

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The prevalence of multimorbidity in South Africa: A systematic review protocol
AUTHORS	Roomaney, Rifqah; van Wyk, Brian; Turawa, Eunice; Pillay-van Wyk, Victoria

VERSION 1 – REVIEW

REVIEWER	Kathryn Nicholson Western University Canada
REVIEW RETURNED	26-Jul-2020

GENERAL COMMENTS	<p>Thank you for this opportunity to review "The prevalence of multimorbidity in South Africa: A systematic review protocol", which aims to synthesize prevalence studies on multimorbidity within South Africa. This is an important topic being explored in an important country, particularly because the study of multimorbidity has predominately been in HIC and it must be more inclusive of LMIC. As a multimorbidity researcher, I applaud the authors for their initiative on this systematic review and I look forward to the team's further work on multimorbidity, which will be a valuable contribution to our global research community and understanding this increasing health issue.</p> <p>INTRODUCTION: -in the second sentence, it is suggested that "Typically, multimorbidity includes a combination ..." is replaced with "Although a gold standard definition of multimorbidity has not been established, it has been recommended that the operationalization of multimorbidity can include a combination ..."</p> <p>METHODS: -can the authors include the date at which anti-retroviral treatment became available in public health services (and perhaps a reference document for this change in services if possible)? -can the authors clarify whether grey literature (such as policy briefs) will be excluded or eligible for inclusion? -can the authors verify whether studies using the term comorbidity will be included if they are actually examining the prevalence of multimorbidity and whether studies that are examining the prevalence of comorbidity will be excluded? -as well, can the authors clarify whether studies will be included if a patient group is receiving health care services for a specific issue, but they also happen to be living with multimorbidity? (for example: will the authors include studies that are focused on heart failure or HIV patients who are also living with multimorbidity?)</p>
-------------------------	---

	<p>-will the authors require that multimorbidity be defined as two or more conditions or will studies be included in this review regardless of the number and type of conditions included?</p> <p>-although the authors have stated that data extraction will follow recommendations for prevalence systematic reviews, have the authors considered extracting any other participant/patient characteristics that might be relevant to understanding the burden/needs of this population, such as extraction of age, sex, socioeconomic status or urban/rural resident (if available within the study)?</p> <p>-likewise, should a data extraction element also be whether clusters were identified in the study to address research question #3?</p>
--	---

REVIEWER	Angela Y. Chang Danish Institute for Advanced Study, Denmark
REVIEW RETURNED	31-Jul-2020

GENERAL COMMENTS	<p>Overall well written and addresses a gap in the literature. Some comments:</p> <ol style="list-style-type: none"> 1. How do the authors plan to consolidate results that apply different definitions of multimorbidity (for example, by cluster, by count of diseases, by a certain threshold (more than 1 disease, by only including chronic conditions ...)? I also highly doubt the possibility of a meta-analysis given the wide range of definitions used, so I would not put much emphasis on this possibility. Much more discussion should be made on how this would be addressed. 2. I would not exclude the gray literature given that there may be national reports from the local/national governments on this topic 3. The paper states that it is essential to have studies done at hospital settings. While I agree, I also agree that all other sources are equally important. For example, are there studies that use administrative data in South Africa to get to prevalence of multimorbidity? 4. Why is the study period set starting in 1998? Is this tied to when ART became more available (don't think so)? 5. On "conditions": I would add "comorbidities" to the list of possible phrases that could fit under the multimorbidity definition 6. Search terms on pubmed (Table 2): any two-word combinations require quotation marks around it. For example, "multi morbidities".
-------------------------	--

REVIEWER	Maria Lisa Odland Institute of Applied Health Research, University of Birmingham
REVIEW RETURNED	05-Oct-2020

GENERAL COMMENTS	<p>Thanks for submitting this protocol for a systematic review on the prevalence of multimorbidity in South Africa. This is a very important topic which has not been properly studied in low and lower middle income countries especially in Sub-Saharan Africa. The methods are rigorous and described thoroughly. I think this review will contribute with important knowledge in regards to research on multimorbidity and health systems in Sub-Saharan Africa. The protocol is well written and the plan for the methods and the analysis is good. However would the authors consider adding a table with exclusion and inclusion criteria? Also have the authors considered how many articles reporting on prevalence of multimorbidity in South Africa there is?</p>
-------------------------	--

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Kathryn Nicholson, Western University, Canada		
<p>Thank you for this opportunity to review "The prevalence of multimorbidity in South Africa: A systematic review protocol", which aims to synthesize prevalence studies on multimorbidity within South Africa. This is an important topic being explored in an important country, particularly because the study of multimorbidity has predominately been in HIC and it must be more inclusive of LMIC. As a multimorbidity researcher, I applaud the authors for their initiative on this systematic review and I look forward to the team's further work on multimorbidity, which will be a valuable contribution to our global research community and understanding this increasing health issue.</p>	<p>Thank you.</p>	
<p>INTRODUCTION: -in the second sentence, it is suggested that "Typically, multimorbidity includes a combination ..." is replaced with "Although a gold standard definition of multimorbidity has not been established, it has been recommended that the operationalization of multimorbidity can include a combination ..."</p>	<p>We agree with the reviewer and have amended the sentence as suggested.</p>	<p><i>"Although a gold standard definition of multimorbidity has not been established, it has been recommended that the operationalization of multimorbidity can include a combination of non-communicable diseases (NCDs), mental health conditions and infectious diseases"</i></p> <p>Lines 60 – 62, Page 4</p>
<p>METHODS: -can the authors include the date at which anti-retroviral treatment became available in public health services (and perhaps a reference document for this change in services if possible)?</p>	<p>Upon further reflection, we have decided to include all articles up to the date of when we will run the search. In other words, we will no longer exclude articles prior to 1998.</p> <p>The text has been updated in several places to reflect this.</p>	<p>Lines 29, 111, 113, 115, Table 1, 156 and Table 2 (search strategy).</p>

<p>-can the authors clarify whether grey literature (such as policy briefs) will be excluded or eligible for inclusion?</p>	<p>This systematic review will form the first phase of a multi-phased project. We plan to exclude grey literature from this systematic review as the analysis of grey literature will form part of a subsequent analysis related to the larger project.</p> <p>To clarify this point, line 159 was edited to include 'grey literature'.</p>	<p><i>The following types of documents or studies will be excluded:</i></p> <ul style="list-style-type: none"> • <i>reviews, opinion pieces, conference presentations, letters, editorials, dissertations, abstracts, grey literature,</i> <p>Line 160-163, Page 7</p>
<p>-can the authors verify whether studies using the term comorbidity will be included if they are actually examining the prevalence of multimorbidity and whether studies that are examining the prevalence of comorbidity will be excluded?</p>	<p>Yes, studies that use the term 'co-morbidity' but actually examine the prevalence of multimorbidity will be considered.</p> <p>Studies that examine co-morbidity (e.g. look at the prevalence of TB in HIV patients) will be excluded.</p> <p>A sentence was added for clarity.</p>	<p><i>This study will exclude the search term 'comorbidity' as was done by another multimorbidity systematic review.[31] However, if the search results include comorbidity studies that examine the prevalence of multimorbidity, the eligibility of these studies will be considered.</i></p> <p>Line 188 – 189, Page 9</p>
<p>-as well, can the authors clarify whether studies will be included if a patient group is receiving health care services for a specific issue, but they also happen to be living with multimorbidity? (for example: will the authors include studies that are focused on heart failure or HIV patients who are also living with multimorbidity?)</p>	<p>We will exclude studies focused on specific sub-groups with an existing disease.</p> <p>This will be done because it is not possible to calculate the general prevalence of multimorbidity using these types of studies as their denominators are restricted to that sub-group. For example, a study of multimorbidity in people with HIV will give the prevalence of multimorbidity in HIV patients.</p> <p>This is a limitation of our planned review and will be noted in our subsequent write up.</p>	<p><i>Table 2. Summary of inclusion and exclusion criteria</i></p> <p>Page 8</p>

	This information has been added to Table 2.	
-will the authors require that multimorbidity be defined as two or more conditions or will studies be included in this review regardless of the number and type of conditions included?	Yes, we will include studies examining at least two conditions, regardless of the type of disease conditions. Each study's definition of multimorbidity and disease conditions included will be documented and form part of the systematic review write up. We have added a sentence for clarity.	<i>Articles will need to define multimorbidity as the co-existence of at least two disease conditions or an operational definition will be applied.</i> Line 152 -153, Page 7
-although the authors have stated that data extraction will follow recommendations for prevalence systematic reviews, have the authors considered extracting any other participant/patient characteristics that might be relevant to understanding the burden/needs of this population, such as extraction of age, sex, socioeconomic status or urban/rural resident (if available within the study)?	We intend to extract data by age and sex. Thank you for the suggestion of adding urban/rural and socioeconomic status. We will extract these variables if they are available. The text has been updated.	<i>Participant characteristics: age, sex, urban/rural, socioeconomic characteristics.</i> Line 230, Page 236
-likewise, should a data extraction element also be whether clusters were identified in the study to address research question #3?	Yes. We have added a sentence to reflect this suggestion:	<i>Information on the most common disease clusters in the study sample.</i> Line 239, Page 11
Reviewer 2: Angela Y. Chang, Danish Institute for Advanced Study, Denmark		
Overall well written and addresses a gap in the literature. Some comments:	Thank you.	
1. How do the authors plan to consolidate results that apply different definitions of multimorbidity (for example, by cluster, by count of diseases, by a certain threshold (more than 1	We expect heterogeneity and where studies are similar, we will conduct a meta-analysis. If it is not possible to do a meta-analysis, we will present included studies in summary tables that will comprise information related to the	<i>If it is not possible to do a meta-analysis, the findings from included articles will be presented in evidence tables summary tables that will include the year of data</i>

<p>disease, by only including chronic conditions ...)?</p> <p>I also highly doubt the possibility of a meta-analysis given the wide range of definitions used, so I would not put much emphasis on this possibility. Much more discussion should be made on how this would be addressed.</p>	<p>reviewer's question (i.e. definition of multimorbidity, disease conditions included, etc).</p> <p>We have added text for more information as suggested.</p>	<p><i>collection, the study type and setting (community of health facility-based), location of study, the definition of multimorbidity used in each study, the diseases and number of diseases included in the study and how they were ascertained (e.g. measured or self-reported).</i></p> <p>Lines 260 -264, Page 12</p>
<p>2. I would not exclude the gray literature given that there may be national reports from the local/national governments on this topic</p>	<p>The systematic review forms the first phase of a multi-phased project. We plan to exclude grey literature from this systematic review as the analysis of grey literature will form part of a subsequent analysis related to the larger project.</p>	
<p>3. The paper states that it is essential to have studies done at hospital settings. While I agree, I also agree that all other sources are equally important.</p> <p>For example, are there studies that use administrative data in South Africa to get to prevalence of multimorbidity?</p>	<p>We agree with the reviewer: we need information from both community-based studies and facility-based studies. A recent systematic review on multimorbidity in low and middle income countries excluded all health-facility based studies (Nguyen 2019). Hence, we thought it was important to include these studies in our analysis, especially since there are studies that use administrative data in South Africa.</p> <p>We have edited the sentence to indicate that both sources of information are important.</p>	<p><i>While community-based studies on multimorbidity are important, it is also essential for reviews on multimorbidity to include studies conducted in health care settings, because these studies can give a good indication of the number of people accessing healthcare for chronic conditions.[29] Both community-based and health facility-based studies provide insight into the scale of the problem.</i></p> <p>Line 97- 101, Page 5</p>
<p>4. Why is the study period set starting in 1998? Is this tied to when ART became more available (don't think so)?</p>	<p>Upon further reflection, we have decided to include all articles up to the date of when we will run the search. In other words, we will no longer exclude articles prior to 1998.</p>	<p>Lines 29, 111, 113, 115, Table 1, 156 and Table 2 (search strategy).</p>

	The text has been updated in several places to reflect this.	
5. On “conditions”: I would add “comorbidities” to the list of possible phrases that could fit under the multimorbidity definition	Unclear where in the text this refers to. If it refers to the search strategy, the explanation for omitting the search term ‘comorbidity’ is given in Lines 186 to 189.	
6. Search terms on pubmed (Table 2): any two-word combinations require quotation marks around it. For example, “multi morbidities”.	Thank you. This has been corrected in the text:	<p><i>“multi morbidities”</i></p> <p>Table 3, Page 9</p> <p>Note a new Table 2 was added hence this table is now Table 3.</p>
Reviewer 3: Maria Lisa Odland, Institute of Applied Health Research, University of Birmingham		
Thanks for submitting this protocol for a systematic review on the prevalence of multimorbidity in South Africa. This is a very important topic which has not been properly studied in low and lower middle income countries especially in Sub-Saharan Africa. The methods are rigorous and described thoroughly. I think this review will contribute with important knowledge in regards to research on multimorbidity and health systems in Sub-Saharan Africa. The protocol is well written and the plan for the methods and the analysis is good.	Thank you.	
However would the authors consider adding a table with exclusion and inclusion criteria?	Thank you for the suggestion. We have added a table (Table 2 Summary of inclusion and exclusion criteria)	<p>Table 2 Summary of inclusion and exclusion criteria</p> <p>Page 8</p>

<p>Also have the authors considered how many articles reporting on prevalence of multimorbidity in South Africa there is?</p>	<p>This is a growing area of interest in South Africa, especially in the context of HIV being viewed as a chronic disease and increased attention to mental health conditions in the country. Preliminary searches indicate that there are numerous studies on the topic. However, the quality of these studies will need to be interrogated.</p>	
---	---	--

VERSION 2 – REVIEW

REVIEWER	Angela Y Chang Danish Institute for Advanced Study
REVIEW RETURNED	21-Nov-2020
GENERAL COMMENTS	no further comments