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Research Article

Multi-morbidities Associated with Tuberculosis in South Africa: A Systematic Review of the Literature

T Sineke[1†], K Hirasen[1†], M Loveday[2,3], L Long[1,4] and D Evans[1,*]

[1]Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[2]HIV Prevention Research Unit, South African Medical Research Council, Cape Town, South Africa
[3]CAPRISA-MRC HIV-TB Pathogenesis and Treatment Research Unit, University of KwaZulu-Natal, Durban, South Africa
[4]Department of Global Health, Boston University School of Public Health, Boston, MA, United States of America

**Correspondence to: Denise Evans, devans@heroza.org*

†Tembeka Sineke and Kamban Hirasen contributed equally to this work.

ABSTRACT

Background: The concept of multi-morbidity is typically defined as the concurrent existence of more than one infectious and/or chronic condition in one person. We conducted a systematic review to quantify and describe the extent of multi-morbidities associated with tuberculosis (TB) in South Africa.

Methods: This systematic review and meta-analysis were developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA). Searches were conducted in PubMed inclusive of MEDLINE using a combination of keywords 'Tuberculosis', 'HIV', 'Diabetes', as well as other non-communicable disease-related terms. Only studies providing data for South Africa and those published in English from January 2013 to December 2019 were included.

Results: A total of 1772 publications were reviewed, of which 81 (4.6%) were identified for full-text review. Of these, 17 (21%) publications, representing 23,839 study participants with at least one multi-morbidity, were included in the final analysis. Human Immunodeficiency Virus (HIV) was the most commonly occurring co-morbidity reported (16/17 publications; 94.1%), followed by diabetes (6/17; 35.3%), smoking (4/17; 23.5%) and alcohol consumption (2/17; 11.8%). Pooled prevalence estimates for co-morbidities were 65% [95% confidence interval (CI): 59–70%], 6% [95% CI: 4–10%], 27% [95% CI: 8–51%] and 73% [95% CI: 70–77%], respectively.

Conclusions: HIV is the most common co-morbidity associated with TB in South Africa. However, other prevalent conditions and patient characteristics known to be strongly associated with TB were not consistently reported. Having a holistic understanding of TB and its associated multi-morbidities is critical to prevent further disease development and to manage patients with existing multi-morbidities more effectively.

Keywords: Communicable diseases, co-morbidity, multi-morbidity, *Mycobacterium tuberculosis* infection, non-communicable diseases, sub-Saharan Africa

INTRODUCTION

South Africa is one of the six countries accounting for 60% of the global Tuberculosis (TB) burden,(1) with an estimated incidence of 615 cases per 100,000 people in 2019.(2) In addition to the country's TB epidemic is an accompanying Human Immunodeficiency Virus (HIV) epidemic with approximately 7.5 million people living with the virus in 2018.(3) In addition, a third epidemic, that of non-communicable diseases (NCDs), has emerged more recently in South Africa.(4)

There are several medical conditions that are risk factors for TB; commonly, these include HIV, diabetes mellitus and malnutrition.(5) Links between TB and smoking, alcohol abuse, chronic lung disease, cancer and immunosuppressive diseases/illness are also well recognised.(6–9) Other demographic and socio-economic risk factors such as an unhealthy lifestyle and living in poverty are commonly associated with TB as well as TB co-infection with both communicable diseases and NCDs.(10) As such, co-existing communicable diseases and NCDs may increase the risk and/or effect of the other.(4) Subsequently, those already living with a communicable disease such as TB and/or HIV are more likely to develop co-morbidities with NCDs.

While rates of both communicable diseases (e.g. HIV/AIDS) and NCDs (e.g. diabetes mellitus, malnutrition, smoking-related and alcohol-related diseases) continue to increase in South Africa, little is known about the complex interactions of several co-existing conditions or multi-morbidities and the prevalence and patterns of these.(11) The concept of multi-morbidity is typically defined as the concurrent existence of more than one infectious and/or chronic condition in one person.(12, 13) Understanding these patterns is imperative not only to gain an accurate understanding of disease burden in the country but also to facilitate an integrated health-care approach that could support efficient resource use, higher quality of care and potentially better treatment outcomes.(14) These latter improvements are particularly important in the context of high disease-burden, resource-limited settings, like South Africa.

This review aimed to quantify and describe the extent of multi-morbidities associated with TB in South Africa. Furthermore, it summarises the extent to which demographics, socio-economic and clinical characteristics, treatment outcomes and patient management models have been reported among patients infected with TB and at least one other co-morbid condition.

METHODS

We developed a systematic review protocol and meta-analysis plan according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA).(15) We conducted a review of peer-reviewed publications in PubMed (inclusive of MEDLINE).

SELECTION CRITERIA

We included human studies with both children and/or adults with the simultaneous presence of two or more infectious and/or chronic conditions, where active TB disease was one of the conditions listed. Patients diagnosed with or on treatment for drug-sensitive (DS-TB), drug-resistant (DR-TB), pulmonary (PTB) or extra-pulmonary TB (EPTB) were considered to have active TB disease.

We included the following co-morbidities related to TB: HIV/AIDS, chronic obstructive lung disease (COPD), diabetes mellitus, hypertension, heart disease, cardiovascular disease (CVD), epilepsy, seizures, cancer (including leukaemia, skin cancer, lung cancer, etc.), osteoporosis, fibromyalgia, mental health-related conditions (including depression, anxiety, mental illness/disorders, Alzheimer's disease) and malnutrition.(16) While the harmful use of alcohol (health conditions such as alcohol dependence or alcohol use disorder), substance use disorders and smoking typically increase TB risk, in countries where TB has become highly concentrated to certain vulnerable groups, these can be important population-level risk factors and are here reported as co-morbidities among TB patients.(4, 16–19) The number and range of these co-morbid disorders complicate diagnosis and treatment and must be simultaneously addressed to achieve health outcome parity.(17)

We included studies published in English that provided data for South Africa between 01 January 2013 and 31 December 2019. Where the data period of respective publications preceeded 01 January 2013, we included the study if the majority (>50%) of the results fell within the data period.

We only included publications in which services were provided in the public sector (i.e. South African national TB programme or through partner/Non-Government Organisation (NGO) programmes or services that cater to the public sector). Both qualitative and quantitative studies were included. Specifically, observational studies such as retrospective cohort, prospective cohort and cross-sectional studies, as well as randomised control trials (RCTs)/intervention studies, were included. We excluded case reports, study protocols, modelling-focused research studies, systematic reviews, pharmacokinetic-focused and genetic studies, commentaries, editorials and guidelines. The full list of inclusion and exclusion criteria can be found in Supplementary Table 1. No human subjects' data was accessed during this review; therefore, ethics review was not required.

SEARCH STRATEGY

We developed a search string in accordance with the Medical Subject Headings (MeSH) thesaurus using a combination of non-case-sensitive keywords.

1. For TB, we used the following keywords: 'tuberculosis', 'TB', 'drug-susceptible TB', 'drug-sensitive TB', 'DS-TB', 'multidrug-resistant', 'drug resistant', 'MDR', 'extensively drug-resistant' and 'XDR'.
2. Keywords for common communicable diseases including 'HIV' and 'human immunodeficiency virus' were also used.
3. For multi-morbidities, we used keywords relating to non-communicable diseases, which included but were not limited to the following: 'multi-morbidity', 'non-communicable disease', 'chronic disease', 'chronic obstructive lung disease', 'diabetes', 'hypertension', 'heart disease', 'cardiovascular disease', 'epilepsy', 'seizures', 'cancer', 'leukemia', 'skin cancer', 'lung cancer', 'osteoporosis', 'depression', 'anxiety', 'mental health', 'Alzheimer's', 'fibromyalgia', 'alcoholism', 'drug abuse' and 'smoking'.
4. The full search string can be found in Supplementary Table 2. Once the search string for the respective disease/condition was confirmed we applied the following Boolean logic to our PubMed search: TB + Disease 1 = A; TB + Disease 2 = B; TB + Disease 3 = C and so on. Our final search logic combined all individual search elements: A or B or C… or Z and 'South Africa' filtered by publications for human studies published between 2013 and 2019.

SELECTION OF PUBLICATIONS

All citations identified through our search strategy were imported from PubMed into EndNote V.X8 (Thompson Reuters, New York, NY, USA). The EndNote library (all relevant full-text publications) was then imported into Rayyan QCRI, a free web application designed for systematic reviews.(20) Once in Rayyan QCRI, duplicate publications were removed.

The title and abstracts of all unique publications were first assessed for full-text review independently by two reviewers (TS and KH). Differences were resolved by discussion with a third reviewer (DE) and inclusion for full-text review

decided through consensus. The full text of each study was reviewed by two authors separately (TS and KH) following a similar resolution process used for the title and abstract screening. Where multiple eligible papers reported results from the same study (i.e. same population, same study period, same site, etc.), only the main paper (with the most data or most complete follow-up) was included while other papers were considered duplicates. Reason(s) for excluding records from the full-text review were documented.

DATA EXTRACTION

Data from eligible full-text publications were extracted by two independent reviewers (TS and KH), and information was collated in a Microsoft (MS) Excel 2016 spreadsheet (Microsoft, Redmond, WA, USA). The spreadsheet was developed and tested using four full-text publications identified from the search and was then revised before data extraction commenced. The following data from full-text publications were extracted (where available).

Publication details

This included the title, name of the first author, year of publication, type of study (quantitative vs. qualitative), study design (retrospective, prospective, RCT, etc.), study period, information about the source (journal name, database, etc.) and geographical location (national, provincial, district and/or name of setting, e.g. Khayelitsha, Cape Town).

Demographics of study participants

Total number of study participants, age, gender, race, education level, marital status, living conditions (urban vs. rural), socio-economic indicators (e.g. employment) and type of TB, where available (DS-TB, DR-TB, etc.), were extracted, when available.

Documentation and quantification of the extent of multi-morbidities associated with TB

We documented the conditions (e.g. diabetes, hypertension, cardiovascular disease, etc.) and the prevalence, cumulative incidence, incidence density or incidence proportion of each disease as reported in individual publications/abstracts.

Identification of the social determinants and risk factors associated with multi-morbidities

In addition to demographic characteristics collected above, we collected data on potential risk factors (e.g. malnutrition, unhealthy/sedentary lifestyle and obesity) and any estimates available for the risk factor (e.g. proportions, relative risks, odds ratios, etc.).

Tuberculosis treatment outcomes

We also collected information on TB treatment outcomes and reporting period (e.g. outcomes reported during respective studies' follow-up periods), if this was available. Tuberculosis outcomes were defined according to World Health Organisation (WHO).(21)

Patient management

To understand how health services manage patients with multi-morbidities, we reviewed the description of the study setting and extracted data about service delivery.

QUALITY ASSESSMENT

Using the Newcastle-Ottawa Scale (NOS), two reviewers (TS and KH) assessed the quality of the included full-text publications, including (1) the risk of bias in the selection of study groups (whether the included participants were representative of the underlying population), (2) validity of the data collection tools and statistical tests used and (3) outcome ascertainment.(22)

For publications that used a cohort design (including prospective, retrospective and observational cohort), we used the quality respective assessment scale, which included eight items across three broad criteria (Supplementary Appendix 1). A maximum score of nine could be awarded.

For publications that used a cross-sectional design, we used an adapted quality assessment scale, which included seven items across three broad criteria.(23) (Supplementary Appendix 2) A maximum score of 10 could be awarded. Grading for cohort and cross-sectional studies was as follows: scores ≤5 were graded as 'low' quality, scores of 6 were graded as 'moderate' quality and scores ≥7 were graded as 'high' quality.(23)

STATISTICAL ANALYSIS

Once extracted, data from the Excel document were imported to Stata v14 (College Station, TX, USA) for analysis. First, on quantifying and describing the extent of multi-morbidities associated with TB, we present the prevalence of each multi-morbidity aggregated at the study level. In publications that reported more than one co-morbid condition in addition to TB, we use the total count of each co-morbid condition (n) and the total study sample (N) to obtain prevalence proportions.

Second, to present these proportions graphically through a consolidated forest plot, we use Stata's 'metaprop' function. The 'metaprop' function is based on a binomial distribution and is appropriate when exclusively analysing proportions.(24) Confidence intervals (CIs) corresponding to each prevalence proportion were calculated using the exact method. This approach yields admissible values, even when estimates are close to 0 or 1. The Freeman–Tukey option was specified in the 'metaprop' function, which performs a double arcsine transformation, computes the weighted pooled estimate (across publications) and performs the back-transformation on the pooled estimate. Results presented were calculated using random effects models. This model recognises that differences in proportions across publications cannot solely be attributed to sample errors but rather to other factors such as differences in study populations and study designs.(24) The heterogeneity of estimates across publications was assessed through significance testing with P-values, being reported where applicable. We present a consolidated forest plot depicting the four most common co-morbid conditions associated with TB, respectively.

Third, to describe the completeness of demographic, socio-economic and clinical characteristics (including

treatment outcomes and patient management models), we aggregated data at the study level.

RESULTS

Selection of full-text publications

A total of 1778 publications were identified through the full-text search strategy. After the removal of duplicates (n=6), 1772 remained. After an initial review of the title and abstract, 1691 (95.4%) were excluded. The remaining 81 (4.6%) publications underwent full-text review. Of these 81, 64 publications were primarily excluded as (1) the study duration fell outside the study period; (2) they contained non-South African data; (3) sub-analysis of the data reported from larger studies already included and (4) there was no reported co-morbidity. A total of 17 full-text publications were included in the final review and meta-analysis (Fig 1).(25–41)

Description of included publications

Of the 17 publications that were included, majority were published in 2017 (10/17; 58.8%) and 2016 (5/17; 29.4%). Most were classified as prospective cohort studies (7/17; 41.2%) or cross-sectional studies (6/17; 35.3%), while some observational cohort studies were included (2/17; 11.8%). Almost half of the studies were conducted in South Africa's Western Cape province (8/17; 47.1%), with close

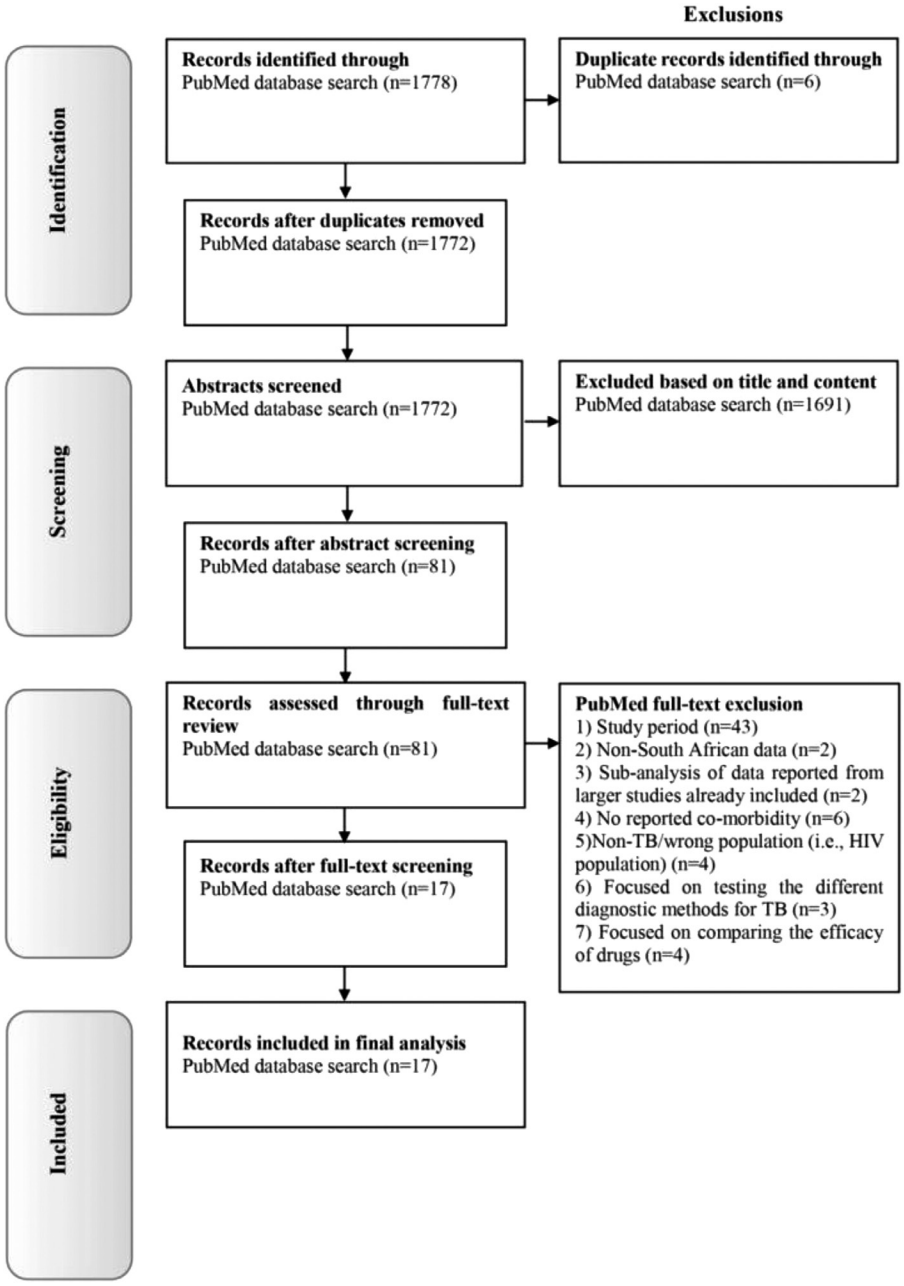

Fig 1: Study Selection Process and Reasons for Exclusions - PubMed

Table 1: Description of full-text manuscripts included in meta-analysis—PubMed (N=17)[1]

#	Author	Reference #	Year of publication	Design	Sample size	Location
1	Bekker et al.	25	2016	Observational cohort	39	Western Cape
2	Beharnu et al.	26	2016	Prospective cohort	214	Gauteng
3	de Kock et al.	27	2014	Prospective cohort	73	Western Cape
4	Harding et al.	28	2016	Cross-sectional	114	Unknown
5	Hilka et al.	29	2017	Observational longitudinal design with prospective repeated measures	131	Western Cape
6	Kelly et al.	30	2016	Cross-sectional	121	KwaZulu Natal
7	Kistan et al.	31	2017	Cross-sectional	474	Gauteng
8	Mcebula et al.	32	2017	Cross-sectional	325	Gauteng
9	McLachlan et al.	33	2016	Cross- sectional	105	Western Cape
10	Mohr et al.	34	2017	Prospective cohort	244	Western Cape
11	Naidoo et al.	35	2017	Sequential design, prospective	58	KwaZulu Natal
12	Ndjeka et al.	36	2015	Cohort analysis	91	South Africa—National
13	Oni et al.	37	2017	Cross- sectional	414	Western Cape
14	Rockwood et al.	38	2017	Prospective cohort	306	Western Cape
15	Schnippel et al.	39	2017	Retrospective cohort	20653	South Africa—National
16	Shah et al.	40	2017	Prospective cohort	404	KwaZulu Natal
17	Walters et al.	41	2017	Prospective cohort	73	Western Cape

[1]All full-text publications were quantitative studies (17/17; 100%).

to a quarter conducted in Gauteng province (4/17; 24.0%). Sample sizes ranged from 39 to over 20,000 (Table 1).

Quality assessment of included full-text publications

To assess the quality of the full-text publications, we used the quality respective assessment scale for the cohort studies (11/17; 64.7%) and an adapted quality assessment scale for the cross-sectional studies (6/17; 35.3%). Of the 11 included cohort studies, most were categorised as 'high' quality (8/11; 72.7%), two studies as 'moderate' quality (2/11; 18.2%) and one study as 'low' quality (1/11; 9.1%). All six cross-sectional publications were classified as 'high' quality (Table 2).

Patterns of multi-morbidities—most commonly reported co-morbidities

We report TB with four most commonly occurring co-morbidities; HIV was the most commonly occurring co-morbidity reported (16/17 publications; 94.1%). The pooled HIV prevalence across all 16 publications was 65% [95% CI: 59–70] (Fig 2). Most of these publications reported an HIV prevalence that was higher than the pooled estimate (26, 28, 30–32, 34, 39, 40), but three publications (25, 27, 41) reported an HIV prevalence less than the pooled estimate. Diabetes was the second most commonly reported co-morbidity (6/17; 35.3%), with a pooled prevalence of 6% [95% CI: 4–10]. Most of these publications reported a diabetes prevalence similar to the pooled estimate (26, 38, 40), with one study reporting a prevalence higher than the overall pooled estimate (37). Smoking was the third most commonly reported co-morbidity (4/17; 23.5%), with a pooled prevalence of 27% [95% CI: 8–51]. Lastly, alcohol consumption was the fourth most commonly reported co-morbidity (2/17; 11.8%), with a pooled prevalence of 73% [95% CI: 70–77] and great variability (25–97%) among TB patients. The respective heterogeneity between groups (P=0.000) showed a significant difference in the prevalence of HIV, diabetes, smoking and alcohol consumption between publications.

Number/extent of co-morbid conditions

Among publications that reported only one co-morbid condition, HIV was the most commonly reported (11/17; 64.7%), with a pooled prevalence of 58% [95% CI:49–68]. The majority of these publications reported an HIV prevalence higher than the overall pooled estimate, with only a few publications reporting a prevalence that was lower than the pooled estimate. Among publications that reported two co-morbid conditions (2/17; 11.8%), where diabetes (26, 29)

Table 2: The detailed assessment process for different types of studies

	Year	Selection				Comparability	Exposure			Score	Categorisation
Cohort studies (*n*=11)											
Study		**1**	**2**	**3**	**4**	**1**	**1**	**2**	**3**		
Mohr et al.	2017	a)	a)	a)	a)	a) b)	b)	a)	b)	9	High
Beharnu et al.	2016	a)	a)	a)	a)	a) b)	b)	a)	a)	9	High
Naidoo et al.	2017	c)	a)	a)	a)	a)	a)	a)	d)	6	Moderate
Hilka et al.	2017	b)	a)	b)	a)	a) b)	c)	a)	d)	7	High
Rockwood et al.	2017	c)	a)	a)	a)	a)	a)	b)	b)	6	Moderate
Schnippel et al.	2017	a)	a)	a)	a)	a) b)	b)	a)	b)	9	High
de Kock et al.	2014	b)	a)	a)	a)	a)	a)	a)	d)	7	High
Bekker et al.	2016	a)	a)	a)	a)	a) b)	a)	a)	a)	9	High
Shah et al.	2017	b)	a)	a)	a)	a) b)	b)	a)	b)	9	High
Ndjeka et al.	2015	b)	b)	a)	a)	a)	d)	b)	b)	5	Low
Walters et al.	2017	b)	a)	a)	a)	a)	b)	a)	d)	7	High
Case–control/cross-sectional studies (*n*=6)											
Mcebula et al.	2017	b)	b)	a)	a)	a)	a)	a)	n/a	8	High
Kelly et al.	2016	b)	a)	c)	b)	a)	b)	a)	n/a	7	High
Kistan et al.	2017	b)	b)	c)	b)	a) b)	a)	a)	n/a	7	High
McLachlan et al.	2016	b)	a)	c)	b)	a)	a)	a)	n/a	7	High
Oni et al.	2017	c)	a)	c)	a)	a) b)	a)	a)	n/a	8	High
Harding et al.	2016	b)	a)	a)	a)	a) b)	c)	a)	n/a	9	High

was one of the two co-morbid conditions, the pooled prevalence of diabetes was 6% [95% CI: 4–9] among TB patients.

Furthermore, a quarter of publications reported three or more co-morbid conditions (4/17; 23.5%). HIV, diabetes and smoking were common among patients in 3/4 publications that reported three or more co-morbid conditions. Specifically, among the patients who had three or more co-morbid conditions, where HIV was one of the conditions (32, 37, 38, 40), the pooled HIV prevalence was 72% [95% CI: 64–80]; 6% [95% CI: 3–10] for patients where one of the conditions was diabetes (32, 37, 38, 40), 27% [95% CI: 6–51] where one of the conditions was smoking (32, 37, 38, 40) and 73% [95% CI: 70–77] where one of the conditions was alcohol consumption (37, 38) (results not shown).

Demographic, socio-economic and clinical characteristics of patients with co-morbidities

Overall, 23,839 patients with TB disease were identified from the full-text publications included. Demographic, socio-economic and clinical characteristics were not reported consistently across included publications. The most complete demographic patient characteristic was sex (17/17; 100%), with 52.8% of the patients male and 47.2% female, followed by median age at study enrolment (11/17; 65.0%) and race (Black—the only race reported) (5/17; 29.4%). Only a few publications reported socio-economic characteristics such as employment status (3/17; 17.7%) (unemployed; 78%) and education level (secondary; 74%). With regard to clinical characteristics, TB type/location

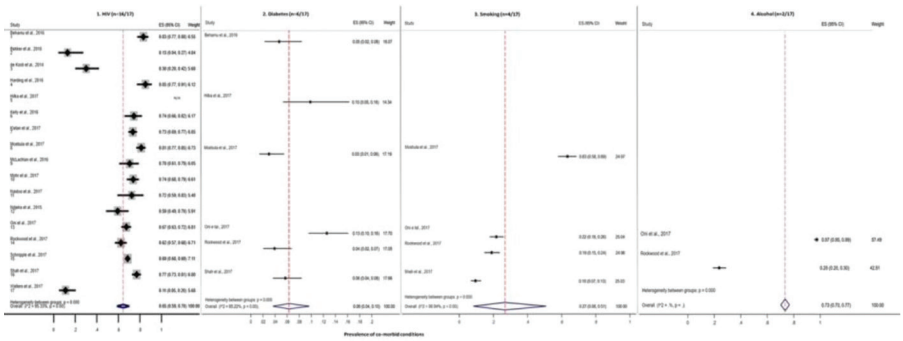

Fig 2: Patterns of multi-morbidities associated with Tuberculosis

Table 3: Completeness of demographic, socio-economic and clinical characteristics of all patients with tuberculosis disease and at least one co-morbid condition at treatment initiation (*n*=17)

	Full-text publication (*n*=17)	Patients (*n*=23,839)
Variable	***n/N***	***N* (%)**
Sex		
Female	17/17	11,247 (47.2%)
Male	17/17	12,590 (52.8%)
Age at ART initiation (years)		
Reported the median (IQR*)	11/17	-
Reported the mean	6/17	-
Mean age range (months/years)§	6.6 months to 39.5 years	
Drug susceptibility pattern		
Drug-sensitive TB	5/17	589 (2.5%)
Drug-resistant TB	11/17	21,607 (90.6%)
TB type		
PTB only	11/17	19,133 (80.3%)
EPTB only	4/17	325 (1.4%)
PTB + EPTB	2/17	34 (0.1%)
Race		
Black	5/17	543 (2.3%)
Other	3/17	13 (0.1%)
Employment status		
Unemployed	3/17	433 (1.8%)
Employed	2/17	122 (0.5%)
Education		
Primary	2/17	159 (0.7%)
Secondary	3/17	527 (2.2%)
Tertiary	2/17	24 (0.1%)
Relationship status		
Married/co-habiting	1/17	23 (0.1%)
Body mass index (kg/m^2)		
Reported either median or mean	5/17	-
Pregnant		
Yes	1/17	6 (0.0%)
Model of care		
Inpatient care (hospitalisation)	3/17	203 (0.9%)
Outpatient care	6/17	1341 (5.6%)
Inpatient and outpatient	1/17	20,653 (86.6%)

**IQR: interquartile range; ART: antiretroviral therapy*
§Minimum and maximum mean reported across six studies including one pediatric study. When limited to adult studies that reported means (n=5) minimum and maximum mean range from 19.1 years to 39.5 years

(PTB only) (11/17; 65.0%) and TB resistance profile (DS-TB and DR-TB) (5/17; 29.4% and 11/17; 64.7%, respectively) were the most reported patient attributes (Table 3).

Treatment outcomes and patient management among TB patients with multi-morbidities

Similarly to demographic, socio-economic and clinical characteristics, treatment outcomes were not reported consistently across included publications. Only a few publications reported at least one treatment outcome (3/17; 17.7%). Mortality and lost to follow-up (LTFU) were both reported in the three publications that assessed treatment outcomes. Mortality ranged from 2.0% (6/306) to 6.1% (13/214), while LTFU ranged from 3.2% (10/306) to 9.4% (20/214) (results not shown). In terms of patient

management models, less than half of the publications reported patients receiving outpatient/decentralised TB care (6/17; 35.0%), a quarter reported inpatient/hospitalised TB care (3/17; 17.6%) and only one (1/17; 5.9%) reported a combination of both inpatient and outpatient TB care (Table 3).

DISCUSSION

As expected in South Africa, HIV was the most commonly reported and most prevalent co-morbid condition among patients with active TB disease. Pooled estimates of HIV prevalence reported here (65% among all publications reporting HIV and 72% among publications reporting at least three or more co-morbid conditions) are similar to those from other publications in the country. The national estimate of new or relapse TB patients estimated to have HIV is 60%,(42), but data from the national electronic drug-resistant TB register (EDRWeb) between 2014 and 2016 suggest that this is higher among those with DR-TB at 71%.(43) This may explain why our estimates are slightly higher than the national estimates.(2) The second most commonly reported co-morbid condition was diabetes, which, in addition to HIV, is another condition commonly associated with TB (6% pooled prevalence estimate of diabetes).

While these co-morbid conditions were commonly reported, there was considerable variation between respective prevalence estimates across publications. Publications may include a description of co-morbid conditions to fulfill either primary or secondary objectives. Thereafter, low reporting of co-morbid conditions could be a result of sparse data due to potentially poor reporting and/or recording. Conversely, publications that focus on co-morbid conditions as a primary objective may report a higher prevalence of respective conditions due to better reporting/recording, more focused data collection efforts and/or intensified screening initiatives. In the case of TB–HIV co-infection reported here, given both the high national prevalence and the immuno-compromising effects of TB and HIV, which may predispose infected patients to infection with the other, treatment integration of these diseases has intensified in recent times. This integrated treatment approach may result in greater screening, closer monitoring and better reporting of TB and HIV infection among patients with at least one of these conditions.

While differences in reporting of multi-morbidities may be explained by disease association, prevalence and treatment programme design, differences in study design and objectives may contribute to both reporting and prevalence estimates. For example, with regard to diabetes, Oni et al. report a diabetes prevalence of 13% (two times higher than the pooled diabetes estimate of 6%).(37) This higher estimate could result from the authors actively screening for diabetes as one of the primary objectives described in their study.

While potentially a function of study design, study populations themselves may also explain differences in prevalence estimates. Mcebula et al. report a smoking prevalence of 63% (approximately two times higher than the pooled smoking prevalence of 27%).(32) This could potentially be explained by a predominantly male population (60.3%), who tend to have higher rates of smoking than their females counterparts. In keeping with this trend, Shah et al. reported a smoking prevalence of 10% (one-third of the pooled estimate) among a predominately female population (60% female).(40)

It is important to note that while alcohol use disorder has been identified as a risk factor for communicable diseases that places people at increased risk for developing TB, the causal relationship of TB with heavy alcohol consumption and alcohol use disorders has been firmly established, and alcohol is therefore considered a co-morbidity among TB patients.(18) Alcohol use disorder is associated with poor treatment outcomes, highlighting the need for intensive patient support and social protection measures.(44) There is an urgent need to invest in identifying the most appropriate and efficient treatment options and delivery models for people affected by TB and alcohol use disorders—including systematic screening for alcohol use and early identification of alcohol use disorders in all patients engaged with prevention and treatment services for TB.(18)

In publications that reported only one co-morbid condition, HIV was again the most commonly reported. This is to be expected in part due to the generally high prevalence of the virus, but may also be attributed to high rates of HIV testing among patients with TB as described above.

HIV, diabetes and smoking were reported in all publications with three or more co-morbid conditions. Other conditions may exist in these populations, but may not be recorded consistently due to a less common association with TB (lower rates of screening). Although CVD remains one of the leading causes of death in South Africa, (45) only one study (1/17; 5.9%) reported its prevalence. This low reporting of CVD is worth noting considering the strong association between TB and CVD that has been previously reported in other systematic reviews.(46) The overlap between some symptoms/cardiorespiratory states for TB and CVD (e.g. feeling weak, tired and short of breath in heart failure or chronic obstructive pulmonary disease or COPD) would prompt clinicians to investigate and screen for either condition. The discrepancy between the reporting of co-morbid conditions observed in this review and that in national estimates of commonly associated diseases further supports the need for more consistent and comprehensive screening and reporting of co-morbid conditions.

Interestingly, although mental health and its associated diseases and conditions were included in the search terms, none of the publications provided estimates on any mental health conditions. This is particularly concerning as reports from sub-Saharan Africa have shown that more than 50% of patients score 10 or higher on the nine-item Patient Health Questionnaire and are classified as having probable depression at the start of TB treatment.(47) In some of our other work using the Kessler Psychological Distress Scale, we have observed that up to 30% of TB patients have some form of psychological distress or anxiety at the start of

treatment, which can often persist on and even after treatment,(48) and these findings are similar to findings from a large-scale population-based study.(49)

With the exception of sex, all other well-known demographic and socio-economic risk factors of TB and multi-morbidities, including age, education level and employment status, were not consistently reported across included publications. Similarly, clinical characteristics such as TB resistance profile were reported in only a third of included publications. Resistance profiles, in particular, are closely associated with the overall level of health in patients infected with TB. For example, those with drug-resistant strains of TB are often in care for longer periods and prescribed a greater number of more toxic medications, commonly resulting in adverse side effects.(50) These factors often lead to poorer health and well-being, which can in turn lead to patients being more susceptible to other diseases and/or conditions.(51, 52)

Only half of all publications reported on patient management models of care. Patients who are treated within inpatient facilities are often in poorer health and being treated for more severe or complicated conditions. This greater burden of disease can again compromise health and predispose patients to developing other conditions. The consistent reporting of demographic, socio-economic and clinical characteristics among patients with TB and at least one other co-morbid condition is imperative to gain a more accurate understanding of the risk factors for multi-morbidities associated with TB.

LIMITATIONS

Demographic and socio-economic risk factors of TB, multi-morbidities and clinical characteristics were not consistently reported across included publications, limiting our ability to conduct a meta-analysis, i.e. an aggregate estimate of risk factors for TB and at least one other communicable/non-communicable condition as well as sub-group analysis. Moreover, while 'Pulmonary Disease and Chronic Obstructive' was included as a MeSH term within the search strategy and as such asthma and related conditions would indirectly be included, asthma as a co-morbidity may be underestimated in this study.

CONCLUSION

Our results show that HIV remains the most common co-morbid condition in South Africa. However, other prevalent conditions known to be strongly associated with TB were not consistently reported. The review highlights a gap in the reporting of demographic, socio-economic and clinical characteristics, treatment outcomes and patient management models.

Due to the sparsity of data relating firstly to co-morbid conditions themselves and secondly to the disaggregation of demographic and socio-economic data across respective conditions, a minimum standard of reporting should be considered in TB-related research. This could include the potential screening of co-morbid conditions, both those commonly associated with TB (HIV, diabetes, etc.) and those thought of as less common (mental health, etc.). Furthermore, where data are routinely available, these estimates should be reported irrespective of their role or impact on study outcomes.

Having a holistic understanding of TB, its associated multi-morbidities, demographic, socio-economic and clinical characteristics as well as patient management models is critical for informing service delivery and improved patient-centred care for TB patients. This would enable health-care providers to identify patients predisposed to multi-morbidities and prevent further disease development and manage patients with existing multi-morbidities more effectively and efficiently. Addressing this gap is critical in ensuring an accurate understanding of the burden and improving health outcomes among TB patients in South Africa.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPLEMENTARY APPENDIX 1: NEWCASTLE–OTTAWA QUALITY ASSESSMENT SCALE

EVALUATION OF COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the 'Selection' and 'Outcome' categories. A maximum of two stars can be given for 'Comparability'. Each star is worth one point and a maximum of nine points can be awarded.

Selection

1) Representativeness of the exposed cohort
   a) Truly representative of the average _____ (describe) in the community ☐
   b) Somewhat representative of the average _____ in the community ☐
   c) Selected group of users, e.g. nurses, volunteers
   d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort ☐
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
   a) Secure record (e.g. surgical records) ☐
   b) Structured interview ☐
   c) Written self-report
   d) No description
4) Demonstration that outcome of interest was not present at start of study
   a) Yes ☐
   b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) Study controls for _____ (select the most important factor) ☐
   b) Study controls for any additional factor ☐ (These criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) Independent blind assessment ☐
   b) Record linkage ☐
   c) Self-report
   d) No description
2) Was follow-up long enough for outcomes to occur?
   a) Yes (select an adequate follow-up period for outcome of interest) ☐
   b) No
3) Adequacy of follow-up of cohorts
   a) Complete follow-up—all subjects accounted for ☐
   b) Subjects lost to follow-up unlikely to introduce bias—small number lost - > ____ % (select an adequate %) follow-up, or description provided of those lost) ☐
   c) Follow-up rate < ____% (select an adequate %) and no description of those lost
   d) No statement

SUPPLEMENTARY APPENDIX 2: NEWCASTLE–OTTAWA QUALITY ASSESSMENT SCALE—ADAPTED FOR THE EVALUATION OF CROSS-SECTIONAL STUDIES (MODESTI ET AL. 2016)

Note: A study can be awarded a maximum of five stars within the 'Selection' category, two stars within the 'Comparability' category and three stars within the 'Outcome' category. Each star is worth one point, and a maximum of ten points can be awarded.

Selection

1) Representativeness of the sample
   a) Truly representative of the average in the target population* (all subjects or random sampling).
   b) Somewhat representative of the average in the target population* (non-random sampling).
   c) Selected group of users.
   d) No description of the sampling strategy.

2) Sample size
   a) Justified and satisfactory.*
   b) Not justified.

3) Non-respondents
   a) Comparability between respondents' and non-respondents' characteristics is established, and the response rate is satisfactory.*
   b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
   c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (risk factor)
   a) Validated measurement tool.**
   b) Non-validated measurement tool, but the tool is available or described.*
   c) No description of the measurement tool.

Comparability

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) The study controls for the most important factor (select one).*
   b) The study control for any additional factor.*

Outcome

1) Assessment of the outcome
   a) Independent blind assessment.**
   b) Record linkage.**
   c) Self-report.*
   d) No description.

2) Statistical test

   a) The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (*P*-value).*
   b) The statistical test is not appropriate, not described or incomplete.

Supplementary Table 1: Inclusion and exclusion criteria

	Include	Exclude
Population	• Human studies	• Does not include TB disease
	• Two or more infectious and/or chronic conditions in one person, where TB disease is one of the conditions listed. *[Note: patients with TB disease are the primary population of interest]*	• Laboratory methods describing/ comparing diagnostic tests (e.g. LAM†, Xpert MTB/RIF, culture) and the cases they identified
	• TB disease (laboratory-confirmed diagnosis or treatment)	• TB preventative therapy (e.g. IPT‡)
	• All ages (children and adults)	• Postmortem studies
	• All genders	
Timing	Data period from 01 January 2013 to 31 December 2019. Majority of data (>50%) within study period	N/A
Setting	Services provided to the public sector through government-managed public health infrastructure or through partner/NGO§ programmes Only papers in English Studies from South Africa (data from South African populations)	Services targeted to those receiving their health services outside of the traditional public health infrastructure (i.e. private health insurance, medical aids, etc.)
Study design	• Qualitative and quantitative studies	• Systematic reviews or other reviews (e.g. literature reviews) •Case reports and case series
	• High-quality observational studies (retrospective or | prospective)	• Treatment guidelines
	• Cross-sectional studies	• Mathematical models
	• Pre/post studies with or without a comparison group	• Cost-effectiveness studies and economic analyses
	• Randomised control trials	• Pharamacokinetic and genetic studies
	• Descriptive studies with individual patient data or health provider information	• Study protocols
Publication type	• Peer-reviewed journals	• Editorial
	• Conference abstracts (TB Union 2013–2019)	• Commentaries/opinion piece

†*LAM: lipoarabinomannan*
‡*IPT: isoniazid preventive therapy*
§*NGO: non-governmental organisation*

Supplementary Table 2: MeSH search string

Tuberculosis	'Tuberculosis'[Mesh] OR Tuberculoses OR Kochs Disease OR Koch Disease OR Kochs Disease OR Mycobacterium tuberculosis Infection OR Infection, Mycobacterium tuberculosis OR Infections, Mycobacterium tuberculosis OR Mycobacterium tuberculosis Infections
Mycobacterium tuberculosis	'Mycobacterium tuberculosis'[Mesh] OR Mycobacterium tuberculosis H37Rv
Therapy	'therapy [Subheading]'[Mesh] OR treatment OR disease management
Tuberculosis diagnosis	('tuberculosis'[MeSH Terms] OR 'tuberculosis'[All Fields]) AND ('diagnosis'[Subheading] OR 'diagnosis'[All Fields]
Tuberculosis treatment	('tuberculosis'[MeSH Terms] OR 'tuberculosis'[All Fields]) AND ('therapy'[Subheading] OR 'therapy'[All Fields] OR 'treatment'[All Fields] OR 'therapeutics'[MeSH Terms] OR 'therapeutics'[All Fields])
Tuberculosis NOT prevention	('tuberculosis'[MeSH Terms] OR 'tuberculosis'[All Fields]) NOT ('prevention and control'[Subheading] OR ('prevention'[All Fields] AND 'control'[All Fields]) OR 'prevention and control'[All Fields] OR 'prevention'[All Fields])
Tuberculosis, multidrug-resistant	'Tuberculosis, Multidrug-Resistant'[Mesh] OR Multidrug-Resistant Tuberculosis OR Tuberculosis, Multidrug Resistant OR Tuberculosis, MDR OR MDR Tuberculosis OR Tuberculosis, Multi-Drug Resistant OR Multi-Drug Resistant Tuberculosis OR Tuberculosis, Multi Drug Resistant OR Tuberculosis, Drug-Resistant OR Drug-Resistant Tuberculosis OR Tuberculosis, Drug Resistant
Extensively drug-resistant tuberculosis	'Extensively Drug-Resistant Tuberculosis'[Mesh] OR Extensively Drug Resistant Tuberculosis OR Extremely Drug-Resistant Tuberculosis OR Drug-Resistant Tuberculoses, Extremely OR Drug-Resistant Tuberculosis, Extremely OR Extremely Drug Resistant Tuberculosis OR Extremely Drug-Resistant Tuberculoses OR Tuberculoses, Extremely Drug-Resistant OR Tuberculosis, Extremely Drug-Resistant OR Tuberculosis, Extremely Drug Resistant OR XDR-TB OR Tuberculosis, Extensively Drug-Resistant OR Drug-Resistant Tuberculoses, Extensively OR Drug-Resistant Tuberculosis, Extensively OR Extensively Drug-Resistant Tuberculoses OR Tuberculoses, Extensively Drug-Resistant OR Tuberculosis, Extensively Drug Resistant
HIV	'HIV'[Mesh] OR Human Immunodeficiency Virus OR Immunodeficiency Virus, Human OR Immunodeficiency Viruses, Human OR Virus, Human Immunodeficiency OR Viruses, Human Immunodeficiency OR Human Immunodeficiency Viruses OR Human T Cell Lymphotropic Virus Type III OR Human T-Cell Lymphotropic Virus Type III OR Human T-Cell Leukemia Virus Type III OR Human T Cell Leukemia Virus Type III OR LAV-HTLV-III OR Lymphadenopathy-Associated Virus OR Lymphadenopathy Associated Virus OR Lymphadenopathy-Associated Viruses OR Virus, Lymphadenopathy-Associated OR Viruses, Lymphadenopathy-Associated OR Human T Lymphotropic Virus Type III OR Human T-Lymphotropic Virus Type III OR AIDS Virus OR AIDS Viruses OR Virus, AIDS OR Viruses, AIDS OR Acquired Immune Deficiency Syndrome Virus OR Acquired Immunodeficiency Syndrome Virus OR HTLV-III
Multiple chronic conditions	'Multiple Chronic Conditions'[Mesh] OR Chronic Conditions, Multiple OR Multiple Chronic Illnesses OR Chronic Illnesses, Multiple OR Multus OR Multiple Chronic Medical Conditions OR Multiple OR, Multiple OR Multiple Chronic Diseases OR Chronic Disease, Multiple OR Chronic Diseases, Multiple OR Multiple Chronic Disease OR Multiple Chronic Health Conditions
Non-communicable diseases	'Noncommunicable Diseases'[Mesh] OR Noncommunicable Disease OR Non-infectious Diseases OR Non infectious Diseases OR Non-infectious Disease OR Non-communicable Diseases OR Disease, Non-communicable OR Diseases, Non-communicable OR Non communicable Diseases OR Noninfectious Diseases OR Noninfectious Disease OR Non-communicable Chronic Diseases OR Chronic Disease, Non-communicable OR Non communicable Chronic Diseases OR Non-communicable Chronic Disease
Chronic disease	'Chronic Disease'[Mesh] OR Chronic Diseases OR Disease, Chronic OR Diseases, Chronic OR Chronic Illness OR Chronic Illnesses OR Illness, Chronic OR Illnesses, Chronic OR Chronically Ill
Pulmonary disease, chronic obstructive	'Pulmonary Disease, Chronic Obstructive'[Mesh] OR COPD OR Chronic Obstructive Pulmonary Disease OR COAD OR Chronic Obstructive Airway Disease OR Airflow Obstruction, Chronic OR Airflow Obstructions, Chronic OR Chronic Airflow Obstructions OR Chronic Airflow Obstruction
Diabetes mellitus	'Diabetes Mellitus'[Mesh]
Hypertension	'Hypertension'[Mesh] OR Blood Pressure, High OR Blood Pressures, High OR High Blood Pressure OR High Blood Pressures
Heart diseases	'Heart Diseases'[Mesh] OR Disease, Heart OR Diseases, Heart OR Heart Disease OR Cardiac Diseases OR Cardiac Disease OR Disease, Cardiac OR Diseases, Cardiac

Cardiovascular diseases	'Cardiovascular Diseases'[Mesh] OR Cardiovascular Disease OR Disease, Cardiovascular OR Diseases, Cardiovascular
Epilepsy	'Epilepsy'[Mesh] OR Epilepsies OR Seizure Disorder OR Seizure Disorders OR Awakening Epilepsy OR Epilepsy, Awakening OR Epilepsy, Cryptogenic OR Cryptogenic Epilepsies OR Cryptogenic Epilepsy OR Epilepsies, Cryptogenic OR Aura OR Auras
Seizures	'Seizures'[Mesh] OR Seizure OR Nonepileptic Seizures OR Nonepileptic Seizure OR Seizure, Nonepileptic OR Seizures, Nonepileptic OR Non-Epileptic Seizures OR Non Epileptic Seizures OR Non-Epileptic Seizure OR Seizure, Non-Epileptic OR Seizures, Non-Epileptic OR Generalized Absence Seizures OR Absence Seizure, Generalized OR Absence Seizures, Generalized OR Generalized Absence Seizure OR Seizure, Generalized Absence OR Seizures, Generalized Absence OR Tonic-Clonic Seizures OR Tonic Clonic Seizures OR Seizures, Tonic-Clonic OR Seizure, Tonic-Clonic OR Seizures, Tonic Clonic OR Tonic-Clonic Seizure OR Generalized Tonic-Clonic Seizures OR Generalized Tonic Clonic Seizures OR Generalized Tonic-Clonic Seizure OR Seizure, Generalized Tonic-Clonic OR Seizures, Generalized Tonic-Clonic OR Tonic-Clonic Seizure, Generalized OR Tonic-Clonic Seizures, Generalized OR Clonic Seizures OR Seizures, Clonic OR Clonic Seizure OR Seizure, Clonic OR Tonic Seizures OR Seizures, Tonic OR Seizure, Tonic OR Tonic Seizure OR Atonic Seizures OR Atonic Seizure OR Seizure, Atonic OR Seizures, Atonic OR Atonic Absence Seizures OR Absence Seizure, Atonic OR Absence Seizures, Atonic OR Atonic Absence Seizure OR Seizure, Atonic Absence OR Seizures, Atonic Absence OR Myoclonic Seizures OR Myoclonic Seizure OR Seizure, Myoclonic OR Seizures, Myoclonic OR Epileptic Seizures OR Epileptic Seizure OR Seizure, Epileptic OR Seizures, Epileptic OR Seizures, Sensory OR Seizure, Sensory OR Sensory Seizure OR Sensory Seizures OR Absence Seizures OR Absence Seizure OR Seizure, Absence OR Petit Mal Convulsion OR Convulsion, Petit Mal OR Convulsions OR Convulsion OR Convulsive Seizures OR Seizures, Convulsive OR Convulsive Seizure OR Seizure, Convulsive OR Seizures, Motor OR Motor Seizure OR Motor Seizures OR Seizure, Motor OR Jacksonian Seizure OR Seizure, Jacksonian OR Seizures, Auditory OR Auditory Seizure OR Auditory Seizures OR Seizure, Auditory OR Seizures, Focal OR Focal Seizure OR Focal Seizures OR Seizure, Focal OR Partial Seizures OR Partial Seizure OR Seizure, Partial OR Seizures, Partial OR Seizures, Generalized OR Generalized Seizure OR Generalized Seizures OR Seizure, Generalized OR Seizures, Gustatory OR Gustatory Seizure OR Gustatory Seizures OR Seizure, Gustatory OR Seizures, Olfactory OR Olfactory Seizure OR Olfactory Seizures OR Seizure, Olfactory OR Convulsion, Non-Epileptic OR Convulsion, Non Epileptic OR Convulsions, Non-Epileptic OR Non-Epileptic Convulsion OR Non-Epileptic Convulsions OR Seizures, Somatosensory OR Seizure, Somatosensory OR Somatosensory Seizure OR Somatosensory Seizures OR Seizures, Vertiginous OR Seizure, Vertiginous OR Vertiginous Seizure OR Vertiginous Seizures OR Seizures, Vestibular OR Seizure, Vestibular OR Vestibular Seizure OR Vestibular Seizures OR Seizures, Visual OR Seizure, Visual OR Visual Seizure OR Visual Seizures OR Complex Partial Seizures OR Complex Partial Seizure OR Partial Seizure, Complex OR Partial Seizures, Complex OR Seizure, Complex Partial OR Seizures, Complex Partial OR Single Seizure OR Seizure, Single OR Seizures, Single OR Single Seizures
Neoplasms	'Neoplasms'[Mesh] OR Neoplasia OR Neoplasias OR Neoplasm OR Tumors OR Tumor OR Cancer OR Cancers OR Malignancy OR Malignancies OR Malignant Neoplasms OR Malignant Neoplasm OR Neoplasm, Malignant OR Neoplasms, Malignant OR Benign Neoplasms OR Neoplasms, Benign OR Benign Neoplasm OR Neoplasm, Benign
Lung neoplasms	'Lung Neoplasms'[Mesh] OR Pulmonary Neoplasms OR Neoplasms, Lung OR Lung Neoplasm OR Neoplasm, Lung OR Neoplasms, Pulmonary OR Neoplasm, Pulmonary OR Pulmonary Neoplasm OR Lung Cancer OR Cancer, Lung OR Cancers, Lung OR Lung Cancers OR Pulmonary Cancer OR Cancer, Pulmonary OR Cancers, Pulmonary OR Pulmonary Cancers OR Cancer of the Lung OR Cancer of Lung
Leukaemia	'Leukemia'[Mesh] OR Leukemias OR Leucocythaemia OR Leucocythaemias OR Leucocythemia OR Leucocythemias
Skin neoplasms	'Skin Neoplasms'[Mesh] OR Neoplasms, Skin OR Neoplasm, Skin OR Skin Neoplasm OR Cancer of Skin OR Skin Cancers OR Cancer of the Skin OR Cancer, Skin OR Cancers, Skin
Osteoporosis	'Osteoporosis'[Mesh] OR Osteoporoses OR Osteoporosis, Post-Traumatic OR Osteoporosis, Post Traumatic OR Post-Traumatic Osteoporoses OR Post-Traumatic Osteoporosis OR Osteoporosis, Senile OR Osteoporoses, Senile OR Senile Osteoporoses OR Osteoporosis, Involutional OR Senile Osteoporosis OR Osteoporosis, Age-Related OR Osteoporosis, Age Related OR Bone Loss, Age-Related OR Age-Related Bone Loss OR Age-Related Bone Losses OR Bone Loss, Age Related OR Bone Losses, Age-Related OR Age-Related Osteoporosis OR Age Related Osteoporosis OR Age-Related Osteoporoses OR Osteoporoses, Age-Related

Depression	'Depression'[Mesh] OR Depressions OR Depressive Symptoms OR Depressive Symptom OR Symptom, Depressive OR Symptoms, Depressive OR Emotional Depression OR Depression, Emotional OR Depressions, Emotional OR Emotional Depressions
Anxiety	'Anxiety'[Mesh] OR Hypervigilance OR Nervousness OR Social Anxiety OR Anxieties, Social OR Anxiety, Social OR Social Anxieties
Mental health	'Mental Health'[Mesh] OR Health, Mental OR Mental Hygiene OR Hygiene, Mental
Alzheimer's disease	'Alzheimer Disease'[Mesh] OR Alzheimers Disease OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Alzheimer-Type Dementia (ATD) OR Alzheimer Type Dementia (ATD) OR Dementia, Alzheimer-Type (ATD) OR Alzheimer Type Senile Dementia OR Primary Senile Degenerative Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Alzheimer Dementia OR Alzheimer Dementias OR Dementia, Alzheimer OR Dementias, Alzheimer OR Senile Dementia, Alzheimer Type OR Acute Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimers Disease, Focal Onset OR Focal Onset Alzheimers Disease OR Familial Alzheimer Disease (FAD) OR Alzheimer Disease, Familial (FAD) OR Alzheimer Diseases, Familial (FAD) OR Familial Alzheimer Diseases (FAD) OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia
Fibromyalgia	'Fibromyalgia'[Mesh] OR Fibromyalgias OR Fibromyalgia-Fibromyositis Syndrome OR Fibromyalgia Fibromyositis Syndrome OR Fibromyalgia-Fibromyositis Syndromes OR Syndrome, Fibromyalgia-Fibromyositis OR Syndromes, Fibromyalgia-Fibromyositis OR Rheumatism, Muscular OR Muscular Rheumatism OR Fibrositis OR Fibrositides OR Myofascial Pain Syndrome, Diffuse OR Diffuse Myofascial Pain Syndrome OR Fibromyositis-Fibromyalgia Syndrome OR Fibromyositis Fibromyalgia Syndrome OR Fibromyositis-Fibromyalgia Syndromes OR Syndrome, Fibromyositis-Fibromyalgia OR Syndromes, Fibromyositis-Fibromyalgia OR Fibromyalgia, Secondary OR Fibromyalgias, Secondary OR Secondary Fibromyalgia OR Secondary Fibromyalgias OR Fibromyalgia, Primary OR Fibromyalgias, Primary OR Primary Fibromyalgia OR Primary Fibromyalgias
Alcoholism/misuse	'Alcoholism'[Mesh] OR Alcohol Dependence OR Dependence, Alcohol OR Alcohol Addiction OR Addiction, Alcohol OR Alcoholic Intoxication, Chronic OR Chronic Alcoholic Intoxication OR Intoxication, Chronic Alcoholic OR Alcohol Use Disorder OR Alcohol Use Disorders OR Use Disorder, Alcohol OR Use Disorders, Alcohol OR Alcohol Abuse OR Abuse, Alcohol
Drug use/misuse	'Drug Abuse' OR Abuse, Drug OR Drug Dependence OR Dependence, Drug OR Drug Addiction OR Addiction, Drug OR Substance Use Disorders OR Disorder, Substance Use OR Substance Use Disorder OR Drug Use Disorders OR Disorder, Drug Use OR Drug Use Disorder OR Organic Mental Disorders, Substance-Induced OR Organic Mental Disorders, Substance Induced OR Substance Abuse OR Abuse, Substance OR Abuses, Substance OR Substance Abuses OR Substance Dependence OR Dependence, Substance OR Substance Addiction OR Addiction, Substance OR Prescription Drug Abuse OR Abuse, Prescription Drug OR Drug Abuse, Prescription OR Drug Habituation OR Habituation, Drug
Smoking	'Smoking'[Mesh] OR Smoking Behaviors OR Behavior, Smoking OR Behaviors, Smoking OR Smoking Behavior OR Smoking Habit OR Habit, Smoking OR Habits, Smoking OR Smoking Habits
South Africa	'south africa'[MeSH Terms] OR ('south'[All Fields] AND 'africa'[All Fields]) OR 'south africa'[All Fields]