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Multimorbidity in South Africa: A systematic review of prevalence studies

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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, 1,407 titles were retrieved; of which and ten articles were included in the narrative synthesis. Six studies had a low risk of bias, three had a moderate risk of bias and one based on a routine health information system was not assessed for risk of bias due to a lack of assessment criteria. The included studies were population-based surveys (n=3), community-based cohorts (n=4) and cross-sectional studies of health facility data (n=3). The prevalence of multimorbidity was low to moderate in studies which included younger people or had a wide range of selected age groups (3 – 23%); and moderate to high in studies of older adults (30 – 87%). The common disease clusters as reported were hypertension and diabetes; hypertension and HIV, and TB and HIV.

Conclusion

Despite differences in settings and study types; studies indicated that multimorbidity is a norm, especially in older adults in South Africa. Hypertension is a driver of multimorbidity. There are still too few studies focused on multimorbidity in South Africa and high-quality studies are needed.

Registration: PROSPERO (CRD42020196895)

295/ 300 words

Article Summary

Strengths and limitations of this study

- To our knowledge, this is the first systematic review of studies that determined the prevalence of multimorbidity in South Africa.
- This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.
- This study included studies conducted in general community and healthcare settings.
- This study was limited to the information reported in the included studies.

Keywords: Multimorbidity, chronic diseases, prevalence, South Africa, trends, disease clusters

INTRODUCTION

A third of adults residing in low and middle-income countries (LMICs) are thought to be afflicted by two or more co-existing 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 co-existing 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 diseases cluster to more efficiently manage patients and organize 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.[17-21] However, many of these studies suffer from the methodological problems that tend to plague multimorbidity studies elsewhere which is a lack of standardization.[22] 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 registered with PROSPERO (CRD42020196895) and published elsewhere.[23] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)[24] guided this study (Appendix 1). 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 epidemiology data on multimorbidity in the adult population of South Africa. The search strategy was reviewed by an expert librarian (Appendix 2). 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 Version X8.[25] The EndNote de-duplication function was employed, and remaining citations were uploaded into an electronic screening website, Rayyan.[26] 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 for potentially eligible articles were independently assessed by two researchers (RAR, EBT) using the electronic data capture system, the Burden of Disease Review Manager (BODREVMAN).[27] 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[28] and Hoy checklist.[29] The tool has been described elsewhere.[30] 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 standard deviation 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 Version 4.3 (California)[31] was used to extract data. STATA 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. This study was given ethical approval by the Biomedical Science Research Ethics Committee of the University of the Western Cape (BM20/5/8).

RESULTS

Search results

In total, 1081 records were screened after de-duplication (Figure 1). By screening titles and abstracts, 1041 articles were excluded. Forty-one full-text articles were assessed for eligibility, of which ten were included in a narrative synthesis.[32-41]

<Figure 1: PRISMA flow diagram>

Study characteristics

The sample sizes of included studies ranged from 422[35] to 47 334 participants[38] (Table 1). All included studies were published after 2015 but the period of data collected ranged from 2003[32] to 2015.[37, 38, 40] Three studies conducted a secondary data analysis of population-based surveys.[32-34] The surveys analysed were the 2003 World Health Survey (WHS),[32] 2007 and 2010 WHO Study on global AGEing and adult health (SAGE),[33, 35] and the 2008 and 2012 South African National Income Dynamics Survey (SANIDS).[34] Three studies were cross-sectional analyses of community-based cohorts and surveys.[36-38] The remaining three studies were of a cross-sectional nature and based in health facilities.[39-41]

Three studies were conducted nationally[32-34] with others conducted in Kwa-Zulu Natal province (n=3),[35, 36, 38] the Western Cape province (n=2) [40, 41] and Mpumalanga province (n=1).[37] One study was conducted in primary healthcare facilities in the Western Cape, North West, Northern Cape and Limpopo provinces.[39] Four studies were conducted in rural areas [35-38], two studies were conducted in urban areas[40, 41] and the remaining studies were conducted in both urban and rural areas.[32, 33, 39, 42] Six studies had a low risk of bias,[32-34, 37-39] three had a moderate risk of bias[35, 36, 40] 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 1: Study 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). [32]	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). [33]	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). [34]	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). [35]	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, Kwa-Zulu Natal (Rural)	Moderate (12)
	van Heerden, Barnabas, Norris *et al* (2017). [36]	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). [37]	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). [38]	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 of rural KwaZulu-Natal (Rural)	Low (14)
Cross-sectional study (Health facility-based)	Lalkhen, Mash (2015). [39]	N=5793 Sub-sample of 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)

Study type	Study	Study population and size	Year	Location	Risk of bias (score)
	Roche, de Vries (2017). [40]	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). [41]	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 i) the definition of multimorbidity used, ii) the number of disease conditions included in the study, iii) the actual disease conditions included and iv) how the disease conditions were measured.

All included studies used a "count" of the number of diseases to define multimorbidity i.e. multimorbidity was defined by having two or more diseases (Appendix 3). Half of these studies specified they were only focused on chronic conditions.[32-34, 37, 41] Two health facility-based studies included acute conditions such as lower respiratory infections.[39, 40] The inclusion of acute disease conditions could inflate the prevalence of multimorbidity. The full list of disease conditions included can be found in Appendix 3.

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.[37] 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 four [41] to 24.[40] (Table 2). Diabetes was included as a disease condition in all ten 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 (Appendix 3). 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 2: Ten common disease conditions reported in articles reporting on multimorbidity

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,[33, 37] reporting each disease with their most common co-morbid condition,[38, 39]

or schematics detailing double and triple morbidities.[34, 37, 41] 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.[32, 35, 36, 40]

While it was not possible to ascertain the largest disease cluster in one study, Garin, Koyanagi [33] 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 co-morbid conditions for all other disease conditions.

Table 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 ten disease clusters[34, 41] and others reporting more than twenty disease clusters[37-39] A more detailed list of disease combinations can be found in Appendix 4.

Hypertension was frequently co-morbid with other diseases (Table 3). Weimann, Dai [34] and Oni, Youngblood [41] 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 [39] also found hypertension and diabetes to be the largest disease cluster in their study. While Chang, Gómez-Olivé [37] 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;[37, 38] 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.[38] 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.[41]

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 e.g. self-reported or biologically measured (Appendix 3).

Table 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**	[34, 38, 39, 41]
Hypertension	HIV		**3**	[34, 38, 41]
TB	HIV		**3**	[34, 38, 41]
Hypertension	TB		**2**	[34, 41]
Diabetes	HIV		**2**	[38, 41]
TB	Diabetes		**1**	[34]
Hypertension	Osteoarthritis		**1**	[39]
Asthma	Hypertension		**1**	[39]
Hypertension	COPD		**1**	[39]
Hypertension	IHD		**1**	[39]
Hypertension	Dyslipidaemia		**1**	[37]
Hypertension	Anaemia		**1**	[37]
Hypertension	Dyslipidaemia	Anaemia	**1**	[37]
Anaemia	HIV		**1**	[37]
Hypertension	Anaemia	HIV	**1**	[37]

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 (Appendix 5). Two studies reported the median/mean age of participants but the age range of participants was not included[39, 40] and one did not report an overall multimorbidity prevalence for their study[36]. 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 2); and moderate to high in studies reporting on adults aged 50 years and older (30% – 71%) (Figure 3).

<Figure 2: Graph of multimorbidity prevalence estimates for studies that include younger age groups>

<Figure 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 4). In those 18 years and above, Afshar, Roderick [32] 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.[34] 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%).[33]

Among community-based cross-sectional studies, the prevalence among older adults ranged from 18%[38] to 69%.[37] However, Chang, Gómez-Olivé [37] 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.[37]

In health facilities, two studies found moderate levels of multimorbidity (14.4% and 22.6%).[39, 41] 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.[40]

Table 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)

	Study	Year	Age band (years)	Prevalence of multimorbidity	
				n/N	% (95% CI)[α]
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
		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.
□ 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 (Appendix 3). Multimorbidity was frequently associated with increasing age. [32-34, 37, 38, 41] However, Garin, Koyanagi [33] noted a decrease in the prevalence in multimorbidity in the age group 60+ years and Chang, Gómez-Olivé [37] noted a decrease from the age 69+ years.

Being female was inconsistently linked to a high prevalence of multimorbidity. The pattern was noted in two studies;[33, 34] although another study reported it was not statistically significant;[37] while one found no distinction between males and females.[41] One study found that living in urban areas was a risk factor for multimorbidity[34] while another found that living in rural areas was associated with multimorbidity.[33] Other factors found to be associated with multimorbidity were: a lower level of education;[32, 33] being separated, divorced or widowed;[33, 37] living in Kwa-Zulu Natal or the Eastern Cape provinces, being Indian/Asian or being obese.[34] Socioeconomic deprivation was found to be associated with multimorbidity in one study,[34] but another found no association between wealth and multimorbidity.[37]

Other studies identified the effects of multimorbidity such as having memory complaints (in women), suffering from depression,[35] decreased well-being and self-reported health.[37, 38] One study found that length of stay in hospital was not related to multimorbidity and also did not link lifestyle risk factors to multimorbidity.[40]

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 low and middle-income countries.[1]

Three of our included studies reported fairly low levels of multimorbidity prevalence.[32, 34, 38] One study standardised the prevalence to the world population which may have resulted in a lower prevalence estimate (11.2%).[32] 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%.[34] 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%).[43] The low prevalence found in this survey could be attributed to a healthier population being sampled or as the authors suggested, underreporting of self-report data due to stigma around HIV and TB.[34] 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.[40] 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-report data.[38] Also, they had missing data on HIV due to additional consent being required.

Age is accepted to be an important predictor of multimorbidity.[40] 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 low and middle-income countries.[12] 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.[44]

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),[45] 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.[46] This cluster of disease was more prevalent than having hypertension or diabetes only. Information on the prevalence of co-morbidities 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.[47] 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 Kharrazi [48] 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.[49]

This systematic review was limited to the information reported in the included studies. It was also limited in that it excluded studies conducted with sub-populations that had a 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 on the African continent and one of the few focused on a 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. They may also be reflective of the situation in other low and middle-income countries.

Our study found that a large component of multimorbidity appears to be 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 observe a trend.

More studies are needed in low and middle-income countries to better understand the prevalence, disease burden and impact of multimorbidity. Future studies on multimorbidity should endeavour to use standardised age groups and report results by age and sex. Many more sources of secondary data could be further exploited to give a better picture of multimorbidity in South Africa.

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Contributorship statement

RAR, VPvW, BvW and EBT conceptualised the study. RAR and EBT conducted screening and data extraction. RAR wrote the first draft. All authors reviewed and gave input into subsequent drafts.

Data Sharing Statement

No additional data available.

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Competing Interests

None declared.

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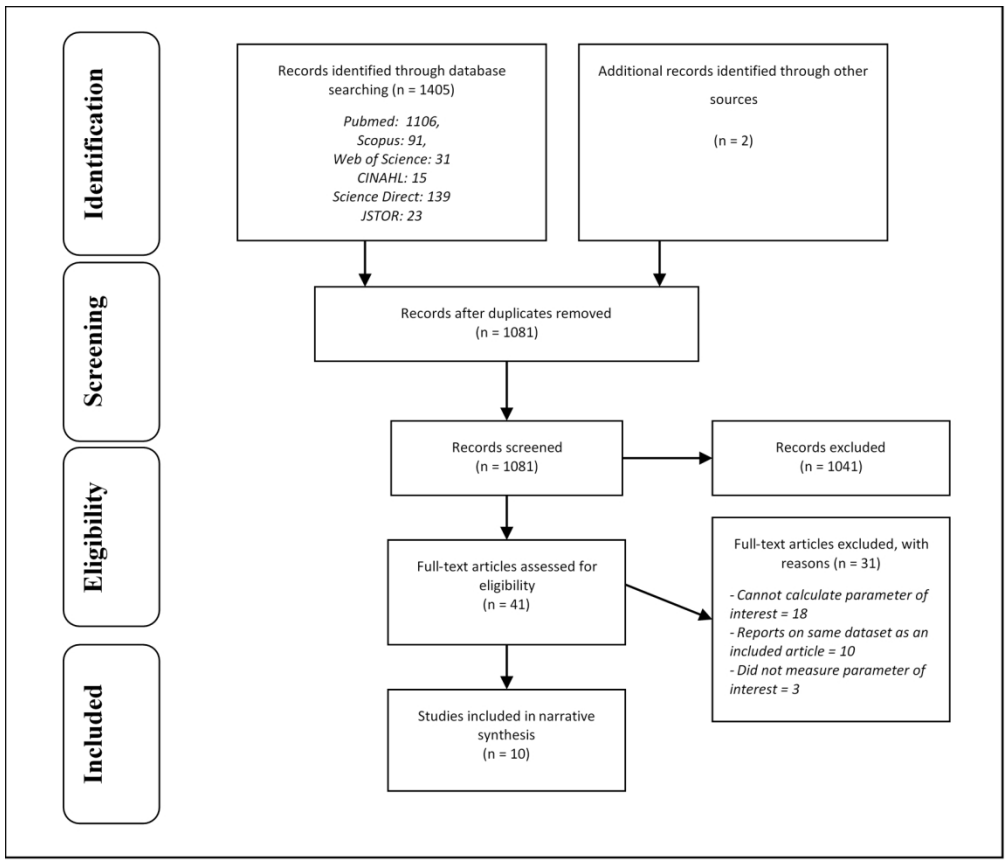

Figure 1: Study flow diagram

153x131mm (300 x 300 DPI)

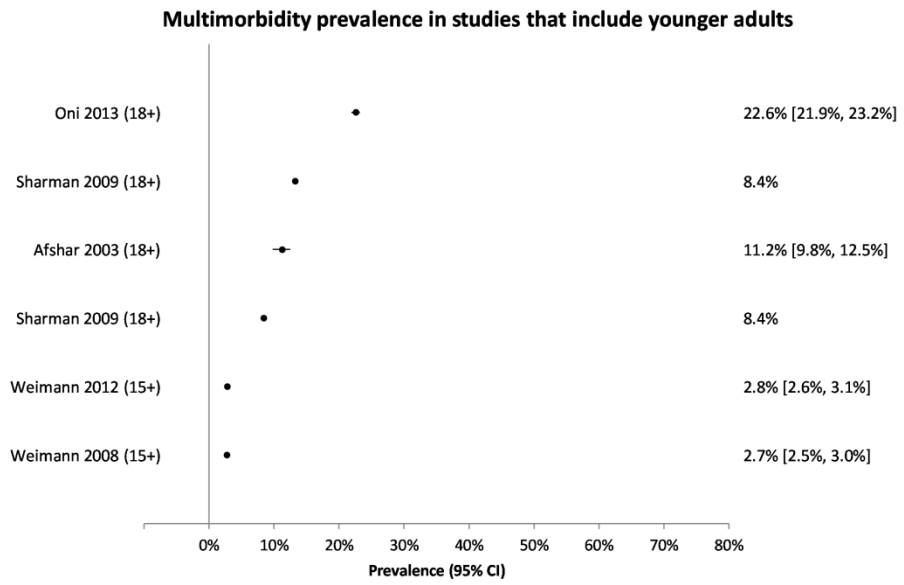

Figure 2: Graph of multimorbidity prevalence estimates for studies that include younger age groups

209x134mm (300 x 300 DPI)

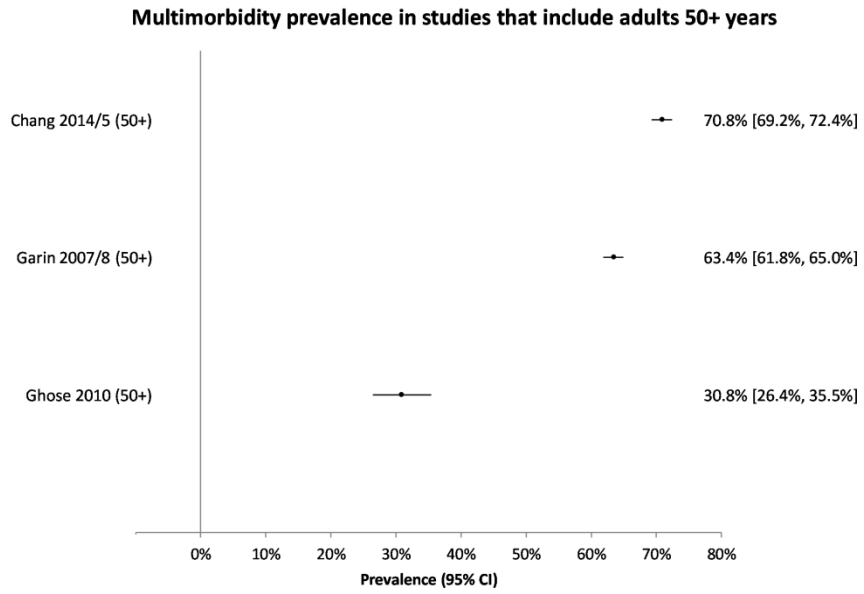

Figure 3: Graph of multimorbidity prevalence in studies including persons aged 50 years and older

209x135mm (300 x 300 DPI)

Supplementary file to *Multimorbidity in South Africa: A systematic review of prevalence studies*

Appendix 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2: Search Strategy

Study search output for multimorbidity study- December 2020

Search number	Query	Results
5	#4 NOT (animals[mh] NOT humans[mh)	1,106
4	(#4) AND (prevalence OR "prevalence"[mh] OR epidemiology OR endemic OR "epidemic outbreaks")	1,145
3	#1 and #2	1506
2	South Africa[mh] OR South Africa*[tiab] OR RSA [tiab] OR Africa, Southern[mh:noexp] OR Southern Africa[tiab]	68485
1	Multimorbidity OR multi-morbidity OR multimorbidity[tiab] OR multi morbidities OR multi morbidities OR multimorbidity[mh] OR multimorbidit* OR multimorbid OR multi-morbidit* OR "multiple morbidities" OR "multiple-morbidit*" OR co-morbid[tiab] OR co-morbid* OR comorbidity OR co-occur OR coexist OR co-exist OR multi-disease* OR multi-disease*	394636

Scopus database search output: 91 document reports

(TITLE-ABS-KEY (multistability OR multi-morbidity OR comorbidities OR multi-morbidities OR multimorbidit* OR multi-morbidit*) AND TITLE-ABS-KEY ("South Africa*" OR rsa OR "Southern Africa") AND TITLE-ABS-KEY (prevalence OR epidemiology OR endemic OR "epidemic outbreaks")) AND DOCTYPE (ar)

Web of science search output: 31 document reports

TOPIC: (multimorbidity OR multi-morbidity OR multimorbidities OR multi-morbidities OR multimorbidit* OR multi-morbidit*) AND TOPIC: ("South Africa" OR rsa OR "Southern Africa") AND TOPIC: (prevalence OR epidemiology OR endemic OR "epidemic outbreaks"). Indexes: SCI-EXPANDED.

Appendix 3: Additional information on each study

Study	Study population and size	Year	Location	Study type	Conditions included	Definition of MM used	Why were conditions included?	Factors associated with multimorbidity (MM)
Afshar, Roderick, Kowal et al. (2015). *Multimorbidity and the inequalities of global ageing: a cross-sectional study of 28 countries using the World Health Surveys*	N= 2629. Adults 18 years and older in the 2003 World Health Survey.	2003	South Africa. (56.3% urban)	Population-based survey. WHS 2003.	• Angina / Angina Pectoris (Heart Disease) • Arthritis • Asthma • Depression • Diabetes • Schizophrenia or Psychosis	The presence of two or more **chronic** diseases.	Chronic conditions were chosen in this survey to reflect health system coverage and corresponded to conditions known to affect older people.	- Increasing country GDP - Increasing age - Lower education
Garin, Koyanagi, Chatterji et al (2016). *Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study*.	N = 3836. Adults older than 50 years in the WHO Study on global AGEing and adult health (SAGE) 2007.	2007-2008	South Africa. Not stated if urban or rural.	Population based survey. SAGE 2007.	• Angina` • Arthritis • Asthma • Cataract • Cognitive impairment' • COPD • Depression` • Diabetes • Edentulism • Hypertension* • Obesity* • Stroke	Having at least 2 of 12 **chronic** conditions included in the study.	Selected 12 chronic conditions with high prevalence in most settings that significantly affect health	- Generally increased with age but decreased in people over 60 years - Being female - Lower education - Being separated/ divorced/widowed - Living in a rural area
Weimann, Dai, Oni (2016). *A cross-sectional and spatial analysis of the prevalence of multimorbidity and its association with socioeconomic disadvantage in South Africa: A comparison*	N=18526 (2008) & N=20015 (2012) Adults (age 15+ years) sub-sample from National Income Dynamic Survey Wave 1	2008, 2012	South Africa. Urban and rural areas included.	Population based survey. NIDS 2008 & 2012.	• Diabetes • HIV • Hypertension (self-reported or measured) • TB	The presence of two or more **chronic** health conditions existing simultaneously in an individual.	Hypertension and diabetes were included due to being the most prevalent non-communicable diseases. HIV and TB were included to monitor trends over time.	- Increasing age - Being female - Socioeconomic deprivation - Obesity - Living in urban areas - Living in Kwa-Zulu Natal or Eastern Cape provinces (Province) - Being Indian/Asian (Race)

between 2008 and 2012.	(2008) and 3 (2012).							
Ghose, Razak (2017). *Memory and Learning Complaints in Relation to Depression among Elderly People with Multimorbidity*.	N=422. Adults aged 50+ infected and / or affected by HIV in the SAGE WOPS 2010.	2010	Hlabisa subdistrict, Kwa-Zulu Natal. Not stated if urban or rural.	Population based survey. SAGE WOPS 2010.	• Arthritis • Asthma • Cancer • Chronic lung disease • Diabetes • Heart Disease • Hypertension • Stroke	>1 condition	Not clearly stated.	- Memory complaints in women - Being diagnosed with depression
van Heerden, Barnabas, Norris et al (2017). *High prevalence of HIV and non-communicable disease risk factors in rural KwaZulu-Natal, South Africa*.	N=570. Participants in a cohort study of a package of HIV testing, referral to care and follow-up visits to increase engagement in HIV care	Nov 2011 - Jun 2012	KwaZulu-Natal. Rural.	Cross-sectional study. Community based.	• Depression • HIV*[1] • Hyperglycaemia* • Hyperlipidaemia* • Hypertension* • Obesity*	Not reported.	Links to study objectives to investigate HIV and NCD risk factors.	Not reported
Chang, Gómez-Olivé, Payne et al. (2019). *Chronic multimorbidity among older adults in rural South Africa*	N = 3889. Adults enrolled in the Health and Ageing in Africa: A longitudinal study of an INDEPTH Community in South Africa (HAALSI) Programme.	2014-2015	Agincourt Health and Demographic Surveillance System, Bushbuckridge subdistrict, Mpumalanga. Rural.	Cross sectional study. Community based.	• Alcohol Dependence` • Anaemia* • Angina` • Chronic Bronchitis • Depression` • Diabetes* • Dyslipidaemia* • HIV* • Hypertension* • Post-Traumatic Stress Disorder`	Two definitions of multimorbidity were applied: the presence of more than one condition and the presence of more than one category of conditions (cardiometabolic conditions, mental disorders, HIV and anaemia).	Based on selection of conditions in sister studies, known health conditions in area and based on consultation with community.	- Increased with age until 69 years and then decreased - Being separated/divorced or widowed - HIV associated with higher levels of MM using the second definition - Physical functioning and well-being and self-rated health were worse with increasing numbers of conditions and categories ---------- - Living with more people (household size) decreased odds of multimorbidity

[1] HIV is measured but data on HIV is presented as a sub-group and thus excluded in this analysis

								- No relationship between wealth and multimorbidity - Females has higher levels of multimorbidity but it was not significantly different
Sharman, Bachmann (2019). *Prevalence and health effects of communicable and non- communicable disease comorbidity in rural KwaZulu-Natal, South Africa.*	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 of rural KwaZulu-Natal. Rural.		• Hypertension (self-reported or on treatment) • Diabetes • TB within past 12 months • HIV (measured or on treatment)*	Proportion of participants with two or more conditions *(termed as co-morbidity)*	Based on research gap where few studies examine the prevalence of communicable and non-communicable diseases.	- Increasing age were associated with MM - Self-reported health poorer with multimorbidity
Lalkhen, Mash (2015). *Multimorbidity in non-communicable diseases in South African primary healthcare.*		2010	Primary healthcare facilities in the Western Cape, North West, Northern Cape and Limpopo. Rural and urban.	Cross sectional study. Facility based.	• Asthma* • COPD* • Diabetes* • Epilepsy* • Hypertension* • Osteoarthritis* • And other diseases	The presence of two or more diseases.	Study aimed to examine non-communicable diseases. All conditions recorded.	Not reported
Roche, de Vries (2017). *Multimorbidity in a large district hospital: A descriptive cross-sectional study.*	N= 491. Consecutive admissions to an internal medicine department of a large district hospital.	2015	District hospital, Cape Town. Urban.	Cross sectional study. Facility based-Internal medicine department	• Anaemia* • Asthma* • Bronchiectasis* • Cancer* • Cardiac failure* • Cerebrovascular accident* • COPD* • Cor pulmonale* • Current TB* • Deep vein thrombosis* • Delirium*	More than one disease concurrently.	Not clearly stated but appears to include all conditions that were seen in the district hospital.	- Length of stay not related to multimorbidity. - Lifestyle risk factors were not associated with multimorbidity.

					• Diabetes* • Dilated cardiomyopathy* • Dyslipidaemia* • Epilepsy* • Gastroenteritis* • HIV* • Hypertension* • Ischaemic heart disease* • Lower respiratory tract infection* • Pneumonia* • Renal failure* • Sepsis* • Urinary tract infection*			
Oni, Youngblood, Boulle et al. (2015). *Patterns of HIV, TB, and non-communicable disease multi-morbidity in peri-urban South Africa- a cross sectional study*.	N=14364. Chronic disease patients (adults) with at least one disease (HIV, TB, diabetes, and hypertension) identified on electronic databases.	Sep 2012 - May 2013	Michael Mapongwana clinic, Khayelitsha, Cape Town. Peri-urban area.	Facility based RHIS. Western Cape Department of Health Data Repository, electronic prescription system.	• Diabetes* • HIV* • Hypertension* • TB*	Coexistence of more than one **chronic** condition in one person.	Informed by the research gap between NCDs and communicable diseases.	- Increasing age associated with MM. --- - No significant differences between males and females.

Appendix 4: Common disease conditions / disease clusters

Study	Year	Conditions included	Common disease clusters identified in South Africa
Garin, et al (2016)	2007-2008	• Angina` • Arthritis • Asthma • Cataract • Cognitive impairment` • COPD • Depression` • Diabetes • Edentulism • Hypertension* • Obesity* • Stroke	**Disease Combinations** - Hypertension was commonly present with diabetes, stroke, angina, cataract and all other conditions. - Obesity and diabetes commonly co-occurred.
Weimann et al (2016)	2008, 2012	• Diabetes • HIV • Hypertension **(self-reported or measured)** • TB	Of the extrapolated 8,6 million people included, 89.2% had a single condition, 10.5% had two conditions, and 0.2% had three conditions. **Disease Combinations (2008):** **Two disease conditions:** 1) Diabetes and Hypertension (70.8%) 2) TB and Hypertension (13.2%) 3) HIV and Hypertension (10.8%) 4) HIV and TB (3.9%) 5) TB and Diabetes (0.8%) 6) HIV and Diabetes (0.3%) **Three disease conditions:** 1) TB, Diabetes and Hypertension (63.9%) 2) Hypertension, HIV and TB (36.0%)
Chang et al (2019)	2014-2015	• Alcohol Dependence` • Anaemia* • Angina` • Chronic Bronchitis • Depression` • Diabetes* • Dyslipidaemia* • HIV* • Hypertension* • Post-Traumatic Stress Disorder`	Disease clusters limited to more than 1.5% of study population. **Disease profile and clusters** - Hypertension only (11.7%) - Hypertension and Dyslipidaemia (9.4%) - None (6.9%) - Hypertension and Anaemia (6.4%) - Hypertension and Dyslipidaemia and Anaemia (4.7%) - Dyslipidaemia (3.9%) - Anaemia (3.8%) - Anaemia and HIV (2.6%) - Hypertension and Anaemia and HIV (2.6%) - HIV (2.4%) - Dyslipidaemia and Anaemia (2.1%) - Dyslipidaemia and Anaemia and HIV (2.0%) - Hypertension and HIV (1.9%) - Hypertension and Dyslipidaemia and Diabetes (1.8%) - Hypertension and Depression (1.7%) - Dyslipidaemia and HIV (1.6%) - Hypertension and Dyslipidaemia and HIV (1.6%)

Study	Year	Conditions included	Common disease clusters identified in South Africa
Sharman, Bachmann (2019).	2009 - 2015	• Hypertension (self-reported or on treatment) • Diabetes • TB within past 12 months • HIV (measured or on treatment)*	Overlapping NCD and infectious disease co-morbidity was seen most frequently in adults older than 40 years where chronic NCDs increase alongside HIV. **Disease Clusters in 2015** (only percentages >2% shown. Percentages may overlap and thus not add up to 100%) **- In participants with hypertension** • Hypertension only (61.3%) • Diabetes (16.8%) • HIV (15.2%) • TB (1.6%) • HIV, diabetes and TB (2.5%) - In participants with diabetes: • Diabetes only (9.7%) • Hypertension (70.5%) • Hypertension and HIV (10.6%) • HIV (3.9%) • TB, HIV and hypertension (2.7%) - In participants with HIV • HIV only (75.9%) • Hypertension (12.1%) • TB (7.6%) • Hypertension, diabetes and TB (2.0%) - In participants with TB • TB only (25.6%) • HIV (61.0%) • hypertension (8.4%) • HIV and hypertension (8.3%) - In all participants over age 40 years • 34% had none of the four diseases examined. • Diabetes and hypertension (9.8%) • Hypertension, HIV and diabetes (6.5%)
Lalkhen et al (2015).	2010	• Asthma* • COPD* • Diabetes* • Epilepsy* • Hypertension* • Osteoarthritis*	- Hypertension and diabetes were the most common combination. - Hypertension was commonly comorbid with diabetes, epilepsy, asthma and COPD. **Disease combinations (only clusters larger than 2% listed)** - Of those that hypertension (n=3219), people also had: • Diabetes (18.2%) • Osteoarthritis (8.0%) • Asthma (3.6%) • COPD (2.1%) • Ischaemic heart disease (2.1%) - Of those that had diabetes (n=946), people also had: • Hypertension (63.1%) • Osteoarthritis (4.3%) - Of those that had epilepsy (n=375), people also had: • Hypertension (14.4%) • Osteoarthritis (2.4%) - Of those that had ashtma (n=485), people also had: • Hypertension (28.7%) • Osteoarthritis (5.8%)

Study	Year	Conditions included	Common disease clusters identified in South Africa
			• Diabetes (5.4%) • Acute bronchitis (4.7%) • Allergic rhinitis (3.1%) • TB (2.2%) - Of those that had COPD (n=140), people also had: • Hypertension (47.9%) • Osteoarthritis (12.1%) • Diabetes (9.3%) • TB (6.4%) • Epilepsy (3.6%) • Ischaemic heart disease with angina (3.6%) • TB (2.1%) • Lipid dysfunction (2.1%) • Tobacco abuse (2.1%) • Ischaemic heart disease with angina (2.1%) - Of those that had Osteoarthritis (n=530), people also had: • Ischaemic heart disease (2.3%)
Oni et al (2015).	Sep 2012 - May 2013	• Diabetes* • HIV* • Hypertension* • TB*	Of the 14364 participants, 21.3% had two diseases, 1.2% had three diseases and 0.1% had four diseases. **Of those that had two diseases (n=3058)** 1. Hypertension and diabetes (69.1%) 2. Hypertension and HIV (21.4%) 3. HIV and TB (6.2%) 4. HIV and diabetes (1.6%) 5. Hypertension and TB (1.5%) 6. TB and diabetes (0.2%) **Of those that had three diseases (n=173)** 1. Hypertension, diabetes and HIV (63%) 2. Hypertension, HIV and TB (26.6%)

Appendix 5: Multimorbidity prevalence by sex and age group

Study	Year	Age band (years)	Prevalence of multimorbidity					
			Persons		Males		Females	
			n/N	% (95% CI)	n/N	%	n/N	%
Population-based surveys								
Afshar, Roderick, Kowal et al. (2015)	2003	18 - 49	-	5.0 (3.9 – 6.0)	-	-	-	-
		50 - 64	-	21.6 (16.6 – 26.0)	-	-	-	-
		65+	-	30.1 (20.6- 39.7)	-	-	-	-
		Overall (18+)	-	**11.2 (9.8 - 12.5)**	-	-	-	-
Garin, Koyanagi, Chatterji et al (2016).	2007/8	50 - 59	-	60.1	-	*50.5*	-	*68.4*
		60 - 69	-	69.1	-	*63.3*	-	*73.2*
		70 - 79	-	65.9	-	*63.6*	-	*67.1*
		80+	-	55.9	-	*61.0*	-	*51.3*
		Overall (50+)	**2376 / 3747***	**63.4**	-	-	-	-
Weimann, Dai, Oni (2016).	2008	15 - 24	-	*0.0*	-	-	-	-
		25 - 34	-	*1.3*	-	-	-	-
		35 - 44	-	*2.1*	-	-	-	-
		45 - 54	-	*5.5*	-	-	-	-
		55 - 64	-	*9.9*	-	-	-	-
		65+	-	*9.0*	-	-	-	-
		Overall (15+)	-	**2.7 (2.5 – 3.0)**	-	-	-	-
	2012	15 - 24	-	*0.0*	-	-	-	-
		25 - 34	-	*0.8*	-	-	-	-
		35 - 44	-	*3.1*	-	-	-	-
		45 - 54	-	*3.1*	-	-	-	-
		55 - 64	-	*9.0*	-	-	-	-
		65+	-	*10.5*	-	-	-	-
		Overall (15+)	-	**2.8 (2.6 – 3.1)**	-	-	-	-
Ghose, Razak (2017).	2010	**Overall (50+)**	**130 / 422**	**30.8**	-	**16.0**	-	**35.8**
Community-based studies (cross-sectional study)								
van Heerden,	2011/12	18 - 25		*10.0*	-	-	-	-

Study	Year	Age band (years)	Prevalence of multimorbidity					
			Persons		Males		Females	
			n/N	% (95% CI)	n/N	%	n/N	%
Barnabas, Norris et al (2017).		26 - 35		*24.3*	-	-	-	-
		36 - 45		*53.2*	-	-	-	-
		46 - 65		*60.9*	-	-	-	-
		66+		*68.9*	-	-	-	-
Chang, Gómez-Olivé, Payne et al. (2019).	2014/15	40 - 49	430 / 685	62.8	-	*61.0*	-	*64.3*
		50 - 59	750 / 1069	70.2	-	*66.2*	-	*72.8*
		60 - 69	754 / 1056	71.4	-	*69.9*	-	*73.0*
		70 - 79	471 / 685	68.7	-	*65.8*	-	*71.7*
		80+	295 / 393	75.1	-	*76.0*	-	*74.3*
		Overall (40+)	**2700 / 3889**	**69.4**	**1182 / 1758**	**67.2**	**1518 / 2130**	**71.2**
Sharman, Bachmann (2019).	2009	**Overall (18+)**		**8.4**				
	2015	**40+**		**18.4**				
	2015	**Overall (18+)**		**13.2**				
Health facility-based studies (cross-sectional surveys and routine health information systems)								
Lalkhen, Mash (2015).	2010	**Overall (Mean ages±)**	**-**	**48.4**	-	-	-	-
Roche, de Vries (2017).	2015	**Overall (Mean age 49 years)**	**371 / 427**	**87.0**	-	-	-	-
Oni, Youngblood, Boulle et al. (2015).	2012/13	**Overall (18+)**	**3246 / 14364**	**22.6**	-	-	-	-

Italicised data extracted from graphs using Webplot digitizer
*estimated from available information
□standardised multimorbidity prevalence
NR indicates Not Reported.
±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).

Appendix 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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Multimorbidity in South Africa: A systematic review of prevalence studies

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Multimorbidity in South Africa: A systematic review of prevalence studies

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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, 1,407 titles were retrieved; of which ten 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 need to be revitalized, and with high-quality study designs.

Registration: PROSPERO (CRD42020196895)

295/ 300 words

Article Summary

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 (PRISMA) statement.
- This review includes studies conducted in general community and healthcare settings.
- A limitation of this study was that it excludes studies conducted in sub-populations with one specific disease (e.g. multimorbidity in cancer patients).
- Grey literature (non-academic literature) was excluded.

Keywords: Multimorbidity, Chronic diseases, Prevalence, South Africa, Trends, Disease clusters.

INTRODUCTION

A third of adults residing in low and middle-income countries (LMICs) are thought to be afflicted by two or more co-existing 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 co-existing 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 organize 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.[17-21] However, many of these studies suffer from the methodological problems that tend to plague multimorbidity studies elsewhere, which is a lack of standardization.[22] 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 registered with PROSPERO (CRD42020196895) and published elsewhere.[23] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)[24] guided this study (Appendix 1). 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 (Appendix 2). 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 Version X8.[25] The EndNote de-duplication function was employed, and remaining citations were uploaded into an electronic screening website, Rayyan.[26] 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).[27] 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[28] and Hoy checklist.[29] The tool has been described elsewhere.[30] 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 standard deviation, 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 Version 4.3 (California)[31] was used to extract data. STATA 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. This study was given ethics approval by the Biomedical Research Ethics Committee of the University of the Western Cape (BM20/5/8).

RESULTS

Search results

In total, 1407 titles were retrieved, and 1081 records were screened after de-duplication (Figure 1). By screening titles and abstracts, 1040 articles were excluded. Forty-one full-text articles were assessed for eligibility, of which ten were included in a narrative synthesis.[32-41] 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.

<Figure 1: PRISMA flow diagram>

Study characteristics

The sample sizes of included studies ranged from 422[35] to 47 334 participants[38] (Table 1). All included studies were published after 2015 but the period of data collected ranged from 2003[32] to 2015.[37, 38, 40] Three studies conducted a secondary data analysis of population-based surveys.[32-34] The surveys analysed were the 2003 World Health Survey (WHS),[32] 2007 and 2010 WHO Study on global AGEing and adult health (SAGE),[33, 35] and the 2008 and 2012 South African National Income Dynamics Survey (SANIDS).[34] Three studies were cross-sectional analyses of community-based cohorts and surveys.[36-38] The remaining three studies were of a cross-sectional nature and based in health facilities.[39-41]

Three studies were conducted nationally[32-34] with others conducted in Kwa-Zulu Natal province (n=3),[35, 36, 38] the Western Cape province (n=2) [40, 41] and Mpumalanga province (n=1).[37] One study was conducted in primary healthcare facilities in the Western Cape, North West, Northern Cape and Limpopo provinces.[39] Four studies were conducted in rural areas [35-38], two studies were conducted in urban areas[40, 41] and the remaining studies were conducted in both urban and rural areas.[32, 33, 39, 42] Six studies had a low risk of bias,[32-34, 37-39] three had a moderate risk of bias[35, 36, 40] and one based on a RHIS was not assessed for risk of bias due to a lack of assessment criteria for this study type.

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201 **Table 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). [32]	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). [33]	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). [34]	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). [35]	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). [36]	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). [37]	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). [38]	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). [39]	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). [40]	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). [41]	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 i) the definition of multimorbidity used, ii) the number of disease conditions included in the study, iii) the actual disease conditions included and iv) how the disease conditions were measured.

All included studies used a "count" of the number of diseases to define multimorbidity i.e. multimorbidity was defined by having two or more diseases (Appendix 3). Half of these studies specified they were only focused on chronic conditions.[32-34, 37, 41] Two health facility-based studies included acute conditions such as lower respiratory infections.[39, 40] The inclusion of acute disease conditions could inflate the prevalence of multimorbidity. The full list of disease conditions included can be found in Appendix 3.

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.[37] 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 four [41] to 24.[40] (Table 2). Diabetes was included as a disease condition in all ten 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 (Appendix 3). 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 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,[33, 37] reporting each disease with their most common co-morbid condition,[38, 39] or schematics detailing double and triple morbidities.[34, 37, 41] 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.[32, 35, 36, 40]

While it was not possible to ascertain the largest disease cluster in one study, Garin, Koyanagi [33] 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 co-morbid conditions for all other disease conditions.

Table 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 ten disease clusters[34, 41] and others reporting more than twenty disease clusters[37-39] (Appendix 4).

Hypertension was frequently co-morbid with other diseases (Table 3). Weimann, Dai [34] and Oni, Youngblood [41] 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 [39] also found hypertension and diabetes to be the largest disease cluster in their study. While Chang, Gómez-Olivé [37] 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;[37, 38] 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.[38] 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.[41]

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 e.g. self-reported or biologically measured.

Table 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**	[34, 38, 39, 41]
Hypertension	HIV		**3**	[34, 38, 41]
TB	HIV		**3**	[34, 38, 41]
Hypertension	TB		**2**	[34, 41]
Diabetes	HIV		**2**	[38, 41]
TB	Diabetes		**1**	[34]
Hypertension	Osteoarthritis		**1**	[39]
Asthma	Hypertension		**1**	[39]
Hypertension	COPD		**1**	[39]
Hypertension	IHD		**1**	[39]
Hypertension	Dyslipidaemia		**1**	[37]
Hypertension	Anaemia		**1**	[37]
Hypertension	Dyslipidaemia	Anaemia	**1**	[37]
Anaemia	HIV		**1**	[37]
Hypertension	Anaemia	HIV	**1**	[37]

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 (Appendix 5). Two studies reported the median/mean age of participants but the age range of participants was not included[39, 40] and one did not report an overall multimorbidity prevalence for their study[36]. 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 2); and moderate to high in studies reporting on adults aged 50 years and older (30% – 71%) (Figure 3).

<Figure 2: Graph of multimorbidity prevalence estimates for studies that include younger age groups>

<Figure 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 4). In those 18 years and above, Afshar, Roderick [32] 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.[34] 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%).[33]

Among community-based cross-sectional studies, the prevalence among older adults ranged from 18%[38] to 69%.[37] However, Chang, Gómez-Olivé [37] 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.[37]

In health facilities, two studies found moderate levels of multimorbidity (14.4% and 22.6%).[39, 41] 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.[40]

Table 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)

	Study	Year	Age band (years)	Prevalence of multimorbidity	
				n/N	% (95% CI)[α]
Cross-sectional study (Community-based)		2012	Overall (15+)	-	2.8 (2.6 – 3.1)
	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
		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.
□ 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 (Appendix 3). Multimorbidity was frequently associated with increasing age. [32-34, 37, 38, 41] However, Garin, Koyanagi [33] noted a decrease in the prevalence of multimorbidity in the age group 60+ years and Chang, Gómez-Olivé [37] 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;[33, 34] although another study reported it was not statistically significant;[37] while one found no distinction between males and females.[41] One study found that living in urban areas was a risk factor for multimorbidity[34] while another found that living in rural areas was associated with multimorbidity.[33] Other factors found to be associated with multimorbidity were: a lower level of education;[32, 33] being separated, divorced or widowed;[33, 37] living in KwaZulu-Natal or the Eastern Cape provinces, being Indian/Asian or

being obese.[34] Socioeconomic deprivation was found to be associated with multimorbidity in one study,[34] but another found no association between wealth and multimorbidity.[37]

Other studies identified the effects of multimorbidity such as having memory complaints (in women), suffering from depression,[35] decreased well-being and self-reported health.[37, 38] One study found that length of stay in hospital was not related to multimorbidity and also did not link lifestyle risk factors to multimorbidity.[40]

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.[1]

Three of our included studies reported fairly low levels of multimorbidity prevalence.[32, 34, 38] One study standardised the prevalence to the world population which may have resulted in a lower prevalence estimate (11.2%).[32] 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%.[34] 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%).[43] 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.[34] 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.[40] 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.[38] Also, they had missing data on HIV due to additional consent being required.

Age is accepted to be an important predictor of multimorbidity.[40] 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.[12] 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.[44]

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),[45] 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.[46] This cluster of disease was more prevalent than having hypertension or diabetes only. Information on the prevalence of co-morbidities 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.[47] 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 Kharrazi [48] 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.[49]

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.[50] 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,[51] 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.[51]

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 on the African continent and one of the few focused on a 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.

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Contributorship statement

RAR, VPvW, BvW and EBT conceptualised the study. RAR and EBT conducted screening and data extraction. RAR wrote the first draft. All authors reviewed and gave input into subsequent drafts.

Data Sharing Statement

No additional data available.

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Competing Interests

None declared.

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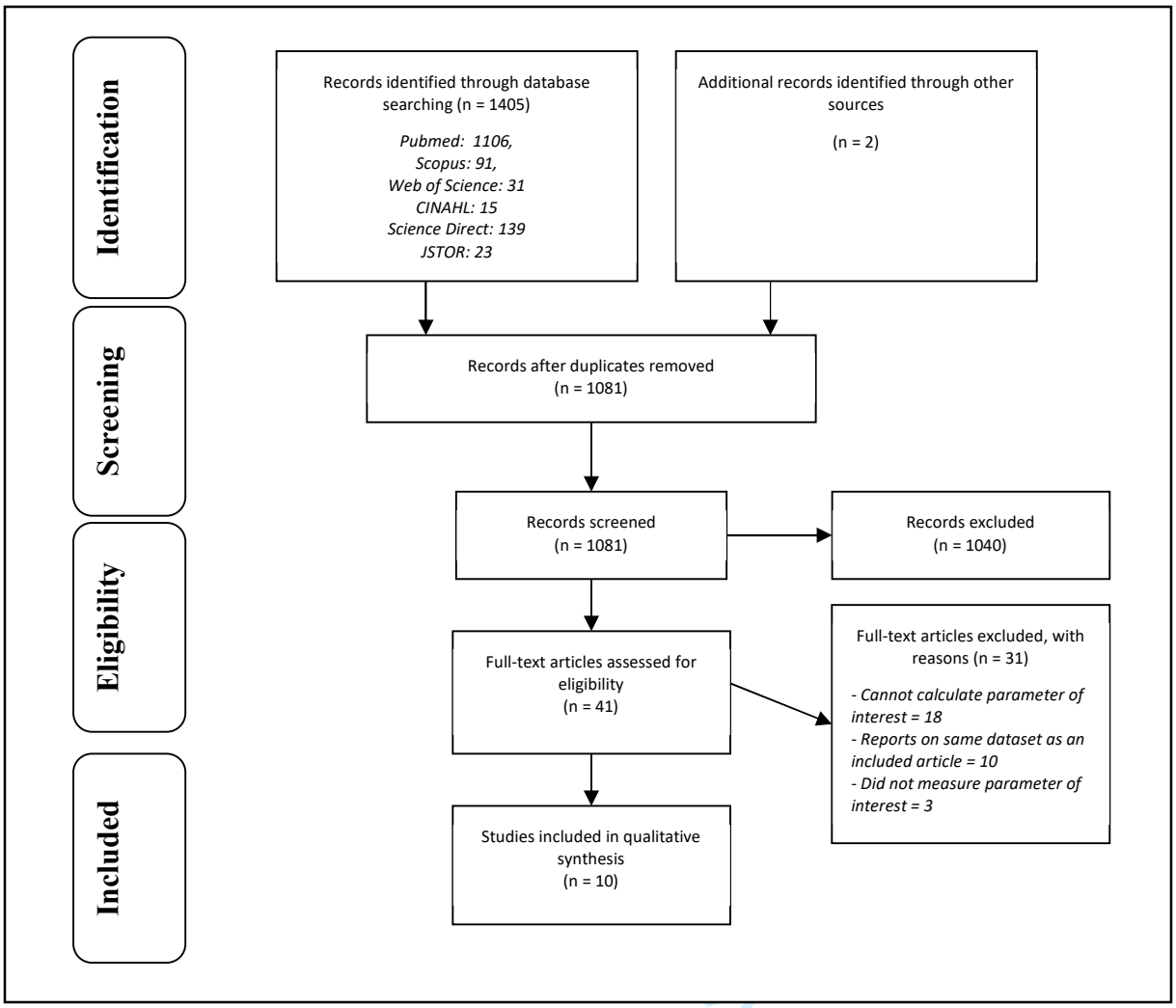

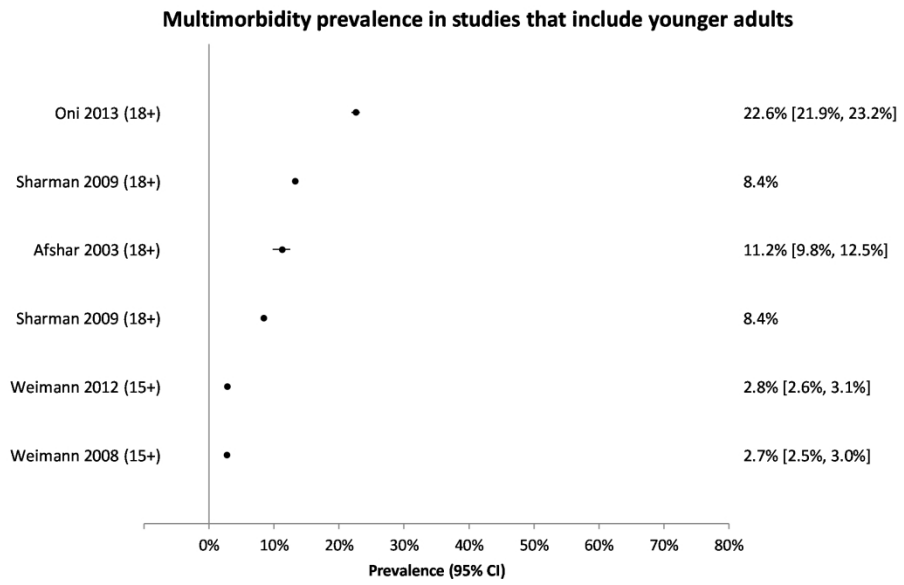

Figure 2: Graph of multimorbidity prevalence estimates for studies that include younger age groups

209x134mm (300 x 300 DPI)

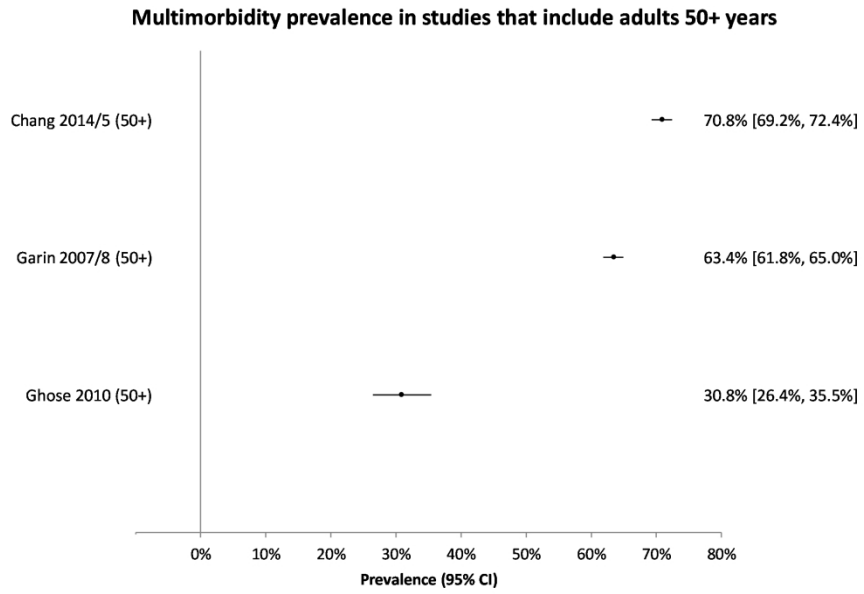

Figure 3: Graph of multimorbidity prevalence in studies including persons aged 50 years and older

209x135mm (300 x 300 DPI)

Supplementary file to *Multimorbidity in South Africa: A systematic review of prevalence studies*

Appendix 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2: Search Strategy

Study search output for multimorbidity study- December 2020

Search number	Query	Results
5	#4 NOT (animals[mh] NOT humans[mh)	1,106
4	(#4) AND (prevalence OR "prevalence"[mh] OR epidemiology OR endemic OR "epidemic outbreaks")	1,145
3	#1 and #2	1506
2	South Africa[mh] OR South Africa*[tiab] OR RSA [tiab] OR Africa, Southern[mh:noexp] OR Southern Africa[tiab]	68485
1	Multimorbidity OR multi-morbidity OR multimorbidity[tiab] OR multi morbidities OR multi morbidities OR multimorbidity[mh] OR multimorbidit* OR multimorbid OR multi-morbidit* OR "multiple morbidities" OR "multiple-morbidit*" OR co-morbid[tiab] OR co-morbid* OR comorbidity OR co-occur OR coexist OR co-exist OR multi-disease* OR multi-disease*	394636

Scopus database search output: 91 document reports

(TITLE-ABS-KEY (multistability OR multi-morbidity OR comorbidities OR multi-morbidities OR multimorbidit* OR multi-morbidit*) AND TITLE-ABS-KEY ("South Africa*" OR rsa OR "Southern Africa") AND TITLE-ABS-KEY (prevalence OR epidemiology OR endemic OR "epidemic outbreaks")) AND DOCTYPE (ar)

Web of science search output: 31 document reports

TOPIC: (multimorbidity OR multi-morbidity OR multimorbidities OR multi-morbidities OR multimorbidit* OR multi-morbidit*) AND TOPIC: ("South Africa" OR rsa OR "Southern Africa") AND TOPIC: (prevalence OR epidemiology OR endemic OR "epidemic outbreaks"). Indexes: SCI-EXPANDED.

Appendix 3: Additional information on each study

Study	Study population and size	Year	Location	Study type	Conditions included	Definition of MM used	Why were conditions included?	Factors associated with multimorbidity (MM)
Afshar, Roderick, Kowal et al. (2015). *Multimorbidity and the inequalities of global ageing: a cross-sectional study of 28 countries using the World Health Surveys*	N= 2629. Adults 18 years and older in the 2003 World Health Survey.	2003	South Africa. (56.3% urban)	Population-based survey. WHS 2003.	• Angina / Angina Pectoris (Heart Disease) • Arthritis • Asthma • Depression • Diabetes • Schizophrenia or Psychosis	The presence of two or more **chronic** diseases.	Chronic conditions were chosen in this survey to reflect health system coverage and corresponded to conditions known to affect older people.	- Increasing country GDP - Increasing age - Lower education
Garin, Koyanagi, Chatterji et al (2016). *Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study*.	N = 3836. Adults older than 50 years in the WHO Study on global AGEing and adult health (SAGE) 2007.	2007-2008	South Africa. Not stated if urban or rural.	Population based survey. SAGE 2007.	• Angina` • Arthritis • Asthma • Cataract • Cognitive impairment' • COPD • Depression` • Diabetes • Edentulism • Hypertension* • Obesity* • Stroke	Having at least 2 of 12 **chronic** conditions included in the study.	Selected 12 chronic conditions with high prevalence in most settings that significantly affect health	- Generally increased with age but decreased in people over 60 years - Being female - Lower education - Being separated/ divorced/widowed - Living in a rural area
Weimann, Dai, Oni (2016). *A cross-sectional and spatial analysis of the prevalence of multimorbidity and its association with socioeconomic disadvantage in South Africa: A comparison*	N=18526 (2008) & N=20015 (2012) Adults (age 15+ years) sub-sample from National Income Dynamic Survey Wave 1	2008, 2012	South Africa. Urban and rural areas included.	Population based survey. NIDS 2008 & 2012.	• Diabetes • HIV • Hypertension (self-reported or measured) • TB	The presence of two or more **chronic** health conditions existing simultaneously in an individual.	Hypertension and diabetes were included due to being the most prevalent non-communicable diseases. HIV and TB were included to monitor trends over time.	- Increasing age - Being female - Socioeconomic deprivation - Obesity - Living in urban areas - Living in Kwa-Zulu Natal or Eastern Cape provinces (Province) - Being Indian/Asian (Race)

between 2008 and 2012.	(2008) and 3 (2012).							
Ghose, Razak (2017). *Memory and Learning Complaints in Relation to Depression among Elderly People with Multimorbidity*.	N=422. Adults aged 50+ infected and / or affected by HIV in the SAGE WOPS 2010.	2010	Hlabisa subdistrict, Kwa-Zulu Natal. Not stated if urban or rural.	Population based survey. SAGE WOPS 2010.	• Arthritis • Asthma • Cancer • Chronic lung disease • Diabetes • Heart Disease • Hypertension • Stroke	>1 condition	Not clearly stated.	- Memory complaints in women - Being diagnosed with depression
van Heerden, Barnabas, Norris et al (2017). *High prevalence of HIV and non-communicable disease risk factors in rural KwaZulu-Natal, South Africa*.	N=570. Participants in a cohort study of a package of HIV testing, referral to care and follow-up visits to increase engagement in HIV care	Nov 2011 - Jun 2012	KwaZulu-Natal. Rural.	Cross-sectional study. Community based.	• Depression • HIV*[1] • Hyperglycaemia* • Hyperlipidaemia* • Hypertension* • Obesity*	Not reported.	Links to study objectives to investigate HIV and NCD risk factors.	Not reported
Chang, Gómez-Olivé, Payne et al. (2019). *Chronic multimorbidity among older adults in rural South Africa*	N = 3889. Adults enrolled in the Health and Ageing in Africa: A longitudinal study of an INDEPTH Community in South Africa (HAALSI) Programme.	2014-2015	Agincourt Health and Demographic Surveillance System, Bushbuckridge subdistrict, Mpumalanga. Rural.	Cross sectional study. Community based.	• Alcohol Dependence` • Anaemia* • Angina` • Chronic Bronchitis • Depression` • Diabetes* • Dyslipidaemia* • HIV* • Hypertension* • Post-Traumatic Stress Disorder`	Two definitions of multimorbidity were applied: the presence of more than one condition and the presence of more than one category of conditions (cardiometabolic conditions, mental disorders, HIV and anaemia).	Based on selection of conditions in sister studies, known health conditions in area and based on consultation with community.	- Increased with age until 69 years and then decreased - Being separated/divorced or widowed - HIV associated with higher levels of MM using the second definition - Physical functioning and well-being and self-rated health were worse with increasing numbers of conditions and categories ---------- - Living with more people (household size) decreased odds of multimorbidity

[1] HIV is measured but data on HIV is presented as a sub-group and thus excluded in this analysis

								- No relationship between wealth and multimorbidity - Females has higher levels of multimorbidity but it was not significantly different
Sharman, Bachmann (2019). *Prevalence and health effects of communicable and non- communicable disease comorbidity in rural KwaZulu-Natal, South Africa.*	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 of rural KwaZulu-Natal. Rural.		• Hypertension (self-reported or on treatment) • Diabetes • TB within past 12 months • HIV (measured or on treatment)*	Proportion of participants with two or more conditions *(termed as co-morbidity)*	Based on research gap where few studies examine the prevalence of communicable and non-communicable diseases.	- Increasing age were associated with MM - Self-reported health poorer with multimorbidity
Lalkhen, Mash (2015). *Multimorbidity in non-communicable diseases in South African primary healthcare.*		2010	Primary healthcare facilities in the Western Cape, North West, Northern Cape and Limpopo. Rural and urban.	Cross sectional study. Facility based.	• Asthma* • COPD* • Diabetes* • Epilepsy* • Hypertension* • Osteoarthritis* • And other diseases	The presence of two or more diseases.	Study aimed to examine non-communicable diseases. All conditions recorded.	Not reported
Roche, de Vries (2017). *Multimorbidity in a large district hospital: A descriptive cross-sectional study.*	N= 491. Consecutive admissions to an internal medicine department of a large district hospital.	2015	District hospital, Cape Town. Urban.	Cross sectional study. Facility based-Internal medicine department	• Anaemia* • Asthma* • Bronchiectasis* • Cancer* • Cardiac failure* • Cerebrovascular accident* • COPD* • Cor pulmonale* • Current TB* • Deep vein thrombosis* • Delirium*	More than one disease concurrently.	Not clearly stated but appears to include all conditions that were seen in the district hospital.	- Length of stay not related to multimorbidity. - Lifestyle risk factors were not associated with multimorbidity.

					• Diabetes* • Dilated cardiomyopathy* • Dyslipidaemia* • Epilepsy* • Gastroenteritis* • HIV* • Hypertension* • Ischaemic heart disease* • Lower respiratory tract infection* • Pneumonia* • Renal failure* • Sepsis* • Urinary tract infection*			
Oni, Youngblood, Boulle et al. (2015). *Patterns of HIV, TB, and non-communicable disease multi-morbidity in peri-urban South Africa- a cross sectional study*.	N=14364. Chronic disease patients (adults) with at least one disease (HIV, TB, diabetes, and hypertension) identified on electronic databases.	Sep 2012 - May 2013	Michael Mapongwana clinic, Khayelitsha, Cape Town. Peri-urban area.	Facility based RHIS. Western Cape Department of Health Data Repository, electronic prescription system.	• Diabetes* • HIV* • Hypertension* • TB*	Coexistence of more than one **chronic** condition in one person.	Informed by the research gap between NCDs and communicable diseases.	- Increasing age associated with MM. ------ - No significant differences between males and females.

Appendix 4: Common disease conditions / disease clusters

Study	Year	Conditions included	Common disease clusters identified in South Africa
Garin, et al (2016)	2007-2008	• Angina` • Arthritis • Asthma • Cataract • Cognitive impairment' • COPD • Depression` • Diabetes • Edentulism • Hypertension* • Obesity* • Stroke	**Disease Combinations** - Hypertension was commonly present with diabetes, stroke, angina, cataract and all other conditions. - Obesity and diabetes commonly co-occurred.
Weimann et al (2016)	2008, 2012	• Diabetes • HIV • Hypertension **(self-reported or measured)** • TB	Of the extrapolated 8,6 million people included, 89.2% had a single condition, 10.5% had two conditions, and 0.2% had three conditions. **Disease Combinations (2008):** **Two disease conditions:** 1) Diabetes and Hypertension (70.8%) 2) TB and Hypertension (13.2%) 3) HIV and Hypertension (10.8%) 4) HIV and TB (3.9%) 5) TB and Diabetes (0.8%) 6) HIV and Diabetes (0.3%) **Three disease conditions:** 1) TB, Diabetes and Hypertension (63.9%) 2) Hypertension, HIV and TB (36.0%)
Chang et al (2019)	2014-2015	• Alcohol Dependence` • Anaemia* • Angina` • Chronic Bronchitis • Depression` • Diabetes* • Dyslipidaemia* • HIV* • Hypertension* • Post-Traumatic Stress Disorder`	Disease clusters limited to more than 1.5% of study population. **Disease profile and clusters** - Hypertension only (11.7%) - Hypertension and Dyslipidaemia (9.4%) - None (6.9%) - Hypertension and Anaemia (6.4%) - Hypertension and Dyslipidaemia and Anaemia (4.7%) - Dyslipidaemia (3.9%) - Anaemia (3.8%) - Anaemia and HIV (2.6%) - Hypertension and Anaemia and HIV (2.6%) - HIV (2.4%) - Dyslipidaemia and Anaemia (2.1%) - Dyslipidaemia and Anaemia and HIV (2.0%) - Hypertension and HIV (1.9%) - Hypertension and Dyslipidaemia and Diabetes (1.8%) - Hypertension and Depression (1.7%) - Dyslipidaemia and HIV (1.6%) - Hypertension and Dyslipidaemia and HIV (1.6%)

Study	Year	Conditions included	Common disease clusters identified in South Africa
Sharman, Bachmann (2019).	2009 - 2015	• Hypertension (self-reported or on treatment) • Diabetes • TB within past 12 months • HIV (measured or on treatment)*	Overlapping NCD and infectious disease co-morbidity was seen most frequently in adults older than 40 years where chronic NCDs increase alongside HIV. **Disease Clusters in 2015** (only percentages >2% shown. Percentages may overlap and thus not add up to 100%) - **In participants with hypertension** • Hypertension only (61.3%) • Diabetes (16.8%) • HIV (15.2%) • TB (1.6%) • HIV, diabetes and TB (2.5%) - In participants with diabetes: • Diabetes only (9.7%) • Hypertension (70.5%) • Hypertension and HIV (10.6%) • HIV (3.9%) • TB, HIV and hypertension (2.7%) - In participants with HIV • HIV only (75.9%) • Hypertension (12.1%) • TB (7.6%) • Hypertension, diabetes and TB (2.0%) - In participants with TB • TB only (25.6%) • HIV (61.0%) • hypertension (8.4%) • HIV and hypertension (8.3%) - In all participants over age 40 years • 34% had none of the four diseases examined. • Diabetes and hypertension (9.8%) • Hypertension, HIV and diabetes (6.5%)
Lalkhen et al (2015).	2010	• Asthma* • COPD* • Diabetes* • Epilepsy* • Hypertension* • Osteoarthritis*	- Hypertension and diabetes were the most common combination. - Hypertension was commonly comorbid with diabetes, epilepsy, asthma and COPD. **Disease combinations (only clusters larger than 2% listed)** - Of those that hypertension (n=3219), people also had: • Diabetes (18.2%) • Osteoarthritis (8.0%) • Asthma (3.6%) • COPD (2.1%) • Ischaemic heart disease (2.1%) - Of those that had diabetes (n=946), people also had: • Hypertension (63.1%) • Osteoarthritis (4.3%) - Of those that had epilepsy (n=375), people also had: • Hypertension (14.4%) • Osteoarthritis (2.4%) - Of those that had ashtma (n=485), people also had: • Hypertension (28.7%) • Osteoarthritis (5.8%)

Study	Year	Conditions included	Common disease clusters identified in South Africa
			• Diabetes (5.4%) • Acute bronchitis (4.7%) • Allergic rhinitis (3.1%) • TB (2.2%) - Of those that had COPD (n=140), people also had: • Hypertension (47.9%) • Osteoarthritis (12.1%) • Diabetes (9.3%) • TB (6.4%) • Epilepsy (3.6%) • Ischaemic heart disease with angina (3.6%) • TB (2.1%) • Lipid dysfunction (2.1%) • Tobacco abuse (2.1%) • Ischaemic heart disease with angina (2.1%) - Of those that had Osteoarthritis (n=530), people also had: • Ischaemic heart disease (2.3%)
Oni et al (2015).	Sep 2012 - May 2013	• Diabetes* • HIV* • Hypertension* • TB*	Of the 14364 participants, 21.3% had two diseases, 1.2% had three diseases and 0.1% had four diseases. **Of those that had two diseases (n=3058)** 1. Hypertension and diabetes (69.1%) 2. Hypertension and HIV (21.4%) 3. HIV and TB (6.2%) 4. HIV and diabetes (1.6%) 5. Hypertension and TB (1.5%) 6. TB and diabetes (0.2%) **Of those that had three diseases (n=173)** 1. Hypertension, diabetes and HIV (63%) 2. Hypertension, HIV and TB (26.6%)

Appendix 5: Multimorbidity prevalence by sex and age group

Study	Year	Age band (years)	Prevalence of multimorbidity					
			Persons		Males		Females	
			n/N	% (95% CI)	n/N	%	n/N	%
Population-based surveys								
Afshar, Roderick, Kowal et al. (2015)‘	2003	18 - 49	-	5.0 (3.9 – 6.0)	-	-	-	-
		50 - 64	-	21.6 (16.6 – 26.0)	-	-	-	-
		65+	-	30.1 (20.6- 39.7)	-	-	-	-
		Overall (18+)	-	**11.2 (9.8 - 12.5)**	-	-	-	-
Garin, Koyanagi, Chatterji et al (2016).	2007/8	50 - 59	-	60.1	-	*50.5*	-	*68.4*
		60 - 69	-	69.1	-	*63.3*	-	*73.2*
		70 - 79	-	65.9	-	*63.6*	-	*67.1*
		80+	-	55.9	-	*61.0*	-	*51.3*
		Overall (50+)	**2376 / 3747***	**63.4**	-	-	-	-
Weimann, Dai, Oni (2016).	2008	15 - 24	-	*0.0*	-	-	-	-
		25 - 34	-	*1.3*	-	-	-	-
		35 - 44	-	*2.1*	-	-	-	-
		45 - 54	-	*5.5*	-	-	-	-
		55 - 64	-	*9.9*	-	-	-	-
		65+	-	*9.0*	-	-	-	-
		Overall (15+)	-	**2.7 (2.5 – 3.0)**	-	-	-	-
	2012	15 - 24	-	*0.0*	-	-	-	-
		25 - 34	-	*0.8*	-	-	-	-
		35 - 44	-	*3.1*	-	-	-	-
		45 - 54	-	*3.1*	-	-	-	-
		55 - 64	-	*9.0*	-	-	-	-
		65+	-	*10.5*	-	-	-	-
		Overall (15+)	-	**2.8 (2.6 – 3.1)**	-	-	-	-
Ghose, Razak (2017).	2010	**Overall (50+)**	**130 / 422**	**30.8**	-	**16.0**	-	**35.8**
Community-based studies (cross-sectional study)								
	2011/12	18 - 25		*10.0*	-	-	-	-

Study	Year	Age band (years)	Prevalence of multimorbidity					
			Persons		Males		Females	
			n/N	% (95% CI)	n/N	%	n/N	%
van Heerden, Barnabas, Norris et al (2017).		26 - 35		*24.3*	-	-	-	-
		36 - 45		*53.2*	-	-	-	-
		46 - 65		*60.9*	-	-	-	-
		66+		*68.9*	-	-	-	-
Chang, Gómez-Olivé, Payne et al. (2019).	2014/15	40 - 49	430 / 685	62.8	-	*61.0*	-	*64.3*
		50 - 59	750 / 1069	70.2	-	*66.2*	-	*72.8*
		60 - 69	754 / 1056	71.4	-	*69.9*	-	*73.0*
		70 - 79	471 / 685	68.7	-	*65.8*	-	*71.7*
		80+	295 / 393	75.1	-	*76.0*	-	*74.3*
		Overall (40+)	**2700 / 3889**	**69.4**	**1182 / 1758**	**67.2**	**1518 / 2130**	**71.2**
Sharman, Bachmann (2019).	2009	**Overall (18+)**		**8.4**				
	2015	**40+**		**18.4**				
	2015	**Overall (18+)**		**13.2**				
Health facility-based studies (cross-sectional surveys and routine health information systems)								
Lalkhen, Mash (2015).	2010	**Overall (Mean ages±)**	**-**	**48.4**	-	-	-	-
Roche, de Vries (2017).	2015	**Overall (Mean age 49 years)**	**371 / 427**	**87.0**	-	-	-	-
Oni, Youngblood, Boulle et al. (2015).	2012/13	**Overall (18+)**	**3246 / 14364**	**22.6**	-	-	-	-

Italicised data extracted from graphs using Webplot digitizer
*estimated from available information
ʿstandardised multimorbidity prevalence
NR indicates Not Reported.
±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).