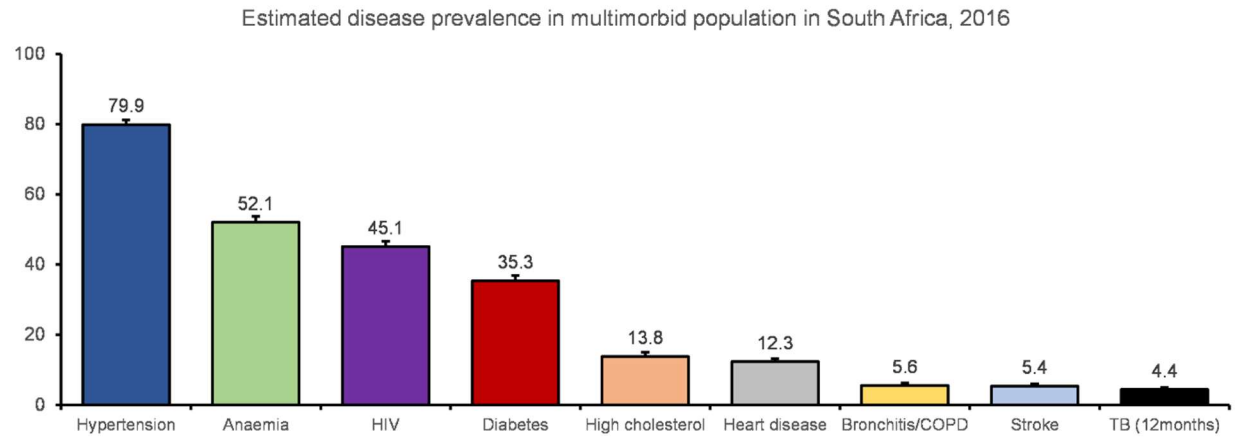

Figure 5B-1. Estimates disease prevalence in the multimorbid population (weighted).

Table 5B-2 shows a comparison of fit statistics for models with different numbers of classes, ranging from two to seven. The BIC and adjusted BIC were minimal for 4 and 5 classes, respectively. The AIC suggested a larger number of classes, but the AIC tends to suggest overly complex models.[68] Using 5 rather than 4 classes produced only a modest decrease in the aBIC but did not improve clinical interpretability (e.g. the "Cardiovascular class" of diseases were further split into smaller groups), hence, we selected a 4-classes model as the optimal one. We

adopted class names based on either the disease/s with the highest probability or categories of clinical significance.

Table 5B-2. Fit statistics for LCA models with different numbers of classes.

Fit statistics	Latent class analysis models					
	2 class model	3 class model	4 class model	5 class model	6 class model	7 class model
Design effect	1.8	1.7	1.5	1.6	1.4	1.4
Degrees of freedom	492	482	472	462	452	442
Entropy R-squared	0.8	0.9	0.8	0.9	0.9	0.9
Entropy Raw	337.5	370.8	566.0	565.6	553.3	489.8
Adjusted BIC	1 699.8	1 359.5	1 160.7	1 135.1	1 159.5	1 158.7
BIC	1 760.2	1 451.6	1 284.6	1 290.8	1 347.0	1 377.9
AIC	1 650.5	1 284.3	1 059.5	1 008.1	1 006.6	979.8
G-squared	1 612.5	1 226.3	981.5	910.1	888.6	841.8
Log likelihood	-8 343.2	-8 150.1	-8 027.7	-7 992.0	-7 981.2	-7 957.9

The reported membership probability represents the "conditional prevalence" for each retained class or the estimated distribution of the multimorbid population across the four latent classes. Four disease classes identified and membership probabilities are shown in Figure 5B-2 (standard errors available in Supplementary material -Table S3). Class 1 (HIV, Hypertension and Anaemia) accounted for almost 40% of the multimorbid population.

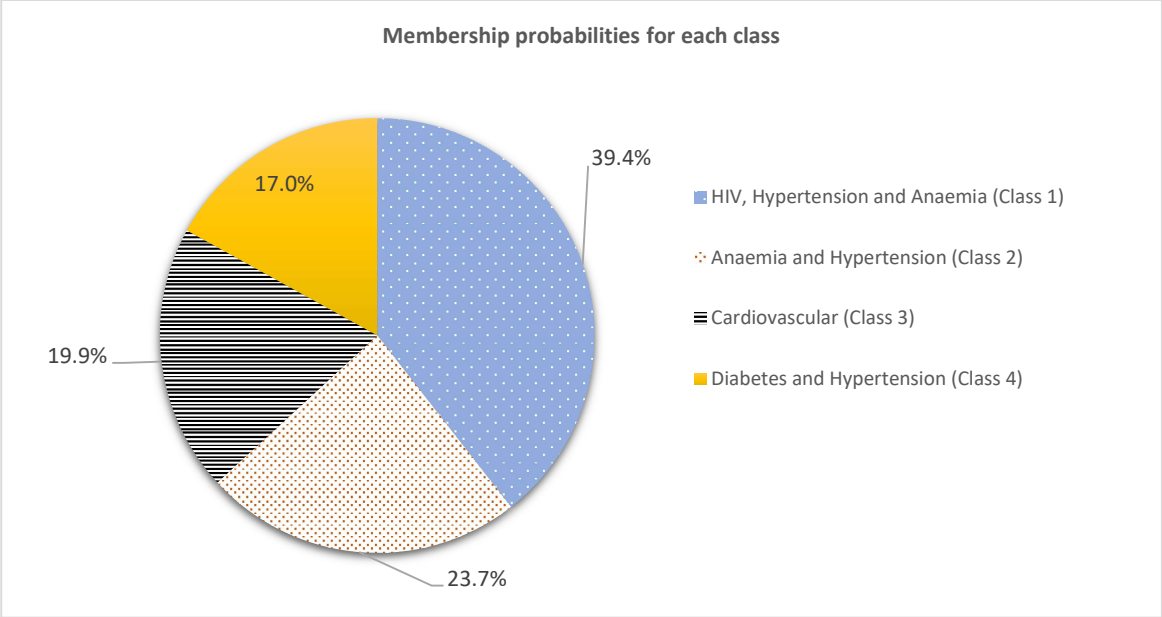

Figure 5B-2. Membership probabilities for each latent class

Class 1 *(HIV, Hypertension and Anaemia)* was characterised by HIV (Table 5B-3). It was predicted that all members have HIV, 61% hypertension, 59% anaemia and other diseases in smaller percentages. Class 2 (*Anaemia and Hypertension*) was characterised by anaemia, with all members predicted to have anaemia, 87% hypertension, followed by the other diseases in smaller percentages. For Class 3 (*Cardiovascular*), 93.8% of members were predicted to have hypertension, 50% high cholesterol, 38% heart disease, 35% diabetes, followed by the other diseases in smaller percentages. Class 4 (*Diabetes and Hypertension*), was characterised by all members predicted to have diabetes and hypertension, followed by the other diseases in smaller quantities. The item response probabilities with standard errors is shown in Supplementary material-Table S4.

Table 5B-3. Item response probabilities, by disease for each class.

Class name		Disease condition (Item response probabilities)								
		Anaemia	Bronchitis/ COPD	Diabetes	Heart disease	High cholesterol	HIV	Hypertension	Stroke	TB*
1	HIV, Hypertension & Anaemia	**0.59**	0.01	0.10	0.05	0.01	**1.00**	**0.61**	0.02	0.08
2	Anaemia and Hypertension	**1.00**	0.03	0.31	0.08	0.04	0.00	**0.87**	0.03	0.02
3	Cardiovascular	0.17	0.22	0.35	0.38	**0.50**	0.08	**0.94**	0.18	0.05
4	Diabetes and Hypertension	0.00	0.00	**1.00**	0.06	0.14	0.09	**1.00**	0.03	0.01

*TB in the last 12 months. Probabilities >50% are bolded. Class names based on either the disease/s with the highest probability or categories of clinical significance.

Factors associated with latent class membership

The latent class model was run with covariates to identify associations with membership of the four latent classes (Table 5B-4, Supplementary material -Table S5, Table S6). Class 1 (*HIV, Hypertension and Anaemia)* was selected as the reference class because it was the largest disease class identified in our study.

Age was significantly associated with class membership. Older adults (people aged 55+ years) were more likely to belong to the three classes compared to Class 1. Sex was associated with two of the classes i.e. males were more likely to belong to the *Anaemia and Hypertension* class or the *Diabetes and Hypertension* class, compared to Class 1.

Those with tertiary education were more likely to belong to the *Anaemia and Hypertension* class, or the *Cardiovascular* class or the *Diabetes and Hypertension*, compared to Class 1. Only the *Cardiovascular* class had an association with locality.

Those that drank alcohol in the past 12 months were less likely to belong to the *Diabetes and Hypertension* class, compared to Class 1. Also, current smokers were more likely to belong to the *Cardiovascular* class. People with higher BMIs (overweight or obese) tended to belong to the *Cardiovascular* class or the *Diabetes and Hypertension* class, compared to Class 1.

Table 5B-4. Factors associated with class membership.

Covariates	OR (95% CI) by class membership			
	Class 1 ***(Reference class)***	**Class 2**	**Class 3**	**Class 4**
	HIV, Hypertension and Anaemia	**Anaemia and Hypertension**	**Cardiovascular**	**Diabetes and Hypertension**
Age category *(Ref: 15–34 years)*				
35-54 years	1.00	1.19 (0.84 - 1.68)	**4.53 (2.40 - 8.57)**	**4.12 (2.58 - 6.57)**
55+ years	1.00	**4.61 (2.99 - 7.11)**	**61.74 (30.17 - 126.36)**	**25.35 (14.10 - 45.61)**
Female (*Ref: Male)*	1.00	**0.61 (0.43 - 0.88)**	1.01 (0.65 - 1.55)	**0.59 (0.42 - 0.84)**
Urban location *(Ref: Rural)*	1.00	1.05 (0.76 - 1.44)	**1.91 (1.24 - 2.94)**	0.76 (0.53 - 1.08)
Education *(Ref: None/Primary)*				
Secondary education	1.00	0.82 (0.61 - 1.10)	1.39 (0.92 - 2.11)	0.92 (0.68 - 1.26)
Tertiary education	1.00	**2.45 (1.37 - 4.38)**	**5.59 (2.91 - 10.73)**	**2.52 (1.48 - 4.28)**
Currently drinks alcohol *(Ref: Not current drinker)*	1.00	0.83 (0.58 - 1.17)	1.11 (0.72 - 1.70)	**0.58 (0.41 - 0.82)**
Currently smokes *(Ref: Not current smoker)*	1.00	0.98 (0.62 - 1.55)	**1.68 (1.04 - 2.72)**	1.39 (0.94 - 2.06)
BMI *(Ref: Normal weight)*				
Underweight	1.00	0.89 (0.43 - 1.86)	1.96 (0.87 - 4.42)	**0.49 (0.28 - 0.87)**
Overweight/Obese	1.00	1.18 (0.83 - 1.68)	**2.90 (1.76 - 4.79)**	**3.93 (2.85 - 5.43)**

Note: Class 1 (HIV, Hypertension & Anaemia) is the reference category. Bold values represent p <0.05

Discussion

Summary of main findings

We examined the profile of multimorbidity in South Africa and found that women made up 70% of the multimorbid population. Multimorbidity also occurred across all age groups in our sample. We found extremely high levels of hypertension in this sample. This study identified four latent classes among the multimorbid in South Africa.

Nearly 40% of the multimorbid population belonged to the *HIV, Hypertension and Anaemia* class. This is a significant finding, showing the large overlap of chronic infectious and NCDs in South Africa. The co-occurrence of HIV, hypertension and anaemia is not well documented, although one Tanzanian study noted the high prevalence of anaemia, hypertension and undernutrition among PLWH. They also noted that PLWH co-morbid with anaemia had higher mortality rates.[72] Individually, HIV and anaemia, as well as HIV and hypertension have been well studied. For example, the prevalence of anaemia among PLWH is known to be high in developing countries.[73] HIV infection can result in haematological complications such as anaemia which ART can be beneficial for reducing, except for zidovudine-based ART regimens which worsens the condition.[73] It is estimated that a quarter of PLWH also have hypertension, with the prevalence being higher in ART-experiencing patients.[74] HIV and hypertension tend to be comorbid due to traditional hypertension risk factors, HIV-specific factors and the effect of ART.[75] The disease cluster *HIV, Hypertension and Anaemia* needs further exploration to determine whether it is preventable, how ART regimens effect the development of these disease and how it affects adherence to ART and quality of life for PLWH.

Approximately, 24% of the multimorbid population belonged to the *Anaemia and Hypertension* class. This disease combination was also identified in a rural South African cohort.[24] However, why these diseases co-occur is less well understood. A study investigated the relationship between hypertension, anaemia and pulse pressure using the Korea National Health and Nutrition Examination Survey and found that while pulse pressure and hypertension were related; the relationship between anaemia and hypertension was confounded by waist measurement and BMI.[76] This is another disease cluster requiring further investigation.

The remaining two disease classes were more probable as they are commonly recognised as being co-morbid. The *Cardiovascular* class members had high probabilities of hypertension; with

moderate probabilities of high cholesterol, heart disease and diabetes. The smallest class (17%) in the multimorbid population was *Diabetes and Hypertension*. Diabetes and hypertension share common aetiologies and disease mechanisms (e.g. genetic and environmental factors, obesity, inflammation, oxidative stress, insulin resistance and physical activity).[77] Though these disease combinations are more well known, whether people are receiving appropriate integrated care for these disease conditions remain a concern.

We also considered the influence of sociodemographic variables and lifestyle risk factors on class membership. Tobacco smokers were more likely to belong to the *Cardiovascular-related* class which makes sense given that smoking is a risk factor for many diseases in that class. Smoking may have also been a factor in the *Diabetes and Hypertension* class but the findings were not significant, possibly due to the small sample size. The effect of alcohol consumption was less clear but it appears alcohol consumption may have been common in the reference class (which was likely younger than the other classes due to the dominance of HIV). Being either overweight or obese increased the probability of belonging to the *Cardiovascular* and *Diabetes and Hypertension* classes. This is also realistic given that the members of the classes were dominated by HIV and anaemia, and may have been slimmer.

Strengths and limitations of this study

Our study is one of a few studies to use LCA to determine multimorbidity patterns in the South African general population and to our knowledge, is the only study to include chronic infectious diseases such as HIV and TB. We also included younger people in our analysis which is useful in investigating disease burden across different age groups.

The data used in this analysis was limited to the available data from the original survey. The analysis included certain self-reported disease conditions (e.g. bronchitis/COPD, heart disease, high cholesterol, stroke and TB); which may have led to under-reporting as people could be unaware that they have a disease.

Comparison with existing literature

To our knowledge, two studies have used LCA locally to determine common disease clusters.[48, 78] Chidumwa *et al.*[48] analysed the 2014/2015 Study on global AGEing (SAGE) in people 45 years and older. The LCA identified three classes: (a) minimal multimorbidity risk (83%), (b) concordant multimorbidity (hypertension and diabetes – 11%) and, (c) discordant multimorbidity (angina, asthma, chronic lung disease, arthritis, depression - 6%). Bayes-Marin *et al.* [78] used baseline SAGE data in people aged 50 years and older and grouped South Africa with Ghana to represent the African region. The LCA identified three classes: (a) *cardio-metabolic* class, (b) *respiratory-mental-articular* class, and (c) *healthy* class. Our study differed to both studies in several ways - we excluded people without multimorbidity, we included younger individuals and we included chronic infectious disease conditions such as HIV.

Implications for future research or clinical practice

First, our findings are important for service delivery in South Africa and affirms that integrated care is immediately needed. The largest multimorbid disease class identified in this study was HIV, hypertension and anaemia – a mixture of chronic infectious diseases and NCDs. This overlap of chronic infectious and NCD burden highlights that HIV cannot be treated in a silo.

Second, the burden of hypertension needs to be addressed urgently. Hypertension was present in our multimorbid population, even at young ages. While South Africa has policies for the major NCD risk factors (tobacco smoking, unhealthy diets, harmful use of alcohol and physical inactivity), implementation is a problem.[79] We have also shown that lifestyle risk factors are associated with disease class membership and reduction in these factors may help prevent future epidemics of multimorbidity.

Third, we have highlighted disease clusters that are not well researched. More studies are needed to assess whether disease associations are spurious, a result of interactions or similar biological pathways. We also need an understanding of whether these diseases are related to medication and whether alternative medication could avert the co-occurrence of disease. These disease clusters could also be used to advocate for better screening and management of patients.

Lastly, we have shown that HIV is an important part of multimorbidity in South Africa. Where possible, it should be included in research. Just as service delivery should not occur in a silo, research also needs to be integrated to uncover realities on the ground.

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Chapter 6. Analysis of the 2017 South African National HIV Prevalence, Incidence, Behaviour and Communication Survey

OVERVIEW OF CHAPTER

This chapter presents the findings of two in-depth analyses using the 2017 South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (SABSSM). This survey provides HIV data, which allowed for comparison with the 2016 South African Demographic Health Survey (SADHS). The analysis revealed a lower prevalence of multimorbidity when compared to the 2016 SADHS. It also identified seven distinct disease classes in the population. The largest disease class was found to be *Diabetes and Hypertension* followed by *HIV and Hypertension*. This shows that the South African multimorbid population has diseases that are considered concordant (i.e. two related NCDs) and discordant (i.e. an infectious disease and an NCD).

In this chapter, co-morbidities among older people living with HIV were also investigated. Since access to antiretroviral treatment (ART) has improved, the life expectancy of people living with HIV (PLWH) has increased. This has led to an increase in the number of older adults living with HIV, which may have implications for the health system. Approximately, 44% of people with HIV aged 50 years and older had at least one other disease (compared to 13.0% of people with HIV under 50 years of age). HIV-infected individuals over the age of 50 years had five times the odds of having a co-morbidity compared to those under 50 years of age. Women and people living in urban areas also had higher odds of having an HIV co-morbidity. Hypertension was prevalent among older people with HIV - confirming the shift towards chronic co-morbidities usually associated with ageing.

Articles

- **Roomaney RA**, van Wyk B, Cois A, Pillay-van Wyk V. Multimorbidity Patterns in a National HIV Survey of South African Youth and Adults. *Frontiers in Public Health.* 2022;10. https://doi.org/10.3389/fpubh.2022.862993
- **Roomaney RA**, van Wyk B, Pillay-van Wyk V. Aging with HIV: Increased Risk of HIV Comorbidities in Older Adults. *Int J Environ Res Public Health.* 2022;19(4):2359. https://doi.org/10.3390/ijerph19042359

6A. Article: Multimorbidity Patterns in a National HIV Survey of South African Youth and Adults.

Abstract

Introduction: Information pertaining to multimorbidity is frequently informed by studies from high income countries and it is unclear how these findings relate to low and middle income countries, where the burden of infectious disease is high. South Africa has a quadruple burden of disease which includes a high HIV prevalence and a growing burden of non-communicable diseases. This study aimed to analyse the prevalence and patterns (disease classes or clusters) of multimorbidity in South Africa.

Methods: A secondary analysis of individuals over the age of 15 years who participated in the Fifth South African National HIV Prevalence, Incidence, Behavior and Communication Survey, 2017 (SABSSM 2017) was done. Six disease conditions were identified in the analysis (cancer, diabetes, heart disease, hypertension/high blood pressure, tuberculosis, and HIV). Chi-square tests were used to test for the differences in disease prevalence by sex. Common disease patterns were identified using a latent class analysis.

Results: The sample included 27,896 participants, of which 1,837 had comorbidity or multimorbidity. When taking population-weighting into account, multimorbidity was present in 5.9% (95% CI: 5.4–6.4) of the population The prevalence of multimorbidity tended to be higher among females and increased with age, reaching 21.9% in the oldest age group (70+). The analyses identified seven distinct disease classes in the population. The largest class was "Diabetes and Hypertension" (36.3%), followed by "HIV and Hypertension" (31.0%), and "Heart disease and Hypertension" (14.5%). The four smaller classes were: "HIV, Diabetes, and Heart disease" (6.9%), "TB and HIV" (6.3%), "Hypertension, TB, and Cancer" (2.8%), and "All diseases except HIV" (2.2%).

Conclusion: As the South African population continues to age, the prevalence of multimorbidity is likely to increase which will further impact the health care system. The prevalence of multimorbidity in the population was relatively low but reached up to 20% in the oldest age groups. The largest disease cluster was the combination of diabetes and hypertension; followed by HIV and hypertension. The gains in improving adherence to antiretrovirals amongst treatment-

experienced people living with HIV, should be expanded to include compliance with lifestyle/behavioural modifications to blood pressure and glucose control, as well as adherence to anti-hypertension and anti-diabetic medication. There is an urgent need to improve the early diagnosis and treatment of disease in the South African population.

Introduction

Multimorbidity is defined as the co-existence of two or more chronic diseases in one individual.[1] While it is not easy to determine the number of people living with multimorbidity, a large proportion of the global population are believed to be affected by multimorbidity.[2] Multimorbidity negatively impacts individuals, health workers and the health system as a whole.[3] At the individual level, people with multimorbidity have reduced chances of survival [4, 5], lower quality of life [6-8], increased healthcare utilization [9, 10] and tend to experience polypharmacy.[11] In 2018, the Academy of Medical Sciences [12] acknowledged that multimorbidity was a global research priority as populations are experiencing multimorbidity on a large scale and predictions that the prevalence of multimorbidity is rising. They also highlighted the inadequate nature of research into multimorbidity, especially in low and middle income countries (LMICs).

LMICs are underrepresented in studies of multimorbidity,[13, 14] even though the prevalence is estimated to be as high as 30%.[2] Countries such as South Africa have a complex disease burden consisting of both communicable and non-communicable diseases.[15] South Africa has a high HIV prevalence with an estimated 7.7 million people living with HIV in 2019.[16] In addition, due to the availability of antiretroviral medication, people living with HIV (PLWH) are living to older ages and developing chronic diseases usually seen among older people.[17] The burden of non-communicable diseases (NCDs) is also increasing, partly attributed to a transition away from traditional food and towards a 'western diet' (i.e. more energy-dense, processed foods, more added sugar, fat and salt),[18] reductions in physical activity [19] and general ageing of the population.[20] These risk factors left unchecked, together with a challenging socioeconomic environment characterised by poverty, high unemployment and alcohol and substance abuse, could lead to devastating increases in the incidence of NCDs.[21] As the epidemics of NCDs and HIV

continue to collide,[22] it is important to gain insight into the extent of multimorbidity and the types of multimorbidity present.

Due to the high HIV prevalence in South Africa, a national HIV survey is undertaken approximately every five years. This survey aims to describe trends in prevalence and incidence of HIV, as well as to monitor other important self-reported health and behavioural indicators. In this paper, we report on the prevalence of multimorbidity and common disease patterns in the adult South African population from a secondary analysis of the Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (SABSSM 2017).

Materials and methods

Sample and data collection

The nationally representative survey aimed to provide surveillance information on HIV infection and behaviour, to evaluate progress towards the South African National HIV, AIDS and STI Strategic Plan for 2012–2016, and to provide data used for HIV indicators for national and international bodies.[23] The 2017 SABSSM survey was a cross-sectional, population-based household survey that used multi-stage stratified random cluster sampling.[23] The survey used the 2015 national sampling frame developed by Statistics South Africa and drew 1000 small area layers, disproportionally allocated across province.[23] Within the small areas, 15 visiting points were randomly selected and all individuals in the household were invited to participate.[23] Sampling and design details have been described elsewhere.[23]

Fieldworkers collected data from participants. For participants aged 15 years and older, a questionnaire was used that focused mostly on sexual health and behaviours. This questionnaire also contained self-report questions about the presence of several diseases. For these self-reported disease conditions, participants were asked '*Do you currently have any of the following illnesses?''* (Supplementary Table 1). In addition, participants were asked to provide a blood sample to test for HIV status. The blood sample was taken using a finger-prick. These samples were then tested for the presence of the virus at accredited laboratories.[23] An algorithm was used with three different enzyme immunoassays (EIAs) whereby if samples tested positive for the HIV during the first two enzyme immunoassays (Roche Elecys HIV Ag/Ab assay, Roche Diagnostics, Mannheim, Germany; and Genescreen Ultra HIV Ag/Ab assay, Bio-Rad Laboratories, California, USA), a

third nucleic acid amplification test was done (COBAS AmpliPrep/Cobas Taqman HIV-1 Qualitative Test, v2.0, Roche Molecular Systems, New Jersey, USA).[23] The results of these tests were then interpreted.[23]

Variables of interest

We considered participants to have multimorbidity if they reported more than one disease condition. We included six disease conditions in our assessment: five were self-report diseases (e.g. cancer, diabetes, heart disease, hypertension/high blood pressure, TB) and one was the result of a biomarker (HIV status). Although HIV was included in the list of self-reported diseases, we opted to use the result of the HIV biomarker. Of the 27 896 youth and adults that responded to the questionnaire, only 69.9% (n=19 511) had results for HIV testing. Those that did not provide blood specimens or had invalid HIV tests (n =8 385) were set to missing for the HIV variable.

Analysis

The statistical analysis was done using STATA 15.0 software (Stata Corporation, College Station, Texas, USA). The STATA survey set ('svy') suite of commands was used to account for complex survey design and the data were weighted using the HIV specimen survey weights. The latent class analysis was conducted using the LCA Stata Plugin which also accounts for complex survey design.[24, 25]

An index variable was created to summarize the number of diseases present in each individual. Unweighted sample data were explored using frequency tables. Bivariate associations were assessed using Pearsons's chi-square tests to test for differences among the sexes. The Wilcoxon Rank Sum Test was used to calculate the median age between the sexes.

A sub-analysis was conducted for only people with multimorbidity, to identify the types of disease clustering present. Disease clustering was assessed with LCA; a statistical procedure used to identify sub-groups or classes within populations.[26] The LCA followed a process as described by Weller, Bowen [26]. The six disease conditions were included as indicator variables and each disease condition was coded as a binary variable (i.e. disease present or disease absent). To identify latent classes, we first estimated a one-class model and then added additional classes to compare the relative fit [26]. We assessed the relative fit of models by comparing the values of a series of information indices (namely the Bayesian information criterion (BIC) [27], the adjusted BIC

(aBIC)[28] and the Akaike Information Criterion (AIC)[29]), with lower values indicating a better fit [30]. Once the appropriate model was selected, individuals were assigned to the class with the highest posterior probability.

Ethical Considerations

This study was a secondary data analysis of an anonymized dataset. The anonymized dataset was obtained from the Data Curation Services at the Human Sciences Research Council with necessary permissions. Ethics clearance to conduct this study was granted by the Biomedical Research Ethics Committee of the University of the Western Cape (BM20/5/8).

Results

Sample description (Unweighted data)

The sample consisted of 27 896 participants: with more females (58.9%) than males (Table 6A-1). The median age of participants was 33 years (IQR 22 – 50 years) with females tending to be slightly older than males (34 versus 31 years of median age, $p<0.001$). A slightly larger proportion of participants lived in urban areas (54.5%) compared to rural areas. The sample was mostly from KwaZulu-Natal (33.9%), Gauteng (15.6%) and Mpumalanga (12.9%) provinces.

Less than a third of participants in the sample were employed (29.5%); with most being either unemployed, unable to work due to a disability or students. Males were significantly more likely to be employed compared to females ($p<0.001$). Approximately 67% of the sample had completed secondary education. In the sample, other than TB, all disease conditions were more prevalent in females than males (Supplementary Table 2). The prevalence of multimorbidity in the sample was 6.6% (Supplementary Table 3).

Table 6A-1. Description of sample by sex (unweighted).

Variable	% (n)			*p*-value*
	Total (N=27 896)	Male (n= 11 456)	Female (n= 16 422)	
Age (Median years and IQR)	33 (22 – 50)	31 (21 – 48)	34 (23 – 51)	<0.001
Urban location	54.5 (15 203)	55.5 (6 359)	53.8 (8 839)	0.005
Province				<0.001
Western Cape	7.6 (2 107)	7.7 (885)	7.4 (1 222)	
Eastern Cape	7.4 (2 074)	7.3 (831)	7.6 (1 243)	
Northern Cape	5.5 (1 522)	5.9 (679)	5.1 (839)	
Free State	4.4 (1 226)	4.6 (527)	4.3 (698)	
KwaZulu-Natal	33.9 (9 469)	31.3 (3 590)	35.8 (5 874)	
North West	6.6 (1 826)	6.8 (779)	6.4 (1 046)	
Gauteng	15.6 (4 339)	16.5 (1 885)	14.9 (2 453)	
Mpumalanga	12.9 (3 598)	13.9 (1 589)	12.2 (2 006)	
Limpopo	6.2 (1 735)	6.0 (691)	6.3 (1 041)	
Education level				<0.001
Primary or less	20.6 (3 832)	18.9 (1 433)	21.8 (2 399)	
Secondary complete	66.8 (12 400)	67.3 (5 097)	66.4 (7 303)	
Tertiary	12.6 (2 344)	13.8 (1 047)	11.8 (1 297)	
Employed	29.5 (7 793)	37.6 (4 092)	23.8 (3 701)	<0.001

*Chi-square tests used, and Wilcoxon rank-sum test used for Age variable. Note: There were 14 observations with missing data for sex.

Disease prevalence in the population (weighted data)

All percentages from this point forward are weighted unless stated otherwise. HIV was estimated to be the most prevalent disease in the population (19.1%, 95% CI: 17.9 – 20.4) (Table 6A-2). Hypertension was estimated to be the most second most common disease (14.3%, 95% CI: 13.5 – 15.2), followed by diabetes (4.4%, 95% CI: 4.0 – 4.9). Most of the diseases were more prevalent in females compared to males; the only exception was TB which was more common in males (1.3%, 95% CI: 1.0 – 1.8) than females (1.0%, 95% CI: 0.8 - 1.4). The prevalence of self-reported disease conditions may have been under-estimated due to participants not knowing whether they had a disease or not wanting to disclose their disease status. For example, among individuals with non-missing HIV test, the estimated prevalence of biomarker HIV (19.1%) was more than double the prevalence of self-reported HIV (6.6%).

Table 6A-2. Estimated prevalence of single disease conditions in South Africa (weighted).

Disease condition	Weighted % (95% CI)		
	Total	Male	Female
Cancer	0.6 (0.5 - 0.8)	0.4 (0.3 - 0.7)	0.8 (0.6 - 1.1)
Diabetes	4.4 (4.0 - 4.9)	3.7 (3.2 - 4.3)	5.0 (4.5 - 5.6)
Heart disease	2.2 (1.8 - 2.5)	1.6 (1.3 - 2.1)	2.6 (2.1 - 3.2)
HIV	19.1 (17.9 - 20.4)	14.3 (12.9 - 15.9)	23.1 (21.7 - 24.7)
Hypertension	14.3 (13.5 - 15.2)	10.4 (9.4 - 11.5)	17.8 (16.7 - 19.0)
TB	1.2 (1.0 - 1.4)	1.3 (1.0 - 1.8)	1.0 (0.8 - 1.4)

With the exception of TB and cancer, the estimated prevalence of disease conditions varied largely by age group (Figure 6A-1). Hypertension, diabetes and heart disease all increased in the older age groups. HIV followed a different pattern and peaked in the 30 – 49-year age group.

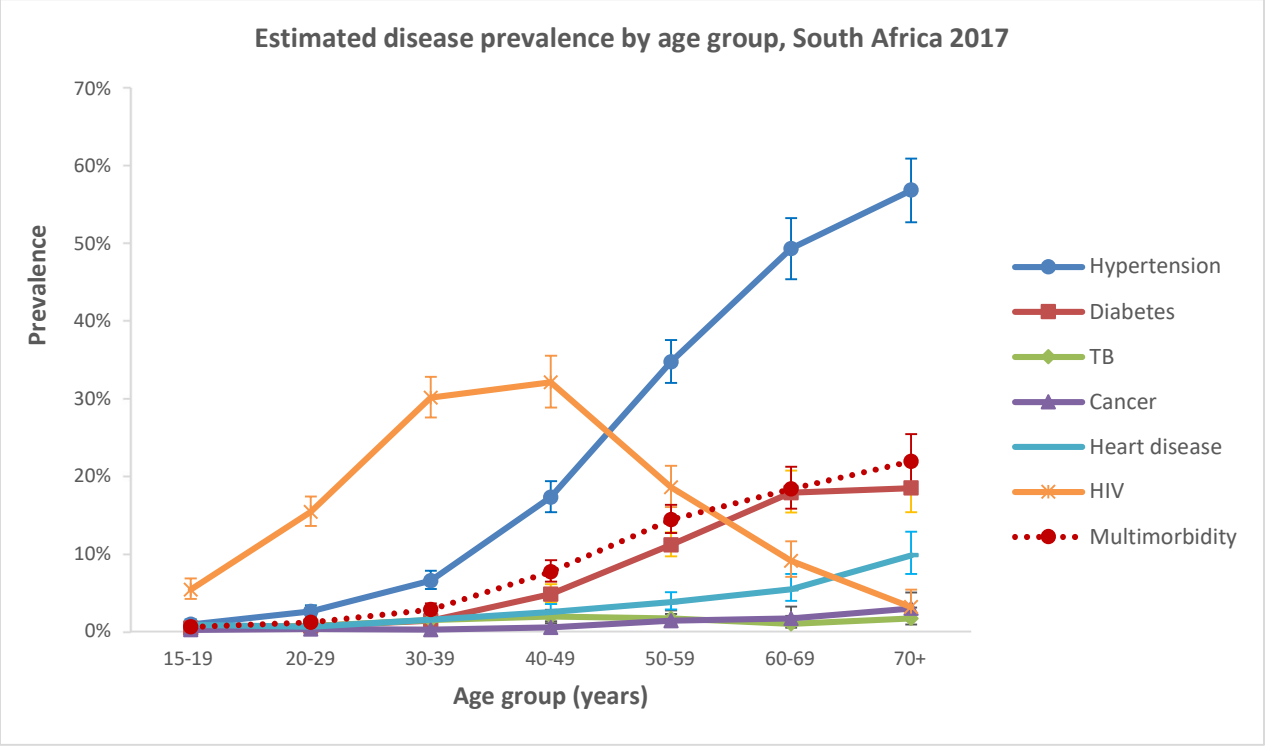

Figure 6A-1. Estimated disease prevalence by age group in South Africa, 2017 (weighted).

The number of diseases present in an individual ranged from zero to six (Table 6A-2). Of the diseases assessed in this study, the majority of population had no diseases (71.9%, 95% CI: 70.8 – 73.1). There were fewer females with no diseases (65.9%, 95% CI: 64.3 – 67.4) compared to males with no diseases (78.6, 95% CI: 77.3 – 67.4). A further 22.8% (95% CI: 21.8 – 23.7) of the population had one disease. Multimorbidity was present in 5.9% (95% CI: 5.4 – 6.4) of the population. It was more prevalent in females (7.5%, 95% CI: 6.8 – 8.2) than males (4.1%, 95% CI: 3.6 – 4.7).

The prevalence of multimorbidity was low in younger age groups for both males and females (Supplementary Figure 1). It increased in the older age groups, reaching 17.0% (95% CI: 15.6 – 18.5) in people over 50 years. It peaked in the 70+ years age group at 21.9% (95% CI: 18.8 – 25.4).

Table 6A-3. Estimated number of diseases in individuals by sex (weighted).

Number of diseases	Weighted % (95% CI)		
	Total	Male	Female
No diseases	71.9 (70.8 - 73.1)	78.6 (77.3 - 79.9)	65.9 (64.3 - 67.4)
1 disease	22.2 (21.2 - 23.2)	17.3 (16.1 - 18.5)	26.7 (25.4 - 28.0)
2 diseases	4.9 (4.5 - 5.4)	3.5 (3.0 - 4.0)	6.3 (5.7 - 6.9)
3 diseases	0.7 (0.6 - 0.9)	0.4 (0.3 - 0.6)	1.0 (0.8 - 1.3)
4 diseases	0.1 (0.0 - 0.2)	0.0 (0.0 - 0.1)	0.1 (0.1 - 0.3)
5+ diseases	0.1 (0.1 - 0.2)	0.2 (0.1 - 0.4)	0.1 (0.0 - 0.2)
Multimorbidity (≥ 2 diseases)	**5.9 (5.4 - 6.4)**	**4.1 (3.6 - 4.7)**	**7.5 (6.8 - 8.2)**

Disease patterns in the multimorbid population

For the subsequent analysis, only people with multimorbidity were included (n = 1 837). The mean age of the population with multimorbidity was 54 years. Most of the population with multimorbidity were female (66.7%, 95% CI: 63.1 – 70.1).

Among those with multimorbidity, hypertension (87.1%, 95% CI: 84.1 – 89.7) was the most common disease condition (Figure 6A-2). Just more than half had diabetes (51.3%, 95% CI: 47.0 – 55.5) and just less than half (49.7%, 95% CI: 45.2 – 54.1) had HIV. The disease prevalence was

similar among males and females with multimorbidity. However, hypertension and HIV were marginally more prevalent among females and, diabetes, TB and cancer were more prevalent among males.

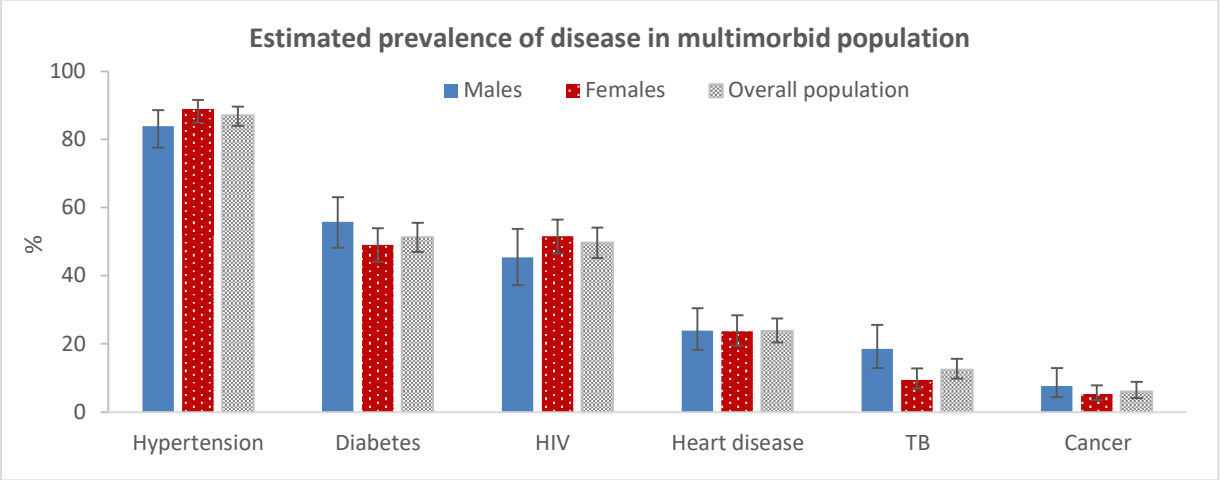

Figure 6A-2. Estimated disease prevalence in the multimorbid population by sex, South Africa 2017.

Table 6A-4 shows a comparison of fit statistics for models with different numbers of classes, ranging from two to eight. The BIC, adjusted-BIC and AIC were minimal for a seven class model and hence a seven class model was chosen.

Table 6A-4. Fit statistics for LCA models with different numbers of classes.

	Latent class analysis models						
	2 class model	**3 class model**	**4 class model**	**5 class model**	**6 class model**	**7 class model**	**8 class model**
Design effect	1.9	1.5	1.4	1.3	1.3	1.0	0.9
DF	50.0	43.0	36.0	29.0	22.0	15.0	8.0
Entropy R-squared	0.8	0.8	0.9	0.9	0.9	0.9	0.9
Entropy Raw	128.3	220.7	111.2	196.7	300.0	155.5	188.5
Adjusted BIC	1037.7	736.3	753.7	479.8	464.4	368.0	386.7
BIC	1079.0	799.8	839.5	587.8	594.7	520.5	561.4
AIC	1012.6	697.8	701.6	414.3	385.4	275.5	280.6
G-squared	986.6	657.8	647.6	346.3	303.4	179.5	170.6
Log Likelihood	-3084.2	-2919.8	-2914.7	-2764.0	-2742.6	-2680.6	-2676.2

The classes were named based on the diseases with the highest prevalence in that class. The model identified the following membership, latent classes, from largest to smallest: 'Diabetes and Hypertension' (36.3%), 'HIV and Hypertension' (31.0%), 'Heart disease and Hypertension' (14.5%), 'HIV, Diabetes and Heart disease' (6.9%), 'TB and HIV' (6.3%), 'Hypertension, TB and Cancer' and 'All diseases except HIV' (2.2%) (Figure 6A-3). Hypertension was common among most of the disease classes.

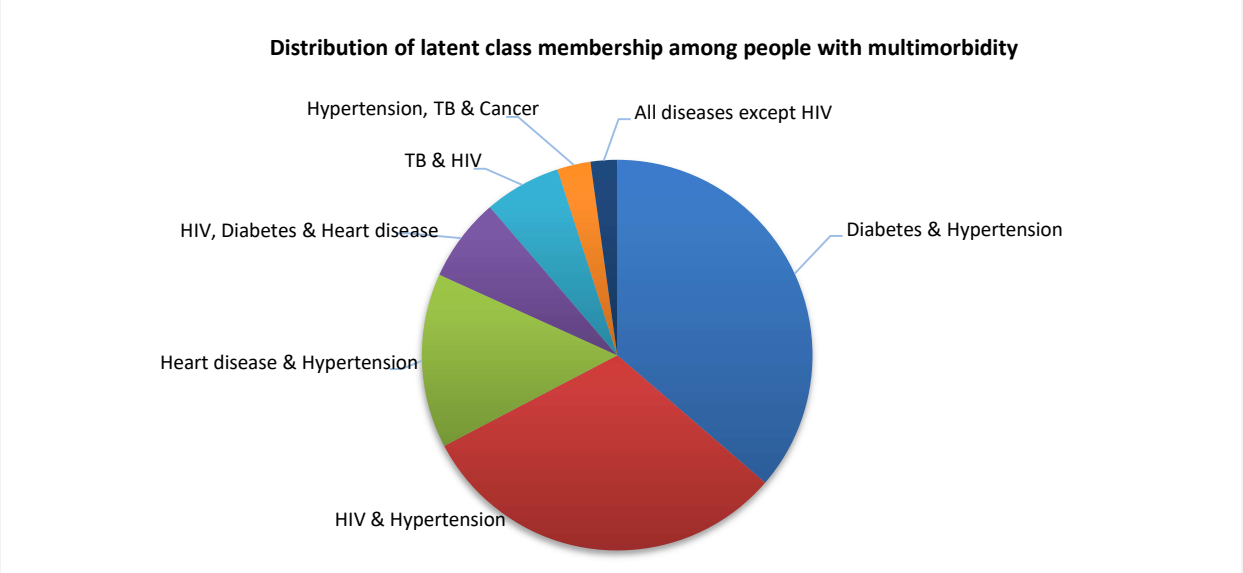

Figure 6A-3. Distribution of latent class membership for people with multimorbidity

Table 6A-5 displays the item response probabilities for each disease by latent class. The largest class among multimorbid people, 'Diabetes and Hypertension', was characterised by high probabilities of having both diabetes and hypertension (100%). Similarly, the 'HIV and Hypertension' class was also a large class among people with multimorbidity and was characterised by a high probability of both HIV and hypertension (100%). The third largest class, 'Heart disease and Hypertension' had high probabilities of heart disease and hypertension (100% and 97%, respectively).

The remaining four classes were small and, together, only accounted for 18.2% of the multimorbid population. The 'HIV, Diabetes and Heart disease' class had a high probability of having HIV (90%) and smaller probabilities of diabetes and heart disease (54% and 51%, respectively). The 'TB and HIV' class had high probabilities of TB and HIV (100% and 99%, respectively). The 'Hypertension, TB & Cancer' class was characterised by a 100% probability of hypertension and

smaller probabilities of TB and cancer (63.0% and 49%, respectively). The smallest latent class had high probabilities of all diseases except for HIV (i.e. high probabilities for hypertension, diabetes, heart disease, TB, cancer). The standard errors for the membership probabilities and disease item response probabilities can be found in Supplementary Tables 4 and 5.

Table 6A-5. Item response probabilities by disease for each latent class.

Latent class name	Probability of disease condition by class					
	Hypertension	Diabetes	HIV	Heart disease	TB	Cancer
1. Diabetes & Hypertension	**1.00**	**1.00**	0.00	0.02	0.01	0.02
2. HIV & Hypertension	**1.00**	0.15	**1.00**	0.07	0.06	0.03
3. Heart disease & Hypertension	**1.00**	0.30	0.01	**1.00**	0.00	0.01
4. HIV, Diabetes & Heart disease	0.04	**0.54**	**0.90**	**0.51**	0.00	0.07
5. TB & HIV	0.01	0.01	**0.99**	0.11	**1.00**	0.00
6. Hypertension, TB & Cancer	**1.00**	0.01	0.01	0.00	**0.63**	0.49
7. All diseases except HIV	**1.00**	**1.00**	0.03	**1.00**	**0.98**	**0.96**

Note: Bold figures represent probabilities higher than 50%.

Discussion

This study indicated that while there was a fairly low prevalence of multimorbidity among South African youth and adults, the prevalence of multimorbidity increased with age, as is consistent with other studies.[2, 31] The prevalence of multimorbidity among older individuals is concerning, especially given that South Africa's population of over-60s is expected to double between 2012 and 2050.[32] This highlights the urgent need for integrated care in the country. Integrated care is considered an essential component in the United Nations Decade of Healthy Ageing (2021-2030).

Women had a higher prevalence of multimorbidity compared to men, and this was true across age groups. This gender differential has been found in other local [31] and international studies.[2, 33, 34] The differential could be attributed to women being more likely to share their conditions in self-reports; which could be attributed to a mix of biological factors and societal gender inequalities which contribute to the size of the gender gap in self-reported health.[35] Women may also be more likely to know their health status as they tend to have higher healthcare utilisation

compared to men.[36, 37] These gender differentials need to be further unpacked to provide insight on how to make health systems more responsive to the needs of men and women with multimorbidity.

The prevalence of multimorbidity estimated in this study is lower than what was estimated by a meta-analysis of multimorbidity prevalence for LMICs (30%).[2] It was also lower when compared to another South African national survey. In the 2007 WHO Study on global AGEing and adult health survey [38] the multimorbidity prevalence was estimated to be 63.4% in people over 50 years of age whereas in our study the prevalence was far lower, around 17% in people over 50 years of age. Compared to the 2003 World Health survey, [39] we estimated a similar prevalence in 18-49-year olds (3.0% versus 5.0%), but a lower prevalence in older ages (50 – 64 year olds: 14.5% versus 21.6%, 65+ year age groups: 19.8% versus 30.1%). However, the estimates of a low multimorbidity prevalence are similar to findings from another national panel survey, the 2008 and 2012 National Income Dynamic Survey.[40, 41] This highlights the complexity in trying to compare multimorbidity prevalence estimates across studies. These studies vary in the number of diseases evaluated, the different disease conditions included and the method of data collection used.

The lower prevalence of multimorbidity observed in this survey could be due to various factors. Firstly, the reported prevalence from self-reported disease conditions was low. This is especially true for hypertension, which is reported to have a higher prevalence in the country (46% women and 44% men) versus 14% in this survey.[42] Similarly, our estimate for diabetes was 4%, while a recent systematic review reported the prevalence of diabetes in South Africa to be close to 15% for people aged 25 years and older.[43] The lower multimorbidity prevalence may be linked to how questions about self-reported disease conditions were asked. In this survey, participants were asked if they 'currently' had the disease in question. In many other surveys, participants are asked if they have 'ever' been diagnosed with a set of diseases. The incorporation of 'current' disease is likely to be more accurate compared to those who have 'ever' been diagnosed. For example, people that have been diagnosed with cancer during their lifetime may have recovered and may be considered disease-free. For future surveys that are conducted, we recommend that participants are asked if they have ever had a disease and whether they currently have the disease. This should lead to more accurate estimations of multimorbidity and allow for data to be more easily compared

between surveys, however, problems with underreporting and under-diagnosis will most likely continue to persist in self-report data.

We had a mix of concordant and discordant multimorbidity disease latent classes in our study. Concordant multimorbidity tends to be similar in its origin or aetiology, whereas discordant multimorbidity is when the co-existing disease conditions tend to be unrelated.[12] A local study defined concordant multimorbidity as hypertension or diabetes with other cardiometabolic conditions (dyslipidemia, angina).[44] They determined discordant conditions to be HIV with any of the following: hypertension/ diabetes/ angina/ dyslipidemia. Using their conceptualization, we would consider the following classes in our study to be concordant: 'Diabetes and Hypertension' and 'Heart disease and Hypertension.' The largest disease class in this study was the combination of hypertension and diabetes. The clustering of diabetes and hypertension is well known and has been termed the 'bad companions.'[45] Their pathophysiological trajectories are interlinked.[45] The 'HIV and Hypertension' class is an example of discordant multimorbidity and was the second largest class in our analysis. These diseases frequently co-occur, especially in ART experienced individuals.[46] Also, this disease combination is predicted to increase as more people access ART and initiate earlier; thereby improving survival rates.[46] The effect of discordant versus concordant multimorbidity on treatment outcomes is unclear.

To reduce, detect and manage multimorbidity a multifactorial approach is required. The South African government has made some progress regarding the management of multimorbidity, as exemplified in the release of the South African National Department of Health Adherence Guidelines for HIV, TB and NCDs in 2016.[47] This policy and service delivery guidelines seek to address issues in non-adherence to long-term therapies amidst the expansion of ART programmes and the rising burden of NCDs.[47] Certain aspects of the programme implementation related to this policy have been positively evaluated.[48, 49] Another part of their strategy was to focus on linkage to care and to implement screening activities to identify diseases early for intervention. These guidelines complement other South African guidelines and strategies that have been put in place to reduce disease burdens. These include the Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2013 -2017,[50] the Strategy for the Prevention and Control of Obesity in South Africa 2015 -2020 [51] and, legislation to decrease sodium levels in the food industry.[52].

Limitations

This study entailed a secondary analysis of survey data and was thus limited to the data reported in the survey. We used a combination of biomarker and self-report data which most likely led to a downward bias in our estimate of multimorbidity prevalence. The prevalence of the self-reported disease conditions was lower than expected compared to other local studies that have used biomarker data. This indicates that participants may have been unaware that they have the disease or may not have disclosed that they have the disease for some other reason. This underestimation of self-reported disease has resulted in a reduced estimate of multimorbidity prevalence in the population. In addition, the number of people that provided blood specimens for HIV testing was lower than the number of people that completed the questionnaire and answered questions about self-reported disease conditions. We also included only a few disease conditions which may have also led to an underestimation in the prevalence of multimorbidity.

Conclusion

This is the first analysis of multimorbidity and disease patterns from a nationally representative HIV survey of South African youth and adults. This study found a relatively low level of multimorbidity prevalence amongst youth and adults in South Africa. The prevalence of multimorbidity increased with age and was also higher in females compared to males. We identified seven classes (sub-groups) for those with multimorbidity, and there was a mix between concordant and discordant disease conditions. The 'Diabetes & Hypertension-related' class was the largest, indicating that far more needs to be done to reduce the common causal factors for these diseases. This is an example of concordant multimorbidity; which indicates that they share common risk factors which can be targeted for intervention. The second-largest class was an example of discordant multimorbidity, the combination of HIV and hypertension. Large-scale implementation of the Adherence Guidelines for HIV, TB and NCDs would help to reduce the impact of multimorbidity.

Contribution to the Field Statement

Much of the literature on multimorbidity is focused on chronic diseases in the elderly in high-income countries. However, multimorbidity is also thought to be a problem in low and middle-income countries but the types of diseases that co-occur may differ. Countries like South Africa have large infectious disease burdens and a growing burden of non-communicable diseases. Since antiretroviral drugs are more accessible than they were previously, people with HIV are living longer and developing diseases usually associated with ageing.

This study contributes to fill the knowledge gap regarding prevalence and characteristics of multimorbidity patterns in LMICs. Our analyses of South African data suggest fairly low level of comorbidity in the adult population as a whole, but substantial prevalence in the older age groups. We found seven distinct patterns of diseases in the multimorbid population. Diabetes and hypertension commonly co-occurred and made up the largest disease class, followed by HIV and hypertension. These disease classes show that both concordant and discordant multimorbidity is present in the country. The disease classes could be used to inform health interventions to build on efficiencies in the health system.

Supplementary material

Supplementary material:

https://www.frontiersin.org/articles/10.3389/fpubh.2022.862993/full#supplementary-material

6B. Article: Aging with HIV- Increased risk of HIV comorbidities in older adults.

Abstract

With improved access to antiretroviral treatment (ART), adults with HIV live longer to reach older age. The number of older adults living with HIV is increasing steadily, giving rise to a new population of interest in HIV research and for invigorated considerations in health service delivery and policy. We analyse the profile of comorbidities in older people (50 years and older) living with HIV in South Africa. We conducted a secondary analysis of all individuals over 15 years, who tested HIV positive in the Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017. We conducted multivariate logistic regression to determine the factors associated with having HIV comorbidity using Stata 15.0 software. We entered 3 755 people living with HIV into analysis; of whom 18.3% (n= 688) were 50 years or older. Older adults had four times greater odds (OR= 4.7 [3.1 – 7.0]) of having a HIV comorbidity compared to younger adults. Being female (OR= 1.6 [1.1 -2.4]) and living in an urban area (OR = 2.6 [1.8 - 3.7]) increased the odds of HIV comorbidity. Older adults with HIV require comprehensive health care to deal with multimorbidity, to maximize the benefits gained by advances in HIV therapies.

Introduction

South Africa has a generalized and mature HIV epidemic.[23] In 2017, the national HIV prevalence was estimated at 14%, which translated to approximately 7.8 million people living with HIV (PLWH). South Africa has the largest public antiretroviral therapy programme (ART),[23] with 5.6 million people on ART in 2020.[53] South Africa has made some progress towards achieving The Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets (that by 2020, 90% of all people living with HIV should know their status, that 90% of people diagnosed with HIV infection should receive treatment and that 90% of all people receiving treatment should have viral suppression [54]). In 2020, it was estimated that 92% of PLWH in South Africa knew their status,[53] of which 75% of were on ART, and of which 92% on ART were virally suppressed.[16] It was further estimated that 70% of all PLWH in South Africa were on ART in 2020.[16] It is envisaged that the number of PLWH on ART is likely to continue to grow as the country endeavors to meet ART coverage targets.[55] Improved access to ART, coupled with

advances in ART regimens have enabled PLWH to live longer lives,[56] effectively changing HIV into a life-long chronic condition.[57] It has been noted that South Africa has a quadruple burden of disease,[15] which includes a growing burden of non-communicable diseases (NCDs).[15] A decade prior, researchers were predicting the negative impacts associated with the collision of these two epidemics in South Africa.[22] More recently, studies have found high and overlapping prevalence of disease conditions such as HIV, tuberculosis and NCDs in both community settings [58-60] and health facilities in the country.[61]

Several studies have shown that PLWH have a higher prevalence of multimorbidity and comorbidity compared to the general population due to premature ageing, side effects of ART and biological effects of HIV infection.[62-66] The most prevalent HIV comorbidities are cardiovascular diseases, cancers, diabetes, dyslipidaemia, chronic renal disease and hepatitis B and hepatitis C.[62] Multimorbidity in PLWH drive healthcare costs and number of hospitalizations as shown in a case-control study in France where the mean total cost of hospitalization was 6 times higher in PLWH compared to matched controls.[62]

The number of older adults (aged over 50 years) living with HIV is increasing globally, which naturally leads to an increase in the prevalence of HIV co-morbidities.[67, 68] This increase is mainly due to earlier initiation on ART compared to pre 'Test and Treat' era, which improved chances for survival for HIV populations.[69] The resultant longer duration of ART exposure has also been linked to increased hypertension-risk.[17] [46, 70] In addition, it is reported that HIV infection occur at older ages as well,[71, 72] and such persons may already have developed NCDs. [17, 73]

Older PLWH experience increased prevalences of non-AIDS illnesses such as cardiovascular disease, malignancies, osteoporosis, cognitive impairment, frailty and disability.[74] Another study found that rates of NCDs were higher among older adults with HIV compared to younger adults with HIV.[75] Also, there are still many uncertainties in treating HIV in older adults when the individual has comorbidities.[17] For example, older people with HIV have higher risks of hospitalization due to adverse events from polypharmacy.[76] In general, older adults face additional barriers to care such as patronizing and ageist communication by health care professionals, exclusion from clinical trials and low income associated with retirement.[77]

While the number of older adults living with HIV is expected to increase, little is known about HIV and ageing in low and middle income countries, especially sub-Saharan Africa.[17] Such information is critical for the provision of integrated care for older adults at primary care level in HIV endemic settings. The current paper reports on the profile and patterns of comorbidities in older adults living with HIV in South Africa.

Materials and Methods

Study design and aim

The South African National HIV Prevalence, Incidence, Behaviour and Communication Survey 2017 (SABSSM 2017) is the fifth iteration of the national household survey of HIV that aimed to estimate the HIV incidence and prevalence in a representative sample of South Africans as well as self-reported health conditions and health behaviours.[23] The methods used in the survey are described in full in Simbayi, Zuma [23]. The main aim of the survey was to provide surveillance information for monitoring trends in HIV incidence, prevalence and related behaviours, in addition to describing self-reported disease conditions.

Sample and data collection

All people in South Africa were eligible to participate in SABSSM 2017 survey. The survey employed a multi-stage, stratified random cluster sampling approach to identify eligible households for inclusion. There were several questionnaires aimed at different age groups. Youth and adults were invited to complete a questionnaire and were asked several questions about their health, risk perceptions and behaviours. Participants were asked if they '…*currently have any of the following illnesses*?'. We included five self-reported health conditions for this study: cancer, diabetes, heart disease, hypertension/high blood pressure, Tuberculosis (Table S1). These disease conditions were included based on common co-morbid conditions.[31, 78] If the participant consented to an HIV test, a finger prick was used to obtain a dry blood spot sample. The dry blood spot samples were then transported to accredited laboratories for linked anonymous HIV testing. The samples were tested for HIV antibodies and if the samples tested positive using the first two immunoassays, a third test was done for confirmation.[23]

Ethics considerations

The SABSSM 2017 data was ethically obtained from participants, and described in full here.[23] For the purpose of the current data analysis, access to anonymised data was obtained from the online portal, the HSRC Research Data Service. Ethics clearance for the analysis of secondary data (as part of first author's PhD study) was granted by the Biomedical Science Research Ethics Committee of the University of the Western Cape (BM20/5/8).

Data analysis

Data cleaning and the statistical analysis was conducted using Stata 15.0 software (Stata Corporation, College Station, Texas, USA). The Stata survey set of commands ('svy') was used to account for the complex survey design.

The analysis was restricted to people over the age of 15 years that tested HIV positive. We created an age variable which separated participants into two groups: those aged 15 – 49 years ('under 50s') and those aged 50 years and above ('over 50s'). Among the sample, we also examined the distribution of people who had HIV only and those who had HIV and at least one other disease (i.e. comorbidity). To do so, we created an indicator variable that counted the number of diseases present in each individual (excluding HIV).

We used frequencies to display categorical data. The bivariate associations between age category and other variable were tested using Chi-square tests. A multivariate logistic regression was conducted to test the associations of factors with participants having HIV only, or having HIV and one or more comorbidity. We included factors based on characteristics that are often associated with multimorbidity and the data available.[1] These factors were: age, sex, locality, educational attainment, employment status and smoking status. We estimated the crude odds ratios and then combined factors in a multivariate model. Model checking was done on the unweighted model. We assessed the model for influential observations using the Pearson residuals, deviance residuals and Pregibon's leverage.[79] Crude and adjusted odds ratios are reported with 95% CIs and we considered *p*-values of less than 0.05 to be statistically significant.

Results

Sample description

Of the 27 896 youth and adults that completed the Adult Health Questionnaire, 69.9% (n = 19 511) had results for an HIV test (Figure 6B-1). Of these tested, 19.3% (n = 3 755) were HIV positive. The majority had HIV only (83.4%, n = 3 132).

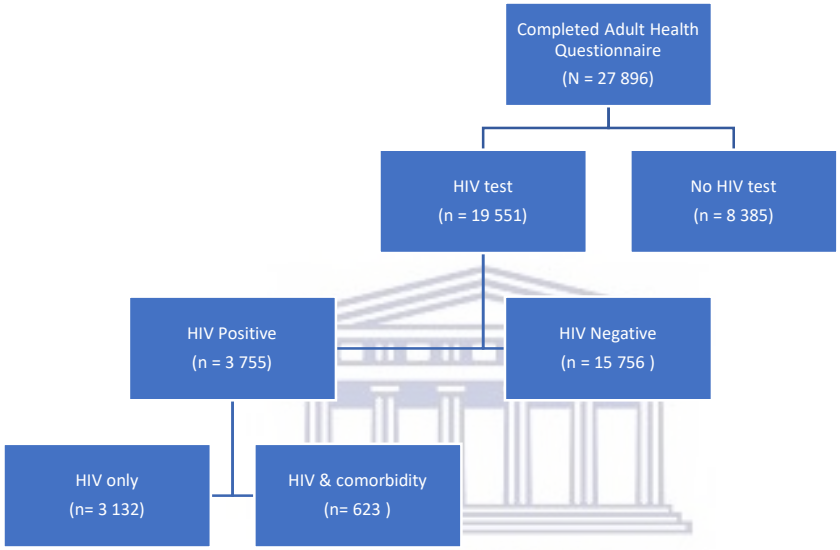

Figure 6B-1. HIV testing in the SABSSM 2017 sample

Table 6B-1 describes the sociodemographic characteristics of the sample population with HIV by age sub-groups (under 50 years versus 50 years and over). Older adults (50 years or older) living with HIV constituted 18.3% (n = 688) of the sample. Most participants were female (73.4%, n = 2 754). Most of the respondents were based in Kwa-Zulu Natal province (38.4%, n = 1 442). Employment was generally low in the sample (27.9%), and it was statistically significantly lower in the older age group compared to the younger age group ($p<0.001$). Most respondents (70.6%) had completed secondary education and the younger group of people had significantly higher levels of educational attainment than the older group of people ($p<0.001$).

Table 6B-1. Sociodemographic characteristics of adults who tested HIV positive by age (under 50 years vs 50 years and older), SABSMM 2017.

Variable	% (n)			*P*-value*
	Total (N= 3 755)	Under 50s (n= 3 066)	Over 50s (n= 688)	
Age (Median years and IQR)	36 (29 – 46)	33 (28 – 40)	56 (53 – 61)	-
Female	73.4 (2 754)	73.9 (2 266)	80.0 (487)	0.115
Urban location	45.6 (1 712)	45.7 (1 402)	45.1 (310)	0.750
Province				**<0.001**
Eastern Cape	7.4 (277)	7.5 (230)	6.8 (47)	
Free State	4.7 (177)	4.2 (130)	6.8 (47)	
Gauteng	13.9 (523)	13.9 (427)	14.0 (96)	
KwaZulu-Natal	38.4 (1 442)	38.6 (1 184)	37.5 (258)	
Limpopo	5.1 (193)	4.5 (137)	8.1 (56)	
Mpumalanga	15.6 (585)	16.0 (490)	13.7 (94)	
Northern Cape	3.4 (126)	3.5 (108)	2.6 (18)	
North-West	7.2 (269)	7.2 (220)	7.1 (49)	
Western Cape	4.3 (163)	4.6 (140)	3.3 (23)	
Employed / Self-employed	27.9 (987)	28.9 (836)	23.6 (151)	**0.007**
Education level				**<0.001**
Primary or less	23.9 (688)	18.4 (446)	52.9 (241)	
Secondary complete	70.6 (2 036)	76.0 (1 844)	42.1 (192)	
Tertiary	5.6 (161)	5.7 (138)	5.0 (23)	

*Chi-square tests

Prevalence of comorbidities in those with HIV

A large proportion of the study population only had HIV (82.2%, 95% CI: 80.0% - 84.3%); with large variation between younger vs older adults (87.0 [84.6 - 89.0] vs. 55.9 [49.7 - 61.9]). Almost 15% of the study population had HIV and one other disease; with a difference among the under 50s compared to the over 50s (11.1% versus 35.5%). A comorbidity was present in 18% (95% CI: 15.7% – 20.0%) of the HIV positive population, and was far more prevalent in older adults (44.1%, 95% CI: 38.1% - 50.3%) compared to younger people (13.0 %, 95% CI: 11.0% - 15.4%).

Table 6B-2. Prevalence of comorbidities in adults living with HIV.

Number of comorbidities	Weighted % (95% CI)		
	Total	Under 50s	Over 50s
HIV only	82.2 (80.0 - 84.3)	87.0 (84.6 - 89.0)	55.9 (49.7 - 61.9)
1 comorbidity	14.8 (12.9 - 16.9)	11.1 (9.2 - 13.2)	35.5 (29.9 – 41.6)
2 comorbidities	2.4 (1.7 - 3.4)	1.6 (1.0 - 2.6)	7.2 (4.6 - 11.0)
3 + comorbidities	0.5 (0.3 - 1.0)	0.4 (0.1 - 0.9)	1.4 (0.4 - 4.1)
HIV and comorbidity	17.8 (15.7 - 20.0)	13.0 (11.0 - 15.4)	44.1 (38.1 – 50.3)

Of the diseases assessed, hypertension was estimated to be the most prevalent comorbidity among people living with HIV (13.3%, 95% CI: 11.5% – 15.3%). Hypertension was more prevalent among people over the age of 50 years compared to those under the age of 50 years (Figure 6B-2). Estimated TB was the next most prevalent disease (3.5%, 95%CI: 2.6 – 4.8), followed by diabetes (3.0%, 95%CI: 2.1 – 4.2), heart disease (2.3%, 95% CI: 1.5 – 3.5) and cancer (0.4%, 95% CI: 0.1 – 0.9). All of the diseases were estimated to be more prevalent among the older group. Generally, females had a higher disease prevalence for hypertension, diabetes, heart disease and cancer (Fig S1).

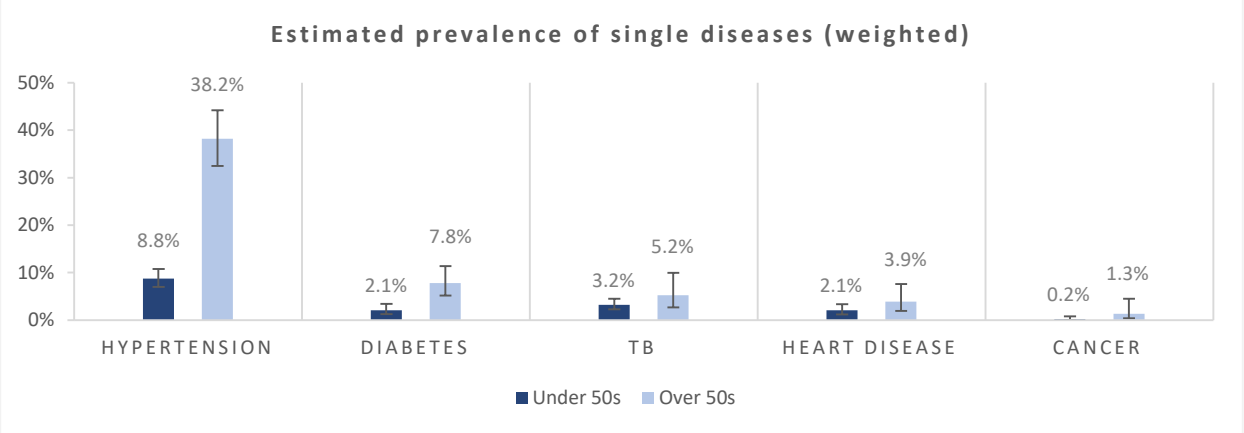

Figure 6B-2. Estimated prevalence of single disease conditions in HIV positive people by age group.

Factors associated with having HIV comorbidity

We assessed factors possibly associated with having an HIV comorbidity compared to only having HIV (Table 6B-3). For the adjusted model, outliers were dropped, and the model was refitted due to the model having limited ability in predicting comorbidity in women 50 years and older that were living in rural areas with secondary education and did not drink alcohol (Table S2, Fig. S2).

Those belonging to the age group 50 years and older had almost 5 times the odds of having a HIV comorbidity compared to those in the under 50 years age group (OR: 4.7, [95% CI: 3.1 – 7.0]). Females had almost double the odds of having comorbidity compared to males (OR: 1.6, [95% CI: 1.1 – 2.4]) Those living in urban areas were more likely to have an HIV comorbidity compared to those living in rural areas (OR: 2.6, [95% CI: 1.8 – 3.7]). Being employed (OR: 0.6, 95% CI: 0.4 – 0.9) was protective against having a comorbidity.

Table 6B-3. Factors associated with having HIV comorbidity

Variable	Unadjusted Odds ratios (95% CI)	Adjusted Odds ratios (95% CI)
Age over 50 years (*Reference: Under 50s*)	**5.3 (3.8 - 7.3)**	**4.7 (3.1 - 7.0)**
Sex (*Reference: Male)*	**1.4 (1.0 – 2.0)**	**1.6 (1.11 – 2.4)**
Urban *(Reference: Rural)*	**1.9 (1.4 - 2.5)**	**2.6 (1.8 - 3.7)**
Education *(Reference: Primary)*		
Secondary	**0.6 (0.4 - 0.9)**	0.7 (0.5 - 1.1)
Tertiary	1.1 (0.5 - 2.7)	1.4 (0.5 – 3.6)
Employed *(Reference: Not employed)*	**0.6 (0.4 - 0.9)**	**0.6 (0.4 - 0.9)**
Current alcohol use *(Reference: No current alcohol use)*	1.0 (0.7 - 1.4)	1.1 (0.8 – 1.7)

Note: Bold figures represent significant values.

Discussion

This analysis of national survey data showed that PLWH over 50 years were more than twice as likely to have an HIV comorbidity compared to PLWH under 50 years. Our study generally confirms other research findings that older adults with HIV had high rates of chronic diseases when compared to younger adults with HIV in South Africa.[75] A survey of HIV amongst educators in South Africa reported a higher overall prevalence of HIV comorbidities compared to our study (36.9 % versus 17.8%).[80] The educator study however, report similar estimates of

older adults with HIV co-morbidities to our study (36.9% versus 44.1%). The differences in estimates of HIV comorbidity could be due to differences in the populations surveyed and the way that chronic diseases were ascertained. The inclusion of employed educators would have automatically excluded young individuals (i.e. youth aged 15 – 20 years). Also, their population of interest differed from ours as they were employed and more likely to have tertiary education; whereas our study was a household survey with few participants employed or possessing tertiary education. The way that chronic diseases were defined between the two studies also differed. In the educator study, disease conditions were included if the educator was diagnosed in the last five years, whereas we included disease conditions that the participant 'currently' had. Despite the differences, all three studies report high levels of HIV co-morbidities and also that hypertension was the most common HIV co-morbidity. The high prevalence of HIV-hypertension comorbidity is also corroborated by other local studies (e.g. hospital admissions in the North West Province [81]) as well as studies in the region (e.g. a retrospective analysis of routine medical records conducted in Malawi [82]).

Our multivariate analysis confirmed that being over the age of 50 years was associated with a nearly 5-fold increase in having a HIV comorbidity. Being female, and living in an urban area also increased the odds of having a comorbidity. Whereas, employment reduced the odds of having a comorbidity. The results of our regression was similar to the educator study [80] in that they found that women, older adults and living in an urban areas increased the odds of having a HIV comorbidity. While women and older adults are known to have higher prevalences of comorbidity or multimorbidity,[83] it is unclear why urban residents would have higher levels of co-morbidities. This could be related to the unmet need for care in rural areas (i.e. people in rural areas could be unaware they have a NCD and thus it is underreported) [84, 85] or it could be due to nutritional shifts and reduced physical activity associated with urbanization.[86]

Our study indicates that a large proportion of older PLWH are managing at least one other co-morbid disease condition. In addition, the prevalent HIV co-morbidities are not necessarily AIDS-related opportunistic infections traditionally associated with HIV. Of the diseases we assessed, hypertension and diabetes were the most prevalent diseases in older PLWH, confirming the shift towards chronic co-morbidities usually associated with ageing. As the ART programme expands and more PLWH reach older ages, the prevalence of NCD co-morbidities can be expected to rise; which has the potential to negatively impact service delivery in South Africa. Concerningly, the

pattern of co-morbidities was also similar among younger PLWH (although TB was more prevalent than diabetes). This means that younger PLWH will have to be on medication for HIV and another disease, possibly for life. This could impact their quality of life and long-term adherence negatively, while also increasing the cost of treatment per individual in the public health sector.

Our study is based on 2017 data and reiterates that the integration of HIV and NCD services at primary care level is urgent. The need for integrated care was acknowledged in the health policy space almost a decade ago (in 2011), when the South African government adopted an Integrated Chronic Disease Management (ICDM) model.[87] However, the implementation of this policy and concomitant regulations at service delivery level has been largely left unattended. As new diseases continue to emerge, it is imperative that the health system aggressively tackle HIV and its co-morbidities. The UNAIDS 95-95-95 testing, treatment and viral suppression targets highlight the need to ensure accessibility, availability and affordability of safe, quality-assured medicines to prevent, diagnose and treat HIV infections, co-infections and co-morbidities.[88] More research is needed on ART in older people as they tend to be underrepresented or excluded from studies on ART.[89] There are multiple toxicities to consider - such as specific agents or drug classes that are known to have adverse bone and renal effects, or increases cardiovascular risk.[89] More research is also needed on adherence, toxicity and on the influence of comorbidities.[90]

This study was limited to the data available in the original survey. It is also limited by the use of self-reported disease conditions for co-morbidities. Self-reported disease conditions could be underestimated if the person is unaware they have a disease or if they choose to not disclose the disease. For example, in a recent comparison of two national South African surveys that took hypertension measurements, the hypertension prevalence among the 15 year and older population was estimated to be 38.4% in the 2012 South African National Health and Nutrition Examination Survey (SANHANES) and 48.2% in the 2016 South African Demographic and Health Survey (SADHS).[91] Our estimate of hypertension in this population was much lower (13.3%) which could be attributed to the use of self-reported data. Similarly, the 2016 SADHS [42] also estimated a higher prevalence of measured diabetes (13% of women, 8% of men) compared to our 3% of self-reported diabetes. This indicates that the true prevalence of co-morbidities among PLWH could be much higher than what was estimated in this study.

Conclusion

This study provides evidence of the extent of co-morbidity in older and younger PLWH from the analysis of the 2017 SABSSM survey. The information from this study (including common co-morbidities) could be used to inform and motivate for service integration for PLWH. Information on common co-morbidities could also be used to inform screening efforts at primary care level, and targeting older people, women and people living in urban areas. Given these high levels of co-morbidity (particularly the 44% among older PLWH), the pressing need for the implementation of integrated care of NCD and HIV services is clear. HIV cannot be treated in silo. Especially as more people are expected to be initiated on ART in an effort to reach the ambitious UNAIDS 95-95-95 targets, whereby 95% of people diagnosed with HIV should be on ART treatment in 2030. Prevention efforts are needed to ensure that the prevalence of HIV co-morbidities is reduced where possible. Regular screening for NCD co-morbidities is also essential to ensure optimal and efficient treatment for PLWH.

Supplementary material

Supplementary material: https://www.mdpi.com/article/10.3390/ijerph19042359/s1

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Chapter 7. Analysis of the National Income Dynamics Study

OVERVIEW OF CHAPTER

This chapter presents an in-depth analysis of the 2017 National Income Dynamics Study (NIDS). This is critical to understanding the economic situation in South Africa and provides a valuable opportunity to examine how multimorbidity is distributed among socioeconomic classes or wealth quintiles. For this reason, an asset index was created to split the population into five quintiles – from poorest to wealthiest.

Our results revealed a two-fold increase in multimorbidity among the wealthiest quintile. This is the reverse of what is found in high-income countries - where poorer people tend to have higher levels of multimorbidity. In South Africa, this could be attributed to wealthier people having more disposable income and thus the ability to access high-calorie fast foods, tobacco, alcohol and other factors that could increase the odds of becoming multimorbid. Greater access to healthcare may also contribute to explaining the association between multimorbidity and wealth.

Article

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7. Article: Inequity in the distribution of non-communicable disease multimorbidity in adults in South Africa: An analysis of prevalence and patterns

Abstract

Objectives

The present study examined the prevalence and patterns of non-communicable disease (NCD) multimorbidity by wealth quintile among adults in South Africa.

Methods

The South African National Income Dynamics Study Wave 5 was conducted in 2017 to examine the livelihoods of individuals and households. We analysed data in people aged 15 years and older (N = 27 042), including self-reported diagnosis of diabetes, stroke, heart disease and anthropometric measurements. Logistic regression and latent class analysis were used to analyse factors associated with multimorbidity and common disease patterns

Results

Multimorbidity was present in 2.7% of participants. Multimorbidity was associated with increasing age, belonging to the wealthiest quintile group, increasing body mass index and being a current smoker. Having secondary education was protective against multimorbidity. Three disease classes of multimorbidity were identified: Diabetes and Hypertension; Heart Disease and Hypertension; and Stroke and Hypertension.

Conclusions

Urgent reforms are required to improve health systems responsiveness to mitigate inequity in multimorbidity patterns in the adult population of South Africa as a result of income inequality.

Introduction

South Africa is an upper-middle-income country,[1] with one of the highest levels of inequality in the world.[2] The country has a quadruple burden of disease; with mortality trends illustrating that 43% of deaths were due to non-communicable diseases (NCDs), 34% to HIV/AIDS and TB, 14% to other communicable diseases (and perinatal conditions, maternal causes and nutritional deficiencies) and 10% to injuries.[3] It is currently observed that NCDs disproportionately affect people in low and middle-income countries (LMICs), where 85% of premature deaths due to NCDs occur.[4]

The observed large increases in NCD burdens in sub-Saharan Africa are driven by the increase in cardiovascular risk factors (i.e. unhealthy diets, physical inactivity, obesity and air pollution).[5] Multimorbidity is the co-existence of multiple health conditions in an individual.[6] It is reported that one in three people are living with multimorbidity globally.[7] Multimorbidity is associated with increases in healthcare costs and utilization, medication use, hospital admissions, and out of pocket healthcare costs.[8] Individuals with multimorbidity have higher mortality risk,[9] a poorer quality of life,[10] and complicated medication adherence requirements.[11] The prevalence of NCD multimorbidity in LMICs is already estimated to be as high as 36%. A scoping review highlighted the urgent need for a better understanding of the epidemiology of multimorbidity in LMICs to inform interventions to improve the outcomes of patients with living with multiple diseases.[12]

The literature on multimorbidity and socioeconomic status remains divided; possibly due to the way in which multimorbidity is operationalised, as well as varying contexts (e.g. high versus low income countries), and the different ways in which socioeconomic status, wealth and deprivation are measured. A systematic review (focused mainly on high income countries) found increasing levels of deprivation associated with increases in multimorbidity.[13] In cross-sectional studies in high income countries (i.e. South Korea[14] USA, Canada, [15] England[15, 16] and Ireland[15]) and China [17] the prevalence of multimorbidity was highest in those with a low socioeconomic status. In contrast, there are reports that multimorbidity could be more prevalent among wealthier people in LMICs.[18] This paper thus reports on the prevalence and patterns of NCD multimorbidity by wealth quintile in a household panel survey of adults in South Africa.

Methods

Description of the NIDS survey sample and data collection

The South African National Income Dynamics Study (NIDS) is the first national household panel study in South Africa that provides information on wealth (livelihoods, how households cope with shocks, poverty, and social capital), sociodemographic (household composition, fertility and mortality, migration, economic activity and education), and health and well-being characteristics [19]. We used data from NIDS Wave 5 conducted in 2017. Health data on diabetes, stroke and heart disease were collected through self-report, and blood pressure and anthropometry measurements were taken at survey administration.

The baseline data collection of the NIDS survey was conducted in 2008, [20] when a two-stage cluster sample design was used to randomly select about 7,300 households across 400 primary sampling units, stratified by district council (a second level administrative division of South Africa's territory into 52 areas). Data were collected on all members of the selected households, resulting in a total sample size of approximately 28000 individuals. [21] In the following waves of data collection the same individuals (continuing sample members) were recontacted and interviewed. In addition, all adults belonging to the same household of the continuing sample members at the moment of the interview (temporary sample members) were also interviewed. A top-up sample was recruited in during Wave 5 to compensate for sample attrition and improve representativity of the national population.

This study uses data from Wave 5 of the survey, where 39 400 individuals in 10 800 households were interviewed between February and December 2017.[22] Additional methodological details from the NIDS Wave 5 survey are available in the Panel User Manual.[23]

Ethics approval for data collection for NIDS Wave 1 to 5 was granted by the University of Cape Town's (UCT) Commerce Faculty Ethics in Research Committee and Faculty of Health Sciences Human Research Ethics.[24] Informed consent in the respondent's preferred language was obtained for all data collection in the survey. Permission and access to the edited and anonymised dataset (available for public distribution) was obtained from the research data service, DataFirst.[24] The current analysis was approved as part of the lead author's doctoral studies and received additional ethics clearance by the Biomedical Research Ethics Committee of the University of the Western Cape (BM20/5/8).

Measures

Outcome variable: Multimorbidity

This study employed a count method for assigning multimorbidity, by counting the number of co-existing disease conditions using a pre-defined list. [25] We created the list of included disease conditions based on recommendations by Holzer *et al.*[26] The disease conditions included were based on a predefined list of disease conditions that are frequently included in multimorbidity assessments and disease conditions that are relevant to the South African disease burden. We included self-reported and measured disease conditions. For self-reported diseases, those that could be deemed as 'current' were included. For the current analysis study, we included diabetes, heart disease, stroke and hypertension.

For each participant, an index variable was created which added up the number of disease conditions present for each person. If there was missing information for a disease condition, the observation was assumed to have 'no disease present.' The Multimorbidity Index was then created by classifying the index variable into those with no disease conditions or one disease condition (i.e. 'no multimorbidity) or those with two or more disease conditions (i.e. 'multimorbidity present').

Self-reported disease conditions: Participants were asked if they were ever told by a doctor, nurse or health care professional that they had the disease condition (i.e. diabetes, heart disease and stroke) (Table S1). The responses were coded in a binary manner (e.g. disease absent or present).

Blood pressure: For blood pressure measurements, duplicate measurements in the left arm after the participant was seated for at least five minutes.[21] Automated oscillometric devices with standard multi-size cuffs were used to take blood pressure measurements.[21] The average of the replicated readings was considered as the subject's blood pressure. Replicated measurements of systolic and diastolic blood pressure were assessed for the presence of implausible values (systolic BP < 70 *mmHg* or > 270 *mmHg*, diastolic BP < 30 *mmHg* or > 150 *mmHg*), which were set to missing. Hypertension was grouped into "no hypertension present" (systolic BP <120-139 *mmHg* & diastolic BP < 80 - 89 *mmHg)* or "hypertension present" (systolic BP 140 to ≥160 *mmHg* & diastolic BP 90 *mmHg* to ≥100 *mmHg*).[27] People on hypertensive medication were included in those that had hypertension.

Sociodemographic and lifestyle risk factors

The following variables were investigated as predictor variables of multimorbidity based on the literature:[28] age, sex, locality, educational attainment, employment status, income, asset index, access to medical aid, smoking status and body mass index (BMI).

Employment status was derived using the script available from the NIDS study.[23] and based on the International Labour Organization's definitions of employed, unemployed (strict definition), unemployed (broad definition) and not economically active.[23] Individual income was split into three categories, with the first representing no income and the third representing the highest income.

An asset-based wealth index, based on the 2016 South African Demographic and Health Survey,[29, 30] was constructed. The index was created using principal component analyses of questions on:

a) access to basic services (e.g. household main source of water, type of toilet facility, main source of energy for heating and cooking, and refuse collection),

b) housing (e.g. number of people living in the dwelling per room, dwelling type, home ownership, material of roof, walls and floors) and

c) ownership of durable assets (e.g. household has electricity, radio, television, phone, computer, fridge, microwave, gas / electric stove, washing machine, cellphone, bicycle, motorbike, motor vehicle, animal cart and boat).

Each variable was coded as binary (i.e. present or absent), except for the number of people in household per room. Scores were predicted for each household and these scores were then divided into five wealth quintiles - with the 1st representing the lowest quintile (i.e. least wealthy) and the 5th representing the highest quintile (i.e. most wealthy). Each individual in the household was assigned the same quintile.

Anthropometry: The NIDS Wave 5 assessed participants based on height and weightmeasurements taken using a digital scale and stadiometer. The data cleaning followed the procedure used for the BMI risk factor in the second South African Comparative Risk Assessment Study.[31] Implausible values were considered as missing. BMI was calculated using the BMI STATA package and was categorized as follows: underweight (15.0 to <18.5 kg/m^2), normal weight (18.5 to <25.0 kg/m^2),

overweight (25.0 to <30.0 kg/m^2), obesity grade 1 (30.0 to <35.0 kg/m^2), obesity grade 2 (35.0 to <40.0 kg/m^2), obesity grade 3 (40.0 to <60.0 kg/m^2).[31]

Statistical analysis

Statistical analyses were conducted using STATA 15.0 (Stata Corporation, College Station, Texas, USA) software. To account for the complex survey design of the NIDS, including clustering, stratification and unequal selection probability, the STATA survey set ('svy') of commands were used. Sampling weights calibrated to the represent the South African demographics were used as provided in the original dataset.[32] Weighted data exploration was conducted. Chi-square tests were used to explore bivariate associations between the wealth index quintile and sex, locality, province, educational attainment, employment status, BMI categories and smoking status. Kruskal-Wallis tests were used to test for differences in age and income between the different quintiles in the wealth index. Similarly, Chi-square tests were used to assess single disease conditions and the number of diseases in an individual by wealth index quintile. Multimorbidity status was also described using histograms and box plots against age.

Multivariate logistic regression was employed to assess the relationship between multimorbidity and potential predictors (i.e. age, sex, location, educational attainment, employment, income, wealth index, smoking status and BMI). For the regression, age was categorised according to the United Nations guidelines for age classifications (i.e, 15-24 years, 25-44 years, 45-64 years and 65+ years).[33] The crude odds ratios were estimated for each predictor variable. The final model included all variables. Model-checking was performed using various statistical tests. The link test[34] was used to determine if there were specification errors. Interaction terms were explored. Pearson residuals, deviance residuals and Pregibon leverage were used to assess influential observations.[35] These tests were done on the unweighted model as they cannot be used on survey weighted data. Crude and adjusted odds ratios were reported with 95% confidence intervals (Cis).; p-values of less than 0.05 were considered statistically significant.

A latent class analysis (LCA) was performed to explore disease clustering with the four selected disease conditions (i.e. diabetes, stroke, heart disease, hypertension). LCA is a statistical method used to identify sub-groups or classes within populations.[36] The analysis was run using the LCA Stata Plugin as the programme accounts for complex survey design.[37, 38] We conducted the

LCA as recommended by Weller *et al.*[36] For example, to identify latent classes, a one-class model was estimated and then additional classes were added to compare the relative fit of models.[36] The relative fit of models were compared using a series of information indices, namely, the Bayesian information criterion (BIC),[39] the adjusted BIC (aBIC),[40] and the Akaike Information Criterion (AIC).[41] Lower values of these information indices indicated a better fit.[42] After selecting the model with the best fit, individuals were assigned to the class with the highest posterior probability.

Results

Sample description

The sample consisted of 27 042 participants, with more females (56.9%, n=15 362) than males (Table 7-1). The median age of the sample was 33 years (IQR: 23 – 51). In terms of population group, most of the sample were Black African (77.9%), followed by Coloured (13.5%), White (6.5%) and Asian (2.1%). Missing data is reported in Table S2.

Just more than half of the sample lived in an urban location (55.7%). Place of residence varied significantly by wealth quintile, with a high proportion of wealth Quintile 1 living in rural areas (83.9%) and a large proportion of Quintile 5 living in urban areas (89.5%).

Approximately 63% of participants completed secondary education, and tertiary educational attainment was highest in wealth Quintile 5 group. Only a third of the sample was employed and income levels varied by wealth quintiles. Income was heavily skewed to the left with median income being R0 in all quintiles (overall interquartile range: R0 – R2000). Approximately 11% of the sample had access to private medical aid, and significantly higher in wealth Quintile 5.

About 42% of the sample had a normal BMI, with females significantly more likely to fall outside the normal BMI range ($p<0.001$) (Table S3). Levels of obesity was highest in wealth Quintile 5. Current smoking status varied by quintiles and peaked in the wealth Quintile 4 group.

Table 7-1. Description of sample by wealth quintiles (Unweighted)

Variable	Total (%, n) *N= 27 042*	Wealth quintiles (%, n)					*p*-value*
		Q1 / Least wealthy *n = 4 772*	Q2 *n = 4 496*	Q3 *n = 4 470*	Q4 *n = 4 541*	Q5 / Most wealthy *n = 4 264*	
Age (Median and interquartile range in years)^	33 (23 -51)	32 (21 -50)	31 (22 - 47)	32 (23 - 46)	33 (23 - 49)	39 (26 - 56)	**<0.001**
Sex							**<0.001**
Male	43.2 (11 659)	40.4 (1 926)	43.6 (1 959)	43.3 (1 936)	45.1 (2 050)	45.0 (1 914)	
Female	56.9 (15 362)	59.6 (2 842)	56.4 (2 534)	56.7 (2 531)	54.9 (2 491)	55.0 (2 343)	
Locality							**<0.001**
Rural	44.4 (11 992)	83.9 (4003)	68.8 (3093)	39.3 (1758)	21.1 (957)	10.5 (449)	
Urban	55.7 (15 050)	16.1 (769)	31.2 (1403)	60.7 (2712)	78.9 (3584)	89.5 (3815)	
Province							**<0.001**
Western Cape	11.5 (3 099)	2.1 (99)	6.1 (273)	10.4 (463)	18.9 (857)	22.8 (970)	
Eastern Cape	11.1 (3 012)	16.4 (781)	11.2 (505)	9.9 (441)	10.3 (469)	7.5 (319)	
Northern Cape	7.2 (1 936)	4.7 (226)	7.5 (338)	8.4 (377)	10.5 (476)	6.1 (262)	
Free State	5.5 (1 493)	1.2 (57)	3.6 (161)	9.2 (410)	9.0 (408)	4.8 (206)	
KwaZulu-Natal	28.6 (7 740)	47.1 (2246)	38.3 (1723)	24.4 (1091)	15.3 (696)	15.2 (648)	
North West	6.1 (1 640)	3.8 (182)	7.7 (346)	8.1 (361)	6.7 (306)	3.9 (164)	
Gauteng	14.6 (3 960)	5.1 (243)	5.8 (262)	14.3 (637)	17.1 (777)	27.7 (1182)	
Mpumalanga	7.2 (1 954)	6.2 (294)	8.8 (396)	8.4 (375)	7.6 (345)	6.3 (268)	
Limpopo	8.2 (2 208)	13.5 (644)	10.9 (492)	7.1 (315)	4.6 (207)	5.8 (245)	
Education level							**<0.001**
Primary or less	23.6 (6 320)	39.2 (1866)	27.7 (1237)	23.2 (1033)	18.5 (834)	9.2 (388)	
Secondary complete	63.2 (16 952)	57.7 (2742)	66.2 (2959)	67.8 (3015)	67.7 (3057)	59.2 (2489)	
Tertiary	13.2 (3 551)	3.1 (147)	6.1 (274)	9.0 (398)	13.9 (628)	31.6 (1328)	
Employed	33.9 (9 157)	26.4 (1258)	31.8 (1429)	37.0 (1655)	40.4 (1833)	45.5 (1939)	**<0.001**
Individual Monthly Income (Median & Interquartile range in ZAR) ~	0 (0-2000)	0 (0-200)	0 (0-1100)	0 (0-2100)	0 (0-3000)	0 (0-7706)	**<0.001**
Private health insurance	11.3 (26 90)	0.8 (36)	2.2 (94)	5.6 (233)	11.5 (475)	37.3 (1415)	**<0.001**
Body Mass Index							**<0.001**
Underweight	8.0 (1 870)	8.8 (388)	8.8 (366)	9.6 (390)	7.6 (308)	5.6 (202)	
Normal weight	42.2 (9 821)	50.0 (2202)	47.8 (1978)	42.4 (1721)	38.4 (1565)	32.8 (1193)	
Overweight	22.8 (5 306)	20.4 (899)	20.7 (857)	22.3 (906)	23.6 (963)	26.9 (977)	
Obesity grade 1	14.6 (3 397)	12.6 (553)	13.1 (544)	13.3 (540)	15.7 (641)	18.3 (664)	
Obesity grade 2	7.4 (1 733)	4.8 (213)	6.1 (254)	7.4 (299)	8.4 (344)	9.6 (350)	
Obesity grade 3	5.0 (1 169)	3.3 (146)	3.5 (143)	5.1 (208)	6.3 (256)	6.9 (252)	
Current smoker	17.7 (4 225)	14.9 (667)	16.6 (702)	19.4 (806)	22.1 (916)	18.3 (695)	**<0.001**

Note: There were 4 449 observations with missing wealth quintile information. *Chi-square tests used for all variables other than age and income where the Kruskal-Wallist test used. ^Age in years. ~Income in South African Rands (1 US Dollar = 14.5 ZAR on 30 March 2022, https://www.x-rates.com/table/?from=ZAR&amount=1)

Disease prevalence in the population

When taking population weighting into account, hypertension was the most prevalent disease condition in the population (27.8%, 95%CI: 26.7 - 29.0) (Table S4). This was followed by diabetes (2.9%, 95%CI: 2.6 – 3.3), heart disease (1.6%, 95%CI: 1.3-1.8) and stroke (0.8%, 95%CI: 0.6-

1.0). The prevalence of hypertension and diabetes rose with increasing wealth quintiles (Table S4). The prevalence of heart disease was similar in wealth Quintiles 1-3 but increased in Quintile 4 and 5. The prevalence of stroke did not appear influenced by wealth quintile.

The prevalence of hypertension was similar among males and females (Table S4). Hypertension prevalence increased with increasing age and peaked in the 70+ year age group at 70.6% in males and 73.6% in females (Fig S1). Diabetes, heart disease and stroke started increasing in the 40 – 49-year age group and peaked in the 70+ year age group.

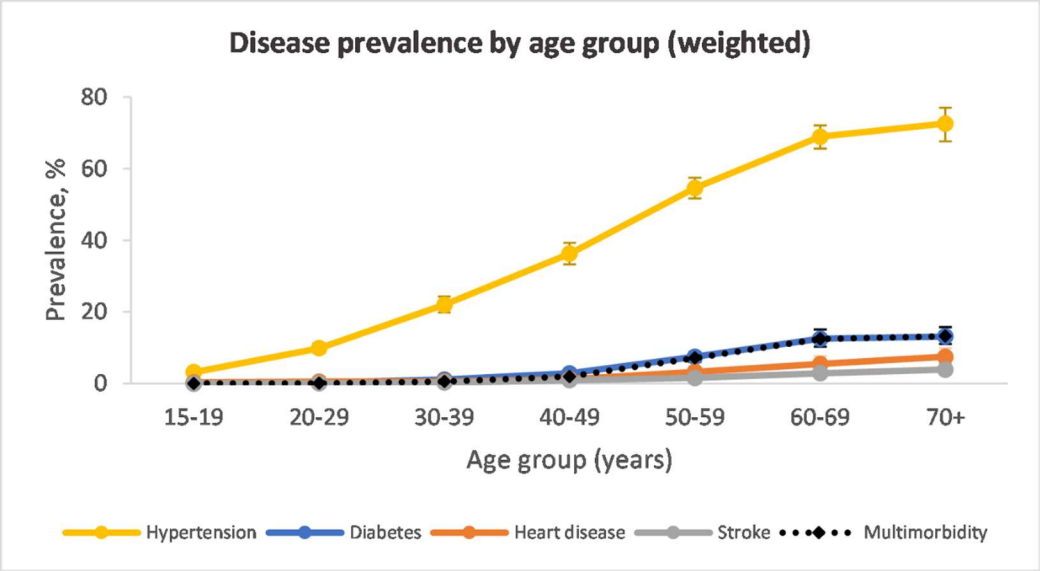

Figure 7-1. Disease prevalence by age group (weighted).

The majority of the population had none of the included diseases (74.5%, 95% CI: 73.5 – 75.4) (Table 7-2). A further 22.8% (95% CI: 21.8 – 23.8) had one disease condition. Multimorbidity was present in 2.7% (95% CI: 2.4 - 3.1) of the population, with it being more prevalent among wealth Quintile 5 compared to the other quintiles. Multimorbidity was also more prevalent among females compared to males (Table S6). The prevalence of multimorbidity was low in younger age groups and peaked at 13.2% among the 70+ age group (Fig S1).

Table 7-2. Number of disease conditions in individuals by wealth index (weighted)

Number of disease conditions	Weighted prevalence (%, 95% CI)					
	Total	Wealth quintiles				
		Q1 (Least wealthy)	Q2	Q3	Q4	Q5 (Most wealthy)
No diseases	74.5 (73.5-75.4)	77.3 (75.3-79.2)	75.4 (73.3-77.4)	75.0 (72.7-77.1)	71.4 (69.0-73.7)	68.2 (65.9-70.5)
1 disease	22.8 (21.8-23.8)	21.1 (19.2-23.1)	22.5 (20.5-24.5)	23.1 (20.9-25.4)	26.0 (23.6-28.4)	26.9 (24.8-29.0)
2 diseases	2.3 (2.1-2.6)	1.4 (1.1-1.8)	1.6 (1.3-2.1)	1.6 (1.3-2.1)	2.3 (1.7-2.9)	4.2 (3.4-5.2)
3+ diseases	0.4 (0.3-0.5)	0.2 (0.1-0.5)	0.5 (0.2-1.0)	0.3 (0.2-0.5)	0.3 (0.2-0.6)	0.7 (0.4-1.0)
Multimorbidity (≥ 2 diseases)	**2.7 (2.4-3.1)**	**1.6 (1.3-2.1)**	**2.1 (1.6-2.7)**	**1.9 (1.5-2.4)**	**2.6 (2.0-3.4)**	**4.9 (4.0-6.0)**

Factors associated with multimorbidity

Multimorbidity was strongly and significantly associated with age, with the odds of having multimorbidity increasing rapidly among older age groups (Table 7-3). In the crude analysis, females had higher odds of multimorbidity compared to males, but this did not remain significant in the adjusted model. Locality was not associated with multimorbidity.

Having secondary education was associated with reduced odds of multimorbidity, compared to those with only primary school education (OR: 0.7, 95% CI: 0.5 – 0.9). While a similar pattern was observed in those with tertiary education, it was not significant in the adjusted analysis – possibly due to a lack of statistical power. People in Quintile 5 (most wealthy) had 2.4 times the odds of having multimorbidity compared to those in Quintile 1 (least wealthy) (95%CI: 1.5 - 3.7). In the adjusted analysis, there was no significant association between multimorbidity and income, having medical aid or being employment.

When compared to those with normal BMIs, those that were overweight had more than double the odds of multimorbidity (OR: 2.6, 95% CI: 1.8-3.8), those with obesity grade 1 had three times the odds of multimorbidity (OR: 3.4, 95% CI: 2.2 – 5.1) and those with obesity grade 2 and 3 had almost four times the greater odds of multimorbidity (OR: 3.8, 95% CI: 2.5 – 5.9 and OR: 3.7, 95% CI: 2.3 - 5.9, respectively). Smokers were more likely to have multimorbidity than non-smokers (OR:1.6, 95% CI:1.1-2.4)

Table 7-3. Factors associated with multimorbidity (crude and adjusted Odds Ratios).

Variable	Unadjusted Odds Ratios (95% CI)	Adjusted Odds Ratios (95% CI)
Age category (*Reference category: 15 -24 years*)		
25-44 years	12.4 (4.8 - 32.3) *	10.0 (3.4-29.5)*
45-64 years	114.1 (45.8 - 284.3) *	60.6 (21.5-170.9)*
65+ years	289.2 (114.4 - 730.8) *	126.7 (44.1-363.7)*
Female (*Reference: Male)*	2.0 (1.6 – 2.5) *	1.1 (0.8-1.5)
Urban location *(Reference: Rural)*	1.2 (1.0-1.5)	1.1 (0.8-1.6)
Education *(Reference: Primary)*		
Secondary	0.3 (0.2 – 0.3) *	0.7 (0.5-0.9)*
Tertiary	0.4 (0.3 -0.6) *	0.7 (0.4-1.2)
Employed *(Reference: Unemployed)*	0.5 (0.4-0.7) *	0.7 (0.3-1.7)
Asset Index *(Reference: Quintile 1*)		
Quintile 2	1.3 (0.9 – 1.8)	1.5 (1.0-2.2)
Quintile 3	1.2 (0.8 – 1.6)	1.4 (1.0-2.1)
Quintile 4	1.6 (1.1 – 2.3)*	1.7 (1.0-2.8)
Quintile 5 (Most wealthy)	3.1 (2.2 – 4.2)*	2.4 (1.5-3.7)*
Individual Income (Lowest)		
Group 2 (Medium)	0.4 (0.3-0.6)*	0.6 (0.2-1.7)
Group 3 (Highest)	0.5 (0.4-0.7)*	0.6 (0.3-1.7)
Medical aid	2.2 (1.7 - 2.9)*	1.4 (1.0-2.1)
Current smoker *(Reference: No current smoking)*	0.7 (0.5 -1.0)	1.6 (1.1-2.4)*
BMI categories *(Reference: Normal BMI)*		
Underweight	0.8 (0.4-1.6)	0.6 (0.3-1.3)
Overweight	3.4 (2.5-4.7) *	2.6 (1.8-3.8)*
Obesity grade 1	5.6 (3.9-8.0) *	3.4 (2.2-5.1)*
Obesity grade 2	6.7 (4.5-9.9) *	3.8 (2.5-5.9)*
Obesity grade 3	6.6 (4.5-9.6) *	3.7 (2.3-5.9)*

* The *p*-value was significant ($p < 0.05$)

Multimorbid population analysis

Only the multimorbid sample was included in the subsequent analysis (n=971). The unweighted mean age of people with multimorbidity was 60 years (58.9 – 61.5 years). Also, 67.7% were female. In terms of included disease conditions (weighted), almost all the multimorbid population had hypertension (98.9%, 95%CI: 97.6 - 99.5), followed by diabetes (68.2%, 95%CI: 63.0 - 72.9), heart disease (37.5%, 95%CI: 32.4 - 43.0) and stroke (16.1%, 95% CI: 13.2-19.4) (Table S6). The

disease prevalence was similar among the sexes, except for stroke which was more prevalent in males (20.1%, 95%CI: 14.4 - 27.4) compared to females (14.1%, 95% CI: 11.0 - 18.0).

Table S8 shows a comparison of fit statistics for models with different numbers of classes, ranging from two to five classes. The BIC, adjusted-BIC and AIC were minimal for a three-class model. A four-class model produced a slightly lower AIC but since the AIC tends to prefer over-complicate models, the three-class model was chosen. Classes were named based on the diseases with the highest prevalence in that class. The model identified the following membership, latent classes, from largest to smallest: 'Diabetes and Hypertension' (52.6%), 'heart disease and Hypertension' (32.1%), and 'Stroke and Hypertension' (15.3%) (Figure 7-2). A high probability of hypertension was common among all the disease classes. Standard errors are available in Table S9.

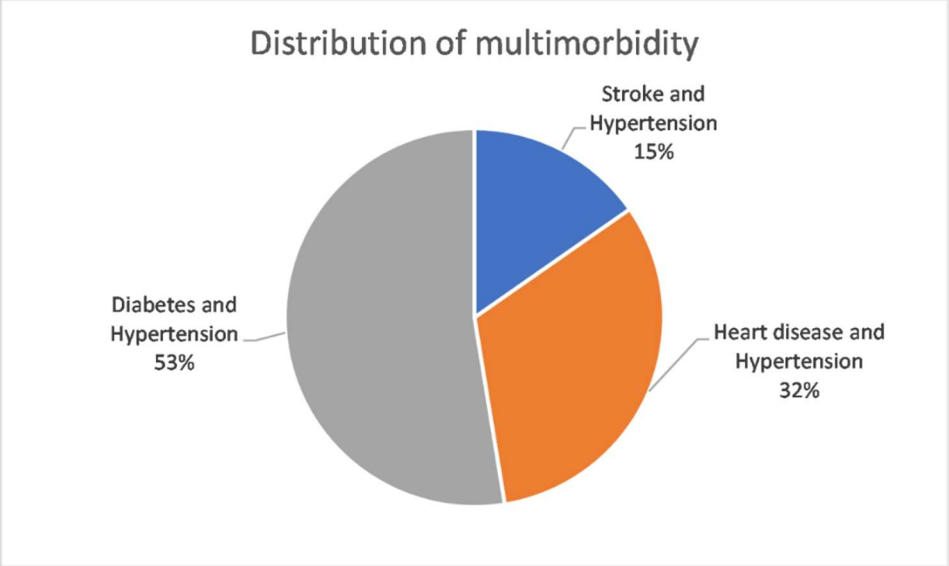

Figure 7-2. Distribution of latent classes in the multimorbid population (weighted)

Table 7-4 shows the item response probabilities for each disease condition by latent class. The largest class (Diabetes and Hypertension) was characterised by 100% certainty of having both diabetes and hypertension. The second-largest class (heart disease and Hypertension) was typified by a 99.9% probability of heart disease and a 98.4% probability of hypertension. The smallest class (Stroke and Hypertension) was characterised by very high probabilities of stroke (99.7%) and hypertension (95.6%).

Table 7-4. Disease probabilities within classes for the 3-class LCA.

Class	Disease probabilities (standard errors)			
	Hypertension	Diabetes	Heart disease	Stroke
Class 1: Stroke & Hypertension	**0.956 (0.023)**	0.240 (0.080)	0.298 (0.084)	**0.997 (0.001)**
Class 2: Heart disease & Hypertension	**0.984 (0.007)**	0.335 (0.046)	**0.999 (0.000)**	0.004 (0.005)
Class 3: Diabetes & Hypertension	**1.000 (0.000)**	**1.000 (0.000)**	0.007 (0.003)	0.008 (0.021)

*Bold text indicates a high probability of that disease condition within a class.

Discussion

Our results support the well-established notion of a positive association between increase in age and NCD multimorbidity; as shown in a recent systematic review of multimorbidity in 22 out of 25 studies in LMICs .[43] South Africa's population is ageing - the proportion of elderly persons (60 years and older) increased from 7.6% in 2002 to 9.1% in 2020[44] – and signals the need to anticipate the needs of an aged population. Further, the National Development Plan 2030 that aims to increase life expectancy of South Africans from 61 to 70 years, propagates for integrated health care delivery through the life course. [45] The life-course approach increases the effectiveness of interventions by targeting the needs of individuals at critical points in their lives.[46] In South Africa, screening older adults for multimorbidity will enable the identification of individuals needing treatment.

Our study found a positive association between multimorbidity and the highest wealth quintile. Studies on the African continent (e.g. Burkino Faso,[47] Ghana,[17] South Africa[48]) have shown that wealthiest groups had higher levels multimorbidity compared to the less wealthy groups. This contrasts with what has been noted in high income countries. In LMICs, this could be explained by wealthier people having access to high-calorie foods, tobacco, alcohol and other factors that can increase the risk of developing multiple conditions.[18] It is possible that residual confounding existed in our regression model and we were not able to fully separate the effects of wealth on education, occupation and BMI. Of course, the relationship with wealth may be mediated or confounded by education and occupation. Wealth and prosperity tends to be related to higher BMI in South Africa,[49, 50] a factor also associated with multimorbidity. Obesity risk in African population groups may also be influenced by cultural norms that associate fatness with beauty.[51]

Access to healthcare may also contribute to explain the association between multimorbidity and wealth. Since South Africa has both private and public health sector systems,[49] wealthier people tend to have better access to healthcare in terms of private health insurance or medical aid. For example, many private medical aid schemes in the country offer - or even require mandatory - annual health screening benefits (blood pressure, BMI, glucose and cholesterol), which would likely increase awareness of these health conditions among those on higher wealth quintiles.

The common disease classes identified among the multimorbid population were 'Diabetes and Hypertension', 'Heart disease and Hypertension' and 'Stroke and Hypertension.' The largest disease class in our study was 'Diabetes and Hypertension.' This combination of diseases has been previously identified in the literature both regionally[49-52] and internationally.[53] A multi-country study based in sub-Saharan Africa found that hypertension was the most common co-morbidity in a cohort of diabetes patients and was present in approximately 71% of patients with diabetes.[54] An analysis of a South African national HIV survey also identified 'Diabetes and Hypertension' and 'Heart disease and Hypertension' as disease classes in the multimorbid population.[55] Hypertension is a condition in which blood vessels have persistently raised pressure and if left untreated, can cause chest pain (angina), heart attacks, heart failure, and an irregular heartbeat, which can lead to a sudden death.[56] It can also cause strokes by blocking or bursting arteries that supply blood or oxygen to the brain.[56] Hypertension has many short and long term consequences [57] – such as the disease conditions identified as co- or multi-morbid in this study (diabetes, stroke, heart disease or heart failure). The number of people with hypertension is increasing and detection but treatment rates remain strikingly low (control rates are below 13% in Sub-Saharan Africa).[58] While prevention and screening are important, of equal importance is the need to effectively manage patients. To reduce fragmentation of care and meet the needs of people with multimorbidity, several European countries have introduced disease management programmes focused on integrated care.[59] The World Health Organization has also suggested that integrated care is beneficial for older people.[60] Given the growing burden of NCDs in many LMICs, integrated care aimed at reducing and managing the burden of NCDs need to be investigated.

Limitations

This study was a secondary analysis of survey data and was limited to the data reported in the survey. Since the NIDS 2017 survey collected information on few disease conditions, this analysis was also limited in the number of disease conditions included. We used a combination of measured and self-reported health data. The self-reported disease condition data was most likely underestimated which would, in turn, lead to an underestimation in the prevalence of multimorbidity. We also included a few disease conditions which may also lead to an underestimation in the assessed prevalence of multimorbidity. In addition, we assumed that missing data for a disease condition meant no disease was present which may have led to a lower estimation of prevalence for disease conditions.

The prevalence of multimorbidity in this study was lower compared to other local studies.[53] However, some multimorbidity prevalence studies that included younger people in South Africa also found lower prevalences i.e. between 6 and 13%.[59, 65, 66] The prevalence in this study was very similar to the prevalence estimates observed in another study of the 2008 NIDS Wave 1 (4.0%)[48] and the 2010 NIDS Wave 3 (2.8%).[67] This could be due to the NIDS being a panel survey that goes back to interview a similar panel of participants. It is also most likely due to the underestimated prevalence of self-reported single diseases found in all three studies based on the NIDS surveys. While each study included variations of disease conditions, all three studies included hypertension and diabetes.

The estimated hypertension prevalence in this analysis appears to be plausible. For example, in this study, approximately 28% of the population 15 years and older was found to have hypertension (27.3% in males and 28.4% in females). In comparison, a meta-regression of hypertension estimates for the population 25 years and older was found to be 38.9% for males and 40% for females.[68] However, the diabetes prevalence in this study was 2.9% whereas other national surveys of people aged 15 years and older (using biomarkers) have placed the diabetes prevalence closer to 14.7% in 2012[69] and 14.9% in 2016.[29] A meta-regression of diabetes prevalence in people 25 years and older determined the prevalence to be 12.8%.[70] This indicates that the diabetes prevalence was most likely underestimated in the 2017 NIDS Wave 5, probably because it was self-reported. In a comparison of self-reported diabetes prevalence and prevalence based on HbA1c in another survey, the author concluded that 61% of cases of diabetes were likely to be

undiagnosed.[71] As 'Diabetes and Hypertension' make up the largest disease class in this study, any underestimation in the prevalence of these two diseases would have impacted the estimation of multimorbidity prevalence. While multimorbidity prevalence may be underestimated in our study, we still had important findings on the factors associated with multimorbidity and disease patterns.

Conclusion

This study builds upon previous studies that examined multimorbidity in earlier waves of the NIDS dataset. As in the previous studies, the multimorbidity prevalence remained low but this is most likely due to the under-reporting of disease conditions. There was still a substantial amount of morbidity in the population, especially due to hypertension which reached extremely high levels among older people. Our study highlighted that age, belonging to the highest wealth quintile, current smoking, being overweight or obese increased the odds of multimorbidity; whereas having secondary education was protective of multimorbidity. Slightly more than half of the participants with multimorbidity were estimated to belong to the 'Diabetes and Hypertension' class. Integrated models of care are needed to prevent, manage and optimise the treatment of NCD multimorbidity.

Supplementary material

Supplementary material:

https://www.ssph-journal.org/articles/10.3389/ijph.2022.1605072/full#supplementary-material

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Chapter 8. Summary of Findings, Discussion and Conclusion

OVERVIEW OF CHAPTER

This concluding chapter summarises the main findings from each study, discusses the implications for policy and practice, and concludes with recommendations for further research and policy.

8.1. Summary of main findings

This thesis aimed to determine the prevalence and trends of disease clusters in South Africa, through analysing the most recent national health surveys available. The thesis was realised through:

- a systematic review of prevalence studies on multimorbidity among adults in South Africa covering a period up to December 2020;
- analysis of three nationally representative survey datasets from which data on the prevalence of multimorbidity could be extracted; and,
- identifying patterns (clusters) of disease among those with multimorbidity.

A brief summary of the most salient findings by chapter follows.

The systematic review of multimorbidity prevalence studies in South Africa **(Chapter 2)** revealed a dearth of research (n=10 published articles). Studies were difficult to compare as the methods used to assess multimorbidity differed. The prevalence of multimorbidity ranged from low to moderate (3 – 23%) for those studies that included younger age groups (e.g. 15 years and older); and moderate to high (30 – 87%) for studies with a more narrow group of selected age groups (e.g. 40 years and older). Half the studies reported on disease clustering and four of the five studies reported 'hypertension and diabetes' as a disease cluster.

The systematic review made it apparent that a revolutionised definition of multimorbidity is required, to stimulate multimorbidity research in low- and middle-income countries (LMICs). I argue in **Chapter 3** that historically, definitions of multimorbidity were derived from studies in high-income countries, and resulted in the current research focus on non-communicable diseases

(NCDs). Infectious diseases need to be considered in studies of multimorbidity as these disease conditions can also be long-term in nature (e.g. HIV, long-COVID, etc.). The Academy of Science has explicitly included HIV in their definition of multimorbidity, making multimorbidity more relevant to countries with high HIV burdens. LMICs have an important role to play, and the knowledge generated through research in LMICs can contribute to the global understanding of multimorbidity and how to efficiently manage it. Researchers in LMICs also need be empowered to do research that is locally relevant and needed, rather than research prioritised through a top-down approach by international donors. The nature of donor funding in South Africa has led to the concentration of research on health-systems strengthening for delivery of care to infectious diseases such as HIV and TB. This has resulted in the development of robust health-information systems for the monitoring and evaluation of HIV, while neglecting NCDs and other disease conditions, and creating siloed information systems. Therefore, it is difficult to monitor multimorbidity through existing health-information systems, in the absence of HIV. In the absence of integrated patient-level data, nationally representative surveys that include health conditions provide an alternative source on which to estimate the national burden of multimorbidity.

In this PhD project, three national survey datasets (in the period 2016 - 2017) were analysed to assess and compare multimorbidity in the country, as described in Chapters 4 - 7.

Chapter 4 describes a systematic method for comparing multimorbidity in national survey datasets. It illustrates a simple and transparent process for estimating multimorbidity in national surveys – one that can easily be adopted in other LMICs. It also describes the prevalence of multimorbidity, the factors associated with it and common disease clusters in three national surveys (2016 South African Demographic and Health Survey [SADHS 2016], 2017 South Africa National HIV Prevalence, Incidence, Behaviour and Communication Survey [SABSSM 2017], and the 2017 National Income Dynamics Study [NIDS 2017]). These surveys were selected because they were the most recent available in South Africa and included information on health data that allowed for the calculation of multimorbidity prevalence, disease patterns and factors associated with multimorbidity. While the overall prevalence of multimorbidity differed between the surveys (20.7% SADHS, 5.9% SABSSM and 2.7% NIDS), results for each followed a similar pattern when disaggregated by age group and sex. Namely, the prevalence rose with age and was higher in women compared to men. Also, hypertension was prominent in 8 out of the 11 disease clusters identified.

Chapter 5 presents the results of two in-depth analyses based on the 2016 SADHS. This national survey was important to this thesis as it includes many measured diseases (HIV, diabetes, anaemia and blood pressure). Analysis of the SADHS also encourages international comparisons of multimorbidity, as the survey is conducted in many different countries and regions.

We found that multimorbidity was present in 20.7% of participants; in 14.8% of males and 26.2% of females. Multimorbidity was higher among females in every age group analysed. From ages 15 to 49 years, multimorbidity in females was almost double that of males. This difference appeared less marked over the age of 50 years.

Several common clusters (classes) of diseases were identified. Among people with multimorbidity, four major classes of disease were found: (1) *HIV, Hypertension and Anaemia,* (2) *Anaemia and Hypertension* (3) *Cardiovascular-related,* and (4) *Diabetes and Hypertension*. Almost 40% of multimorbid people belonged to the HIV, Hypertension and Anaemia class. These findings indicate the need for integrated care, especially between NCDs and infectious diseases.

Chapter 6 presents the findings of two in-depth analyses using the 2017 SABSSM. This survey provides HIV data, which allowed for comparison with the 2016 SADHS. The analysis revealed a lower prevalence of multimorbidity when compared to the 2016 SADHS. It also identified seven distinct disease classes in the population. The largest disease class was found to be *Diabetes and Hypertension* followed by *HIV and Hypertension*. This shows that the South African multimorbid population has diseases that are considered concordant (i.e. two related NCDs) and discordant (i.e. an infectious disease and an NCD).

In this chapter, co-morbidities among older people living with HIV were investigated. Since access to antiretroviral treatment (ART) has improved, the life expectancy of people living with HIV (PLWH) has increased. This has led to an increase in the number of older adults living with HIV, which may have implications for the health system. Approximately, 44.1% of people with HIV aged 50 years and older had at least one other disease (compared to 13.0% of people with HIV under 50 years of age). HIV-infected individuals over the age of 50 years had five times the odds of having a co-morbidity compared to those under 50 years of age with HIV. Women and people living in urban areas also had higher odds of having an HIV co-morbidity. Hypertension was prevalent among older people with HIV - confirming the shift towards chronic co-morbidities usually associated with ageing.

Chapter 7 presents an in-depth analysis of the 2017 NIDS. This survey is critical to understanding the economic situation in South Africa and provides a valuable opportunity to examine how multimorbidity is distributed among socioeconomic classes or wealth quintiles. For this reason, an asset index was created to split the population into five quintiles – from poorest to wealthiest.

Our results revealed a two-fold increase in multimorbidity among the wealthiest quintile group. This is the reverse of what is found in high-income countries - where poorer people tend to have higher levels of multimorbidity. In South Africa, this could be attributed to wealthier people having more disposable income and thus the ability to access high-calorie fast foods, tobacco, alcohol and other factors that could increase the odds of becoming multimorbid. Greater access to healthcare may also contribute to explaining the association between multimorbidity and wealth.

8.2. Discussion: Implications for policy and practice

A comparison of the results from the systematic review of prevalence studies and the multimorbidity analyses based on three nationally representative surveys, highlight three emerging issues, namely (i) the high levels of multimorbidity among three key groups - older adults, women, and the wealthy; (ii) disease clusters among the multimorbid; and, (iii) the general paucity of multimorbidity studies in LMICs. The implications of each of these for health systems policy and practice are discussed below.

Multimorbidity among older adults

In all three surveys assessed, multimorbidity increased with older age and peaked in the 70+ years' age group. The increased odds of multimorbidity in older age are consistent with what has been observed internationally.[1-3] The prevalence of multimorbidity among older individuals is concerning, especially given that the number and proportion of older people are increasing dramatically in LMICs.[4] Population ageing is being driven by falling fertility rates, improved survival at younger ages, fewer adults dying of infectious diseases, and socioeconomic development in the past 50 years.[4, 5]

South Africa is ageing

Although definitions differ, a country is defined as 'ageing' when the proportion of people aged 65 years and older exceeds seven percent.[5] Like other LMICs, South Africa's population is

considered to be ageing. Statistics South Africa estimated that the proportion of older persons (60 years and older) increased from 3.5 million people in 2002 to 5.4 million people in 2020 (i.e. from 7.6% to 9.1%).[6] It is further predicted that the population over 60 years will double between 2012 and 2050.[7]

Population ageing shapes the demographic profiles and impacts the needs of countries.[5] Several repercussions need to be considered when catering to the needs of an ageing population. There are macroeconomic considerations – for example, ageing populations impact labour markets, social security systems and social cohesion.[8] There are also many health-service implications. A 2020 report on ageing in Africa highlighted that older adults experience a disproportionate burden of disease - NCDs dominate the disease burden but infectious (e.g. HIV, Tuberculosis, lower respiratory infections) and nutrition-related disease still account for a sizeable proportion of the disease burden, compared to other regions.[8] The report highlighted that disability, frailty and mental health needs were likely to impact the quality of life for older Africans.[8] Older people also struggle to access healthcare due to financial constraints, as shown by a study in Cape Town, which found income-related disparities in accessing quality care.[9] Mobility issues, the physical effort of spending hours waiting in lines, and dealing with rude and ageist healthcare staff were some of the challenges faced by participants. Poor and dismissive communication contributed to confusion in participants trying to navigate the health system.[9]

Policy environment on ageing

The rights of older people have been recognised internationally by several legal and policy frameworks. Since 2002, two major international policy instruments have guided action on ageing – the *Political declaration and Madrid international plan of action on ageing* [10] and the World Health Organization's *Active ageing: a policy framework* [4, 11]. Both documents detail the importance of health in older age but there has been a lack of prioritisation of the issue and a consequent lack of progress in implementing these instruments.[4] Another policy document is important to the African region. In 2016, *The Protocol to the African Union Charter on Human and Peoples Rights on the Rights of Older Persons in Africa* was adopted by the African Union.[12] Article 15 pertains to access to health services and guarantees the rights of older people to access health services that meet their needs, facilitate reasonable access to health services and

medical insurance, and ensure the inclusion of geriatrics and gerontology in the training of healthcare workers.[12]

South Africa has endorsed these policies on ageing. After signing the *Madrid international plan of action on ageing*, the South African government developed the *South African Policy for Older Persons* [13] in 2005.[14] The policy is comprehensive. It calls for older persons to remain in their communities for as long as possible and for a developmental approach to rendering services to older people.[14] It promotes a life-course approach, focused on the prevention of disease, and also emphasises the need for integrated services. However, not much of the plan has been implemented.[14]

Ensuring a healthy life for all remains a key commitment of the South African government. In 2010, the government adopted an outcome-based approach to service delivery (Negotiated Service Delivery Agreement 2010-2014) and one of the key outcomes was "A long and healthy life for all South Africans."[15] Four key outputs included: increasing life expectancy; reducing maternal and child mortality rates; combatting HIV and AIDS and Tuberculosis; and, strengthening the effectiveness of the health system. [15] There have been considerable improvements in life expectancy – in 2005, it was 51.6 years and by 2015 had increased to 62.9 years.[16] This has largely been attributed to the introduction of antiretroviral treatment for people living with HIV in 2004.[16, 17] More recently, in the National Development Plan (NDP) 2030, the South African government stated that they are aiming to increase the average life expectancy at birth for males and females to 70 years.[18] The NDP noted that a change in the demographic profile will affect government spending in terms of healthcare and pension provisions, and that high levels of unemployment in the working-age population may make it difficult to absorb these costs.[18] However, no clear strategies exist on how to meet these needs.[14] Also, little direct mention is made of multimorbidity.

Multimorbidity could be indirectly managed through the implementation of Goal 4 (reduce the prevalence of NCDs) and Goal 6 (complete health-system reform) of the NDP 2030. Another plan could also indirectly impact multimorbidity. *The Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2013 – 17* was a direct result of the South African Summit on the Prevention and Control of Non-communicable diseases held in September 2011.[19] It sets ten clear targets to be reached by 2020; with the first aiming to reduce relative premature mortality in

people under 60 years of age due to NCDs by 25%;[19] effectively excluding older people. Other targets included the reduction of tobacco, alcohol and salt use. The plan also sought to reduce the prevalence of obesity/overweight, raised blood pressure, and increase physical activity and cervical cancer screening. There was no focus on population ageing but achieving these targets would impact older people [14] and multimorbidity.

Provincial policies

While national policies have not explicitly mentioned multimorbidity, the Western Cape Department of Health has been quite innovative in their recognition of multimorbidity (termed 'co-morbidity' in their official documents). For example, they acknowledge that during the adulthood phase, there is a risk of co-morbidities which is why they have put a strong focus on mental health integration into primary healthcare services, HIV and chronic disease health services.[20]

This forms part of their 2013 plan, *Healthcare 2030: A Future Health Service for the Western Cape*.[20] The document sets out a strategic framework for increasing health and wellness in the Western Cape and focuses on four pillars to address the burden of disease, increase wellness in communities and ensure patient-centred quality care in the province. [21] These pillars are: a person-centred approach, integrated provision of care, continued support for the patient and a life-course approach to treating patients throughout their lives and not once-off interactions.[21] By definition, a life-course approach would ensure the inclusion of older adults. The plan acknowledges the importance of integrated care and that a great deal of effort is needed to overcome historical service-delivery approaches (i.e. based on a specific set of problems or diseases).

Implications

Multimorbidity is common among older adults. As the number of older people increases, the health system will need to service the needs of this key population by providing integrated, patient-centred care. Older people tend to have additional needs (e.g. disabilities, lack of funds for transport, etc.) and may require additional assistance in accessing health facilities.

The policy environment is supportive of the needs of older people. In South Africa, much noise is made about increasing life expectancy. However, a longer life does not guarantee a healthy life.

While some documents recognise co-morbidity as an issue, few mention multimorbidity and its high prevalence in the elderly. Many of the policies have not been implemented and it may be essential to further prioritise the needs of the elderly – in the same way the needs of children under 5s years have been prioritised.[14]

Multimorbidity in women

In all three surveys it was noted that women had a higher prevalence of multimorbidity compared to men, and this was true across most age groups. This gender differential has been found in other local [22] and international studies.[23-25] While fairly well established, it is unclear why these differences exist. Possible reasons could be that women are more likely to self-report their disease conditions, that women are more likely to know their health status due to increased contact with healthcare services or, that certain disease burdens are more prevalent among women. Another partial explanation could relate to the previous theme, in that women have longer life expectancies compared to men and thus more time to develop multiple chronic disease conditions. Some of these reasons are further explored below.

First, the gender gap in self-reported health status has been attributed to biological factors (e.g. certain diseases affect women) and societal gender inequalities (in employment, education, etc).[26] Secondly, women are more likely to know their health status as they tend to have higher healthcare utilisation compared to men.[27, 28] For example, women of reproductive age (15 – 49 years) are more likely to utilise health services for infant and child care, and family planning. This may make women more likely to be screened and, as a result, more aware of their health conditions compared to men. Thirdly, the gender differential could also reflect disease burdens that are more prevalent in women, such as HIV and obesity. For example, women had higher rates of HIV in both the SADHS 2016 and SABSSM 2017 surveys. This high prevalence of HIV among women has been attributed to multiple related factors, including biological, behavioural, socioeconomic, cultural and structural risks.[29] Similarly, women have higher rates of obesity, which is associated with increased odds of multimorbidity.

The role of gender in studies of multimorbidity has not been thoroughly explored.[30] Multimorbidity could heavily impact women's lives by affecting their ability to earn an income. Women are already overrepresented in low-paying, part-time, temporary and informal work.[31] As women have less secure forms of income, many have little to no social protection.[32] Financial

constraints are a significant barrier to accessing healthcare. For example, an estimated 6 out of 10 women (62%) in sub-Saharan Africa face barriers to accessing healthcare due to financial constraints and the large distances they need to travel to access health facilities.[33] A study of pregnant women in India documented increased levels of out-of-pocket expenditure in those with multimorbidity and the authors concluded that the high financial burden could push households into poverty.[30] In addition, due to social norms, women spend many hours caring for the sick and the elderly. Multimorbidity could indirectly impact many women by increasing their care burden.

Policy environment

Few policy documents speak directly to multimorbidity and even less speak to multimorbidity in women. The Sustainable Development Goals (SDG) have several goals that would be hampered by rising levels of multimorbidity in women. For example, those of eliminating poverty (Goal 1); ensuring healthy lives and promoting well-being for all at all ages (Goal 3); and, achieving gender equality (Goal 5).

Implications

On average, women live longer than men. Women also have higher levels of multimorbidity than men, a trend present across age groups. The interaction of age and sex results in older women being the group with the highest prevalence of multimorbidity. This group may also be highly vulnerable to the financial setbacks accompanying managing multiple diseases which, in turn, affects their ability to receive quality care and treatment.

Another issue to consider is that of multimorbidity in pregnancy. Depending on the type of multimorbidity present, it could lead to high-risk pregnancies; which also require additional monitoring and visits to healthcare facilities. More research is needed to fully understand the impact of multimorbidity in women.

Multimorbidity and inequality

In high-income countries, multimorbidity is associated with poverty.[34] However, our analysis of the National Income Dynamics (NIDS) 2017 survey revealed higher odds of multimorbidity among wealthier people in South Africa. Other studies on the African continent (Burkino Faso [35] and Ghana [36]) have confirmed this pattern. This could be linked to lifestyle risk factors

among the wealthy, where disposable income could facilitate access to fast foods and increase the odds of being obese. Obesity has also been linked to being wealthy (prosperous) in South Africa [37, 38] a factor also associated with multimorbidity. Obesity risk in African population groups may also be influenced by cultural norms that associate fatness with beauty.[39]

The association between wealth and multimorbidity may also point to a different disparity altogether – which is access to healthcare. South Africa has a two-tiered health system comprising private and public-health sectors.[40] Wealthier people may be more aware of their disease conditions as they tend to have better access to healthcare due to being able to afford the cost of private health insurance or medical aid. Many private medical aid schemes in the country offer - or require - annual health screening (blood pressure, BMI, glucose and cholesterol), which would likely increase awareness of these health conditions among those in higher wealth quintiles. They may also have access to work programmes that do health screenings. In addition, wealthier individuals may be forced to undergo health screening to determine insurance premiums. If the cause for higher observed levels of multimorbidity among wealthy people is greater access to healthcare, it points to a gross level of unmet need among average South Africans. One local study found disparities in healthcare utilisation by socioeconomic level – with the disadvantaged far more likely to postpone care seeking due to monetary reasons.[41]

Policy

The movement toward universal health coverage (UHC) has gained momentum globally.[42] UHC recognises that all people should have the access they need to health services without incurring financial hardship.[42] Achieving UHC is a target of the SDGs explicitly stated in SDG 3.8.[42] In 2019, a United Nations High-Level Meeting on UHC was held and a political declaration affirming high-level political commitment to UHC was adopted by member states.[42]

South Africa has taken up the cause of UHC, in the form of a National Health Insurance (NHI) scheme. NHI is a health-financing system designed to pool funds to provide quality, affordable healthcare services to South Africans, based on need rather than socioeconomic status.[43] The implementation of the NHI is being done using a phased approach.[43] In 2019, President Ramaphosa launched the 'Presidential Health Summit Compact' which lays out a five-year roadmap for accelerating UHC in South Africa.[44]

The implementation of the NHI and achievement of UHC will undoubtedly benefit South Africans in general, and those with multimorbidity. Assessments of progress toward UHC in South Africa found that there has been some progress in terms of service coverage.[45] However, there has been a lack of support from the public for the NHI.[46] These concerns are echoed by civil society groups which believe that the current health system is not ready for the NHI, and first needs to be improved. [46] These concerns are not unfounded and transparency and clarity has not been well managed. [46]

Implications

If lifestyle risk factors rise, the prevalence of multimorbidity is likely to increase. Increases in multimorbidity are known to impact healthcare utilisation and could put a strain on the system.

If the NHI is successfully implemented, hopefully more screening will take place. This will allow people, regardless of socioeconomic status, to be aware of the diseases they have and enable access to quality treatment that does not negatively impact them financially.

Disease clusters

In examining the different disease clusters (classes) in the multimorbid population, hypertension was prominent in 8 of the 11 clusters. Hypertension co-occurred with other NCDs and with an infectious disease such as HIV – thus a mix of concordant and discordant multimorbidity classes exist in the population. Concordant multimorbidity tends to be similar in its origin or aetiology, whereas discordant multimorbidity is when the co-existing disease conditions tend to be unrelated.[47] This highlights the need for integrated care and a 'one-stop-shop approach' where treatment is available, no matter the underlying cause.

Policy

The need for integrated care has been acknowledged by the Department of Health. This was exemplified in the release of the 2016 South African National Department of Health Adherence Guidelines for HIV, TB and NCDs.[48] This policy and the service-delivery guidelines seek to address issues in non-adherence to long-term therapies amidst the expansion of ART programmes and the rising burden of NCDs [48]. Certain aspects of the programme implementation related to this policy have been positively evaluated [49, 50]. Another part of the strategy focused on linkage

to care and implementing screening activities to identify diseases early for intervention. While the Adherence Guidelines do not cover every disease combination possible, they are a step in the right direction.

The Adherence Guidelines complement other South African guidelines and strategies that have been put in place to reduce disease burdens, such as the Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2013 -2017 [19], the Strategy for the Prevention and Control of Obesity in South Africa 2015 -2020 [51] and, legislation to decrease sodium levels in the food industry [52]. Although South Africa has policies for the major NCD risk factors (tobacco smoking, unhealthy diets, harmful use of alcohol and physical inactivity), implementation is a problem.[53] Much more work is still needed to tackle the drivers of multimorbidity such as hypertension. The number of people with hypertension continues to increase, yet treatment rates remain extremely low (control rates are below 13% in sub-Saharan Africa).[54]

A paucity of studies on multimorbidity in LMICs

Given that high levels of multimorbidity can severely affect the health system, it is concerning to note the lack of literature on multimorbidity in LMICs (including South Africa). The existing literature on multimorbidity was difficult to compare due to the diverse ways in which studies reported their findings. The absence of age and sex disaggregation in reporting of results was alarming as it is fairly well established that multimorbidity is influenced by these factors. A multimorbidity prevalence systematic review conducted for South Asia highlighted the insufficient work conducted in the area of multimorbidity and called for greater methodological rigour to build better scientific evidence in this domain.[55] Similarly, we also advocate for more studies to be conducted with rigorous study designs.

A robust health information system in South Africa is needed to monitor changes in multimorbidity and disease patterns over time. With plans to implement the NHI scheme, an electronic health record (EHR) system would be essential for registering and tracking patients.[56] However, current sources of patient-level data are fragmented and poorly coordinated.[57, 58] Problems with the routine health-information system should be addressed to enhance the monitoring of the disease burden in South Africa.

8.3. Recommendations

Given the implications discussed in the previous section, the following recommendations are offered to strengthen research on multimorbidity and reinforce the critical need for policy development around multimorbidity in South Africa.

i. Appropriate policies are in place but these need to be translated into action. Implementation of policies like the *South African Policy for Older Persons* would help to ensure access to healthcare for key groups affected by multimorbidity. It is recommended that a desktop review of existing health policies be conducted, to identify gaps in health policy and regulation to address multimorbidity at service implementation level.

ii. Research is needed into the effects of gender differentials in multimorbidity and whether this is related to a lack of access to healthcare. The gender differentials need to be unpacked to provide insight on how to make health systems more responsive to the needs of men and women. For example, men may need to be actively targeted in screening programmes to increase levels of awareness. In addition, further research is needed to establish the impact that multimorbidity has on quality of life, and the financial burden for individuals and the health system.

iii. A robust health-information system is needed to monitor trends and changes in disease burdens. The current system needs to be better utilised to enable monitoring of multimorbidity trends in the population and to better manage patient care. Integration between private and public healthcare information systems would also provide a more comprehensive understanding of disease trends in the country.

iv. Improved research standards should be adopted for reporting multimorbidity. For example, the following should be reported:

- Define how multimorbidity is used in the study.
- Detail which disease conditions are included and the reason(s) for their inclusion.
- Describe how data were collected for each included disease condition.
- Report weighted and non-weighted proportions of people with multimorbidity.
- Report prevalence estimates by age and sex, in at least 10-year age bands.

- Establish a standard set of health conditions to ask patients about for future health surveys.

8.4. Conclusion

Multimorbidity has been largely overlooked in South Africa due to previously mentioned limitations related to routine health-information systems as well as the current focus on single disease burdens. This thesis provides the first attempt at estimating the prevalence of multimorbidity, common disease clusters and risk factors associated with multimorbidity in South Africa.

This thesis used a systematic analysis of three national health survey datasets, together with a contemporary systematic review, to provide a comprehensive, up-to-date view of the state of multimorbidity and multimorbidity research in the country. These surveys are currently the most recent national data available in the country and can serve as baseline estimates for future assessments.

This thesis presents and applies a transparent, consistent methodological approach to examining multimorbidity in national surveys.[59] This method could be easily adopted by other studies, particularly in countries that lack robust health-information systems. This thesis thus presents a way to overcome methodologically fragmented research in the area.

Multimorbidity is a growing concern in South Africa, and therefore requires urgent action. The findings of this thesis highlight the need to tackle multimorbidity by providing robust estimates of prevalence.[60] It further highlights pertinent issues that drive multimorbidity such as ageing, gender and access to healthcare. In addition, this thesis provides information on high-risk groups which can be used to target individuals who are at high risk of developing multimorbidities. Multimorbidity poses a threat to the ailing health system in South Africa. Activists, researchers and the public need to pressure decision makers in government to act and provide responsive healthcare to the population.

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Appendix A: Ethics letter

UNIVERSITY *of the* WESTERN CAPE

60 YEARS *of hope, action & knowledge*

10 September 2020

Ms RA Roomaney
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM20/5/8

Project Title: Burden of Multimorbidity in South Africa: Implications for health policy and service delivery

Approval Period: 12 June 2020 – 12 June 2023

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for the duration of the project.

Permission to conduct the study must be submitted to BMREC for record-keeping.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

Director: Research Development
University of the Western Cape
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NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

Appendix B: Article 1 (https://doi.org/10.1136/bmjopen-2020-042889)

Open access Protocol

BMJ Open

Prevalence of multimorbidity in South Africa: a systematic review protocol

Rifqah A Roomaney ,[1,2] Brian van Wyk ,[2] Eunice Bolanle Turawa ,[1,3] Victoria Pillay-van Wyk [1]

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ABSTRACT

Introduction Multimorbidity has increased globally over the past two decades, due to ageing populations and increased burden of non-communicable diseases (NCDs). In a country like South Africa, with a growing burden of NCDs and a high prevalence of HIV, information on multimorbidity can improve planning for healthcare delivery and utilisation, and reduce costs in the context of constrained health resources. This review aims to synthesise prevalence studies on multimorbidity, and identify dominant clusters and trends of multimorbidity in South Africa.

Methods and analysis We will search electronic bibliographic databases (PubMed, Scopus, JSTOR, POPLINE, PsycINFO, ScienceDirect, Web of Science and CINAHL), and the reference lists of included articles. Two researchers will independently screen title and abstracts, and then full text to identify studies published before and in 2020 that report on prevalence of multimorbidity in South Africa. Risk of bias assessments will be done for each study. Information on the prevalence of multimorbidity and disease clusters will be extracted from each study. Where possible, prevalence of specific clusters of multimorbidity will be pooled using a random effects meta-analysis to account for variability between studies. The I^2 statistic will be used to establish the extent of heterogeneity due to variation in prevalence estimates rather than due to chance. The systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Ethics and dissemination Only published journal articles will be included in the systematic review. This review received ethics approval as part of a larger project by the University of the Western Cape Biomedical Science Research Ethics Committee (BM20/5/8). The findings from this research will be used to estimate the prevalence of multimorbidity in South Africa and will contribute to the design of future research projects. The findings will be disseminated in a peer-reviewed journal article.

PROSPERO registration number CRD42020196895.

Strengths and limitations of this study

- ► To our knowledge, this will be the first systematic review to estimate the prevalence of multimorbidity in South Africa.
- ► This systematic review will include articles conducted in community/general and health-facility settings.
- ► This protocol follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols 2015[35] guidelines.
- ► The findings will be used to inform future research projects and can guide health policy and planning for service delivery in South Africa.
- ► The study may be limited by the way in which source articles define multimorbidity.

INTRODUCTION

Multimorbidity, defined as the coexistence of two or more chronic conditions, has increased globally in the past two decades.[1 2] Although a gold standard definition of multimorbidity has not been established, it has been recommended that the operationalisation of multimorbidity can include a combination of non-communicable diseases (NCDs), mental health conditions and infectious diseases.[1] The increase in multimorbidity is attributed to ageing populations[3] and the growing burden of NCDs.[1] Whereas the increase in NCDs was initially predominantly observed in high-income countries; recently this increase was also reported in low and middle-income countries (LMICs).[4]

The prevalence of multimorbidity places additional stress on already severely strained health systems in LMICs[5] by driving up healthcare utilisation and costs.[6–9] Furthermore, multimorbidity alters the patterns of individual health behaviours and access of health services; which in turn, has further implications for health systems responsiveness and pressing the urgency for further health reforms away from a programmatic approach to comprehensive, integrated services delivery. The need for reforms to integrate the treatment of various chronic conditions has been acknowledged.[10 11] Researchers have since highlighted the need to incorporate elements specific to people living with multimorbidity. These include the need for: multimorbid patients to have access to coordinated and multidisciplinary teams of health professionals; support for patients to self-manage their workload, and evidence-based guidelines applicable to multimorbid

Appendix C: Article 2 (https://bmjopen.bmj.com/content/11/10/e048676 / http://dx.doi.org/10.1136/bmjopen-2021-048676)

Open access Original research

BMJ Open

Multimorbidity in South Africa: a systematic review of prevalence studies

Rifqah Abeeda Roomaney [1,2] Brian van Wyk [2] Eunice Bolanle Turawa [1,3] Victoria Pillay-van Wyk [1]

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ABSTRACT

Objectives To review prevalence studies of multimorbidity in South Africa to identify prevalence estimates, common disease clusters and factors associated with multimorbidity.

Design Systematic review.

Setting South Africa (general community and healthcare facilities).

Data sources Articles were retrieved from electronic databases (PubMed, Web of Science, Scopus, CINAHL, Science Direct and JSTOR).

Eligibility criteria Studies addressing the prevalence of multimorbidity in South Africa were eligible for inclusion. A systematic search was done in various databases up to December 2020. A risk of bias assessment was conducted for each article using a modified checklist.

Study selection Two researchers independently screened titles and abstracts; assessed the risk of bias of each study and extracted data. Included studies were described using a narrative synthesis.

Results In total, 1407 titles were retrieved; of which 10 articles were included in the narrative synthesis. Six studies had a low risk of bias and three had a moderate risk of bias. One study was not assessed for risk of bias, because there was no criteria that apply to routine health information systems. Three of the included studies were population-based surveys, four were community-based cohorts and three cross-sectional studies of health facility data. The prevalence of multimorbidity was low to moderate (3%–23%) in studies that included younger people or had a wide range of selected age groups; and moderate to high (30%–87%) in studies of older adults. The common disease clusters were hypertension and diabetes, hypertension and HIV, and TB and HIV.

Conclusion All studies indicated that multimorbidity is a norm in South Africa, especially among older adults. Hypertension is the main driver of multimorbidity. Research on multimorbidity in South Africa needs to be strengthened with high-quality study designs.

PROSPERO registration number CRD42020196895.

Strengths and limitations of this study

- ► To our knowledge, this is the first systematic review of multimorbidity prevalence studies in South Africa and of an African country.
- ► This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.
- ► This review includes studies conducted in general community and healthcare settings.
- ► A limitation of this study was that it excludes studies conducted in subpopulations with one specific disease (eg, multimorbidity in patients with cancer).
- ► Grey literature (non-academic literature) was excluded.

INTRODUCTION

One-third of adults residing in low-income and middle-income countries (LMICs) are thought to be afflicted by two or more coexisting health conditions; also known as multimorbidity.[1] The last two decades have seen an exponential growth in the number of studies about multimorbidity.[2] This can be attributed to more research into ageing populations,[2] and the recognition that multimorbidity impacts patient care and healthcare systems.[3] Other consequences of multimorbidity include increased mortality levels,[4] lowered quality of life,[5] the risk of polypharmacy[6] and intensified utilisation of health services and associated costs.[7 8] More recently, multimorbidity was implicated as a risk factor for COVID-19 mortality.[9 10]

Most research to date has been conducted in high-income countries; sparking calls for similar research in LMICs.[2 11 12] Research is needed into multimorbidity in LMICs, like South Africa, where disease burdens differ to those in high-income countries. South Africa has a unique disease burden—it has the largest number of people living with HIV in the world.[13] With the availability of antiretrovirals, people with HIV are living longer and developing age-related non-communicable diseases (NCDs).[14] At the same time, the burden of disease due to NCDs is increasing in the country; giving rise to a disease pattern of coexisting infectious diseases and NCDs.[15 16]

In resource-constrained health settings, it is imperative that we estimate the magnitude of multimorbidity as well as the nature and type of disease clusters to more efficiently manage patients and organise health service delivery. South Africa lacks a robust national routine

Appendix D: Article 3 (https://doi.org/10.11604/pamj.2022.41.140.32104)

Article

PanAfrican Medical Journal

Commentary

Decolonising multimorbidity? research gaps in low and middle-income countries

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Keywords: Multimorbidity, low and middle-income countries, comorbidity

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Decolonising multimorbidity? research gaps in low and middle-income countries

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Abstract

Multimorbidity is defined as the co-existence of multiple health conditions in one person. However, its use in research has been predominantly applied to non-communicable diseases, because research was conducted almost exclusively in developed countries. More recently, infectious diseases of long duration, such as human immunodeficiency virus (HIV), have also been included in the conceptualization of multimorbidity. While multimorbidity is a growing area of research globally; much less is known about the phenomenon in low and middle-income countries (LMICs) where disease burdens are heavily

Appendix E: Article 4 (https://doi.org/10.1186/s13104-022-06164-3)

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BMC Research Notes

RESEARCH NOTE Open Access

A systematic method for comparing multimorbidity in national surveys

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Abstract

Objective: Due to gaps in the literature, we developed a systematic method to assess multimorbidity using national surveys. The objectives of this study were thus to identify methods used to define and measure multimorbidity, to create a pre-defined list of disease conditions, to identify potential national surveys to include, to select disease conditions for each survey, and to analyse and compare the survey findings.

Results: We used the count method to define multimorbidity. We created a pre-defined list of disease conditions by examining international literature and using local data on the burden of disease. We assessed national surveys, reporting on more than one disease condition in people 15 years and older, for inclusion. For each survey, the prevalence of multimorbidity was calculated, the disease patterns among the multimorbid population were assessed using a latent class analysis and logistic regression was used to identify sociodemographic and behavioural factors associated with multimorbidity. The prevalence of multimorbidity varied for each survey from 2.7 to 20.7%. We used a systematic and transparent method to interrogate multimorbidity in national surveys. While the prevalence in each survey differs, they collectively indicate that multimorbidity increases in older age groups and tends to be higher among women.

Keywords: Multimorbidity, Disease patterns, Latent class analysis, Prevalence, South Africa

Introduction

Multimorbidity (the co-existence of a minimum of two long term disease conditions in one individual) is associated with a range of negative impacts, including a reduced quality of life [1], problems with medication adherence [2] and premature death [3]. There is a dearth of studies on multimorbidity in low and middle income countries (LMIC) [4]. While there is a growing research interest on multimorbidity in South Africa, the variability in survey methods led to disparate estimates on the prevalence of multimorbidity [5–7].

Several South African nationally representative surveys (e.g. South African Demographic and Health Survey [SAHDS], South Africa National HIV Prevalence, Incidence, Behaviour and Communication Survey [SABSSM], and the National Income Dynamics Study [NIDS]) provide important information about health conditions in the general population, particularly adults, and can be used to determine the prevalence and patterns of multimorbidity [6]. Information on the prevalence of disease clusters, trends and the characteristics associated with disease clusters present an opportunity to advocate for improved service delivery and target high-risk individuals. In the current paper, we illustrate a uniform method of analysing multiple national surveys to create a composite overview of multimorbidity disease prevalence and disease clustering and, compare findings of three nationally representative surveys in South Africa.

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Main text

Methods

The objectives of this study were to: (a) identify methods used to define and measure multimorbidity, (b) create

Appendix F: Article 5 (https://doi.org/10.1371/journal.pone.0269081)

PLOS ONE

RESEARCH ARTICLE

One in five South Africans are multimorbid: An analysis of the 2016 demographic and health survey

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Data Availability Statement: The third party data underlying the results presented in the study are available from The DHS Program. Users can register on The DHS Program website (https://dhsprogram.com/). Once registered, interested researchers can request access to the DHS

Abstract

Multimorbidity is a global research priority, yet relatively little is known about it in low and middle income countries. South Africa has the largest burden of HIV worldwide but also has a growing burden of non-communicable diseases; potentially leading to uncommon disease combinations. Information about the prevalence of multimorbidity and factors associated with it can assist in healthcare planning and targeting groups of people for interventions. This study aimed to determine the prevalence of multimorbidity by age and sex, as well as factors associated with multimorbidity in people 15 years and older. This study analyses the nationally representative 2016 South African Demographic Health Survey. The sample included 10 336 people who participated in the Adult Health questionnaire and approximately 7 961 people who provided biomarkers. Multivariate logistic regression was used to measure the association of multimorbidity with age, sex, living in an urban or rural area, education level, wealth level, employment status, body mass index, current alcohol or tobacco use. All analyses were conducted using STATA 15. Multimorbidity was present in 20.7% (95% CI: 19.5%– 21.9%) of participants; in 14.8% (95% CI: 13.4% - 16.3%) of males and 26.2% (95% CI: 24.7–27.7%) of females. Multimorbidity increased with age; with the highest odds in the 55–64 years old age group (OR: 24.910, 95% CI: 14.901–41.641, $p < 0.001$) compared to those aged 15–24 years. The odds of multimorbidity was also higher in young females compared to young males (OR: 2.734, 95% CI: 1.50–4.99, $p = 0.001$). Possessing tertiary education (OR: 0.722, 95% CI: 0.537–0.97, $p = 0.031$), being employed (OR: 0.813, 95% CI: 0.675–0.979, $p = 0.029$) or currently using alcohol (OR: 0.815, 95% CI: 0.686–0.968, $p = 0.02$) was protective against multimorbidity. Multimorbidity is prevalent within the South African population, with females and older adults being most affected. However, multimorbidity is also observed in younger adults and most likely driven by the high prevalence of HIV and hypertension.

Appendix G: Article 6 (https://doi.org/10.3389/fpubh.2022.862993)

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ORIGINAL RESEARCH
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Multimorbidity Patterns in a National HIV Survey of South African Youth and Adults

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Introduction: Information pertaining to multimorbidity is frequently informed by studies from high income countries and it is unclear how these findings relate to low and middle income countries, where the burden of infectious disease is high. South Africa has a quadruple burden of disease which includes a high HIV prevalence and a growing burden of non-communicable diseases. This study aimed to analyse the prevalence and patterns (disease classes or clusters) of multimorbidity in South Africa.

Methods: A secondary analysis of individuals over the age of 15 years who participated in the Fifth South African National HIV Prevalence, Incidence, Behavior and Communication Survey, 2017 (SABSSM 2017) was done. Six disease conditions were identified in the analysis (cancer, diabetes, heart disease, hypertension/high blood pressure, tuberculosis, and HIV). Chi-square tests were used to test for the differences in disease prevalence by sex. Common disease patterns were identified using a latent class analysis.

Results: The sample included 27,896 participants, of which 1,837 had comorbidity or multimorbidity. When taking population-weighting into account, multimorbidity was present in 5.9% (95% CI: 5.4–6.4) of the population The prevalence of multimorbidity tended to be higher among females and increased with age, reaching 21.9% in the oldest age group (70+). The analyses identified seven distinct disease classes in the population. The largest class was "Diabetes and Hypertension" (36.3%), followed by "HIV and Hypertension" (31.0%), and "Heart disease and Hypertension" (14.5%). The four smaller classes were: "HIV, Diabetes, and Heart disease" (6.9%), "TB and HIV" (6.3%), "Hypertension, TB, and Cancer" (2.8%), and "All diseases except HIV" (2.2%).

Conclusion: As the South African population continues to age, the prevalence of multimorbidity is likely to increase which will further impact the health care system. The prevalence of multimorbidity in the population was relatively low but reached up to 20% in the oldest age groups. The largest disease cluster was the combination of diabetes and hypertension; followed by HIV and hypertension. The gains in improving adherence to antiretrovirals amongst treatment-experienced people living with HIV,

Appendix H: Article 7 (https://doi.org/10.3390/ijerph19042359)

International Journal of *Environmental Research and Public Health*

MDPI

Article

Aging with HIV: Increased Risk of HIV Comorbidities in Older Adults

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Abstract: With improved access to antiretroviral treatment (ART), adults with HIV live longer to reach older age. The number of older adults living with HIV is increasing steadily, giving rise to a new population of interest in HIV research and for invigorated considerations in health service delivery and policy. We analysed the profile of comorbidities in older people (50 years and older) living with HIV in South Africa. We conducted a secondary analysis of all individuals over 15 years who tested HIV positive in the Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017. We conducted multivariate logistic regression to determine the factors associated with having HIV comorbidity using Stata 15.0 software. We entered 3755 people living with HIV into the analysis, of whom 18.3% (n = 688) were 50 years or older. Older adults had four times greater odds (OR = 4.7 (3.1–7.0)) of having an HIV comorbidity compared to younger adults. Being female (OR = 1.6 (1.1–2.4)) and living in an urban area (OR = 2.6 (1.8–3.7)) increased the odds of HIV comorbidity. Older adults with HIV require comprehensive health care to deal with multimorbidity, to maximise the benefits gained by advances in HIV therapies.

Keywords: HIV; comorbidity; multimorbidity; aging; South Africa

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1. Introduction

South Africa has a generalised and mature HIV epidemic [1]. In 2017, the national HIV prevalence was estimated at 14%, which translated to approximately 7.8 million people living with HIV (PLWH). South Africa has the largest public antiretroviral therapy programme (ART) [1], with 5.6 million people on ART in 2020 [2]. South Africa has made some progress towards achieving The Joint United Nations Programme on HIV/AIDS (UNAIDS) 90–90–90 targets (that by 2020, 90% of all people living with HIV should know their status, that 90% of people diagnosed with HIV infection should receive treatment and that 90% of all people receiving treatment should have viral suppression [3]). In 2020, it was estimated that 92% of PLWH in South Africa knew their status [2], of which 75% were on ART and of which 92% on ART were virally suppressed [4]. It was further estimated that 70% of all PLWH in South Africa were on ART in 2020 [4]. It is envisaged that the number of PLWH on ART is likely to continue to grow as the country endeavors to meet ART coverage targets [5]. Improved access to ART, coupled with advances in ART regimens, have enabled PLWH to live longer lives [6], effectively changing HIV into a life-long chronic condition [7]. It has been noted that South Africa has a quadruple burden of disease [8], which includes a growing burden of non-communicable diseases (NCDs) [8]. A decade prior, researchers were predicting the negative impacts associated with the collision of these two epidemics in South Africa [9]. More recently, studies have found a high and overlapping prevalence of disease conditions such as HIV, tuberculosis and NCDs in both community settings [10–12] and health facilities in the country [13].

Several studies have shown that PLWH has a higher prevalence of multimorbidity and comorbidity compared to the general population due to premature ageing, side effects of

Appendix I: Article 8 (https://doi.org/10.3389/ijph.2022.1605072)

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Inequity in the Distribution of Non-Communicable Disease Multimorbidity in Adults in South Africa: An Analysis of Prevalence and Patterns

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Objectives: The present study examined the prevalence and patterns of non-communicable disease multimorbidity by wealth quintile among adults in South Africa.

Methods: The South African National Income Dynamics Study Wave 5 was conducted in 2017 to examine the livelihoods of individuals and households. We analysed data in people aged 15 years and older (N = 27,042), including self-reported diagnosis of diabetes, stroke, heart disease and anthropometric measurements. Logistic regression and latent class analysis were used to analyse factors associated with multimorbidity and common disease patterns.

Results: Multimorbidity was present in 2.7% of participants. Multimorbidity was associated with increasing age, belonging to the wealthiest quintile group, increasing body mass index and being a current smoker. Having secondary education was protective against multimorbidity. Three disease classes of multimorbidity were identified: Diabetes and Hypertension; Heart Disease and Hypertension; and Stroke and Hypertension.

Conclusion: Urgent reforms are required to improve health systems responsiveness to mitigate inequity in multimorbidity patterns in the adult population of South Africa as a result of income inequality.

Keywords: multimorbidity, disease patterns, latent class analysis, wealth index, South Africa

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INTRODUCTION

South Africa is an upper-middle-income country [1], with one of the highest levels of inequality in the world [2]. The country has a quadruple burden of disease; with mortality trends illustrating that 43% of deaths were due to non-communicable diseases (NCDs), 34% to HIV/AIDS and TB, 14% to other communicable diseases (and perinatal conditions, maternal causes and nutritional deficiencies) and 10% to injuries [3]. It is currently observed that NCDs disproportionately affect people in low and middle-income countries (LMICs), where 85% of premature deaths due to NCDs occur [4].

The observed large increases in NCD burdens in sub-Saharan Africa are driven by the increase in cardiovascular risk factors (i.e., unhealthy diets, physical inactivity, obesity and air pollution) [5].