PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparing the prevalence of multimorbidity using different operational definitions in primary care in Singapore based on a cross-sectional study using retrospective, large administrative data
AUTHORS	Lee, Yi An Janis; Xie, Ying; Lee, Poay Sian Sabrina; Lee, Eng Sing

VERSION 1 – REVIEW

REVIEWER	Dr Caroline Potter University of Oxford, United Kingdom
REVIEW RETURNED	04-Jun-2020

GENERAL COMMENTS	This manuscript addresses an important issue: the inconsistent use of 'multimorbidity' as both clinical concept and analysis tool. In this study the authors aim to arrive at an operational definition of multimorbidity (MM) that reflects the clinical context of primary care in Singapore, testing alternative proposed definitions identified in the literature within a large-scale existing dataset. The stated potential impact of a consistent operational definition of MM is comparability of studies / datasets within the Singaporean context. The methods used might also have wider impact for defining MM appropriately in other geographical / healthcare contexts. Overall the work is sound and is publishable with some amendments to improve clarity. Introduction: Authors state the rationale/potential implications for the work: "Single disease clinical practice guidelines that have traditionally been used for the management of chronic diseases are inappropriate in the management of patients". This is a key point that needs returning to in the discussion. What are the alternatives to single disease management? How will a consistent definition of MM enable those alternative treatment pathways? This is the missing link that needs to be clarified for the full value of the work to be realized. The issue raised is that different definitions of MM will give different prevalence rates (and therefore differences in whether or not an individual patient will be identified as having MM). This is acceptable justification for the work, but needs linking to the clinical impacts of differential identification of patients/populations with MM – e.g. if the wrong definition is used, does this mean that some patients miss out on being identified with MM and don't receive appropriate treatment? Methods:

	Two publicly-funded 'polyclinics' are referred to (NHGP and SHP), but study data stem from only one (NHGP). Clarify how much of the population NHGP covers, and if there are systematic differences in patient population between the two polyclinics and between the public/private sectors (as the private sector appears to be dominant) – i.e. how representative is the NHGP sample?
	Presumably the choice to use data only from NHGP was a pragmatic one owing to authors' affiliations with this organisation which would enable data access. This needs to be clearly stated.
	Fortin's earlier work is cited as justification for defining MM as three or more chronic conditions (versus two or more). The argument that authors wanted to identify patients with highest needs, so went with the higher threshold, is logical. But given they are arguing for consistency of MM definition, it is notable that their choice is at odds with findings from a recent systematic review (Johnston et al 2019) and the World Health Organization's definition of MM (see 2018 report by Academy of Medical Sciences), which uses a threshold of two conditions. Authors need to acknowledge this discrepancy in justifying their choice of 3 or more conditions as the threshold – please incorporate the references below into your bibliography:
	Johnston et al. 2019. Defining and measuring multimorbidity: a systematic review of systematic reviews. The European Journal of Public Health, Vol. 29, No. 1, 182–189. doi:10.1093/eurpub/cky098
	The Academy of Medical Sciences. 2018. Multimorbidity: a priority for global health research. Report available at: https://acmedsci.ac.uk/file-download/82222577

REVIEWER	Marjan van den Akker Institute of General Practice, Goethe University, Frankfurt/Main, Germany
REVIEW RETURNED	23-Jun-2020

| GENERAL COMMENTS | Thank you for giving me the opportunity to read this paper.
• The authors have analysed national Singapore data to show the differences of the application of different multimorbidity definitions, to come to a recommendation which definition to use in Singapore. The authors have missed some publications that I consider relevant in the context of their work: (1–4).
• Furthermore, the discussion is very much focused on the application in Singapore. As a result, I question the broader relevance of this work. In my opinion there is no one ideal definition or operationalisation of multimorbidity. It can depend on the specific research question, but more often will depend on the availability of data, which was also the case in the study presented here. Furthermore, it should not be neglected that also the data source can have a relevant impact on the prevalence of multimorbidity. (4)
• The selection of diseases with a prevalence of at least 1% in primary care is debatable, with 3.5% - 5.9% of the general population suffering from a rare disease (5). Because of this surprisingly high joint prevalence, it is likely that many people consulting the GP for a more common condition will also suffer from a rare disease. |

	• I'm not convinced that the authors would not have reached the exact same conclusion without the presented prevalences, but based on the contents of the different definitions used. • The authors have added 2 conditions to their ideal definition of which one is 'physical disability'. This is then defined as 'hearing loss', why not call it that? In my understanding 'physical disability covers a lot more that hearing loss. Literature Cited 1. Harrison C, Britt H, Miller G, Henderson J. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. BMJ Open 2014; 4(7):e004694. 2. Fortin M, Hudon C, Dubois MF, Almirall J, Lapointe L, Soubhi H. Comparative assessment of three different indices of multimorbidity for studies on health-related quality of life. BMC Health and quality of life outcomes 2005; 3(74). 3. Sakib MN, Shooshtari S, St John P, Menec V. The prevalence of multimorbidity and associations with lifestyle factors among middle-aged Canadians: an analysis of Canadian Longitudinal Study on Aging data. BMC Public Health 2019; 19(1):243. 4. Gontijo Guerra S, Berbiche D, Vasiliadis H-M. Measuring multimorbidity in older adults: comparing different data sources. BMC Geriatrics 2019; 19(1):166. 5. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 2020; 28(2):165–73.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Dr Caroline Potter):

1)   This manuscript addresses an important issue: the inconsistent use of 'multimorbidity' as both clinical concept and analysis tool. In this study the authors aim to arrive at an operational definition of multimorbidity (MM) that reflects the clinical context of primary care in Singapore, testing alternative proposed definitions identified in the literature within a large-scale existing dataset. The stated potential impact of a consistent operational definition of MM is comparability of studies / datasets within the Singaporean context. The methods used might also have wider impact for defining MM appropriately in other geographical / healthcare contexts. Overall the work is sound and is publishable with some amendments to improve clarity.

Author Response: Thank you!

2)   Authors state the rationale/potential implications for the work: "Single disease clinical practice guidelines that have traditionally been used for the management of chronic diseases are inappropriate in the management of patients". This is a key point that needs returning to in the discussion. What are the alternatives to single disease management? How will a consistent definition of MM enable those alternative treatment pathways? This is the missing link that needs to be clarified for the full value of the work to be realized.

Author Response: Thank you for pointing this out. It is of our view that a consistent definition of multimorbidity can facilitate the identification of common patterns of multimorbidity within the country. In doing so, clinical practice guidelines tailored to the needs of these groups of patients with multimorbidity can be created with a focus on ensuring coordination of care across various specialities, improving medications management to avoid polypharmacy and addressing shared disease risk factors amongst these patients, which are critical points in the management of multimorbid patients as highlighted by Wallace et al. As suggested by you, we have addressed this in our concluding remarks (Page 15, Ref. 44).

3) The issue raised is that different definitions of MM will give different prevalence rates (and therefore differences in whether or not an individual patient will be identified as having MM). This is acceptable justification for the work, but needs linking to the clinical impacts of differential identification of patients/populations with MM – e.g. if the wrong definition is used, does this mean that some patients miss out on being identified with MM and don't receive appropriate treatment?

Author Response: Thank you for highlighting this. We have clarified in the background that having differing definitions of multimorbidity and hence wide variability in the prevalence estimates of multimorbidity would prevent accurate estimations of disease burden and hinder resource distribution for effective disease management (Page 4, Ref. 25).

4) Two publicly-funded 'polyclinics' are referred to (NHGP and SHP), but study data stem from only one (NHGP). Clarify how much of the population NHGP covers, and if there are systematic differences in patient population between the two polyclinics and between the public/private sectors (as the private sector appears to be dominant) – i.e. how representative is the NHGP sample?

Author Response: Thank you for raising this up. We have clarified the representativeness of the NHGP sample in the manuscript. The public primary healthcare sector was organised into two main clusters in Singapore in 2015/2016 - National Healthcare Group Polyclinics (NHGP) and SingHealth Polyclinics (SHP). The remainder of primary care services in the country were provided by private General Practitioners. In 2016, according to statistics published by the Ministry of Health (MOH), Singapore, a total of 3,916,711 individuals (approximately 70% of the 2016 Singapore population) consulted a doctor in the polyclinics. Out of which, 58.9% of these individuals attended the NHGP (Page 5, Ref. 28).

5) Presumably the choice to use data only from NHGP was a pragmatic one owing to authors' affiliations with this organisation which would enable data access. This needs to be clearly stated.

Author Response: We have stated the authors' affiliations with National Healthcare Group Polyclinics (NHGP) in the title page.

6) Fortin's earlier work is cited as justification for defining MM as three or more chronic conditions (versus two or more). The argument that authors wanted to identify patients with highest needs, so went with the higher threshold, is logical. But given they are arguing for consistency of MM definition, it is notable that their choice is at odds with findings from a recent systematic review (Johnston et al

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2019) and the World Health Organization's definition of MM (see 2018 report by Academy of Medical Sciences), which uses a threshold of two conditions. Authors need to acknowledge this discrepancy in justifying their choice of 3 or more conditions as the threshold – please incorporate the references below into your bibliography:

Johnston et al. 2019. Defining and measuring multimorbidity: a systematic review of systematic reviews. The European Journal of Public Health, Vol. 29, No. 1, 182–189. doi:10.1093/eurpub/cky098
The Academy of Medical Sciences. 2018. Multimorbidity: a priority for global health research. Report available at: https://acmedsci.ac.uk/file-download/82222577

Author Response: Thank you for pointing this out. We have acknowledged this discrepancy and incorporated the above references as per your suggestion (Page 6, Ref. 31/32).

Reviewer 2 (Marjan van den Akker):

1)   The authors have analysed national Singapore data to show the differences of the application of different multimorbidity definitions, to come to a recommendation which definition to use in Singapore. The authors have missed some publications that I consider relevant in the context of their work: (1–4).

1. Harrison C, Britt H, Miller G, Henderson J. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. BMJ Open 2014; 4(7):e004694.
2. Fortin M, Hudon C, Dubois MF, Almirall J, Lapointe L, Soubhi H. Comparative assessment of three different indices of multimorbidity for studies on health-related quality of life. BMC Health and quality of life outcomes 2005; 3(74).
3. Sakib MN, Shooshtari S, St John P, Menec V. The prevalence of multimorbidity and associations with lifestyle factors among middle-aged Canadians: an analysis of Canadian Longitudinal Study on Aging data. BMC Public Health 2019; 19(1):243.
4. Gontijo Guerra S, Berbiche D, Vasiliadis H-M. Measuring multimorbidity in older adults: comparing different data sources. BMC Geriatrics 2019; 19(1):166.

Author Response: Thank you for these suggestions. We have read through the above publications and we have noted the many valuable points brought up by each author.

Harrison et al. had discussed how multimorbidity prevalence estimates are affected by the number of conditions considered in each study, minimum number of disease entities required to define multimorbidity and the manner in which 'disease entities' are defined. In our study, we had acknowledged the significance of the number of conditions in each multimorbidity list and had chosen a cut-off of 'three or more' chronic conditions to identify patients with higher needs. We also recognize that the way in which 'disease entities' are defined, that is either by body systems or individual chronic conditions, has an influence on prevalence estimates of multimorbidity, as illustrated by Fortin et al.'s list vs. Quah et al.'s list of chronic conditions. In our opinion, we recognize that while there are advantages in classifying 'disease entities' by body systems as highlighted by Harrison et al., not all chronic conditions of the same body system can be classified together as a single 'disease entity' due to differing care needs. An example (as illustrated in Quah et al.'s list of chronic conditions) includes neurological conditions such as Parkinson's disease which requires multi-disciplinary care to maintain functional capabilities of affected individuals as opposed to epilepsy which has a greater focus on avoidance of seizure triggers and seizure first aid. This manner of classification risks overlooking individuals who require greater care and would fail to give a discerning estimate of multimorbidity. It is

of our view that clinical judgement should be exercised in defining 'disease entities' taking into account the care needs of each chronic condition. We have incorporated this into our manuscript (Page 12, Ref. 37).

Fortin et al. had compared the strength of association of health-related quality of life with three multimorbidity indices: the Cumulative Illness Rating Scale (CIRS), the Charlson index and the Functional Comorbidity Index (FCI), and concluded that CIRS is a better choice as a measure of multimorbidity amongst the three when health-related quality of life (HRQOL) is the outcome of interest. We recognize that our study is limited in failing to analyse the impact of each chronic condition on affected individuals. Further analysis of the impact of each chronic condition on affected individuals and comparison of our proposed operational definition with CIRS with HRQOL as the outcome of interest could be conducted moving forward. Members in our team have also conducted a systematic review on the instruments used for measuring levels of multimorbidity. (1) This is, however, beyond the scope of our current study.

1. Lee, Eng Sing E S, "Measuring Multimorbidity" (2019). Electronic Thesis and Dissertation Repository. 6202. https://ir.lib.uwo.ca/etd/6202

Sakib et al. examined the prevalence of multimorbidity among middle-aged Canadians and the association between lifestyle factors and multimorbidity in this age group. The authors highlighted that a substantial number of younger people are now living with multimorbidity and many of these conditions can have a significant impact on their lives and affect healthcare utilization differently compared to older adults. It is of our view that further work based on the proposed operational definition in our study can be done moving forward to identify common patterns of multimorbidity in younger patients and the impact of multimorbidity on their lives and healthcare utilization. It is, however, beyond the scope of our current study. Members in our team have already submitted a paper titled "Health-related quality of life in middle age adults with multimorbidity" which is currently being reviewed by BMC Family Practice.

Gontijo Guerra et al. studied how different data sources (self-reported and/or administrative data) influence the prevalence of multimorbidity and highlighted the possibility of underestimating cases when a single data source is used. We acknowledge that our study is limited as we only utilized a single administrative data source and we were not able to collect self-reported data given the large database used. We have included this into our limitations (Page 14, Ref. 41). Members in our team are currently in the final stages of a scoping review on the definitions and data sources used in the determination of the prevalence of multimorbidity using large databases.

2)   Furthermore, the discussion is very much focused on the application in Singapore. As a result, I question the broader relevance of this work. In my opinion there is no one ideal definition or operationalisation of multimorbidity. It can depend on the specific research question, but more often will depend on the availability of data, which was also the case in the study presented here. Furthermore, it should not be neglected that also the data source can have a relevant impact on the prevalence of multimorbidity. (4)

Author Response: Thank you for bringing up your concerns. We do recognize that the discussion is largely focused on the application in the primary care setting in Singapore, however, it is our view that the broader relevance of this work lies in the replicability of our study. In our opinion, similar studies using the criteria we outlined in the comparison of the six operational definitions can be performed in different contexts depending on the researcher's area of interest. This may include a different geographic region of the world or a different healthcare setting such as a tertiary institution, and in doing so aid in the formation of a suitable operational definition ideal for use in each specific context.

We do recognize that the data source can have an impact on the prevalence of multimorbidity and have included this into our limitations (Page 15, Ref. 41).

3)   The selection of diseases with a prevalence of at least 1% in primary care is debatable, with 3.5% - 5.9% of the general population suffering from a rare disease (5). Because of this surprisingly high joint prevalence, it is likely that many people consulting the GP for a more common condition will also suffer from a rare disease.

5. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 2020; 28(2):165–73.

Author Response: Thank you for the reference. Our decision to use a standardized prevalence rate of 1% as our cut-off for chronic conditions of high burden in our population of interest was based on Violan et al.'s paper as we could not find any other references in the literature. Violan et al. considered only diagnoses with greater than 1% prevalence in each sex in their selection of diseases in their study of multimorbidity patterns in adult patients in the primary care setting, to obtain consistent and clinically interpretable patterns of association and to avoid spurious relationships that could bias the results. (2)

2. Violan C, Roso-Llorach A, Foguet-Boreu Q, et al. Multimorbidity patterns with K-means nonhierarchical cluster analysis. BMC Fam Pract 2018;19(1):108. doi: 10.1186/s12875-018-0790-x [published Online First: 2018/07/05]

4)   I'm not convinced that the authors would not have reached the exact same conclusion without the presented prevalences, but based on the contents of the different definitions used.

Author Response: We acknowledge that the presented prevalences in the manuscript (Table 2) were not part of the criteria used in the comparison of the six operational definitions. The presented prevalences, however, do serve as a reflection of how different operational definitions, with consideration of different numbers of and types of chronic conditions, have vastly different prevalence estimates of multimorbidity.

5)   The authors have added 2 conditions to their ideal definition of which one is 'physical disability'. This is then defined as 'hearing loss', why not call it that? In my understanding 'physical disability covers a lot more that hearing loss.

Author Response: Thank you for bringing up your concerns. We recognise that the chronic condition 'physical disability' is not synonymous with the ICD-10 code 'hearing loss'. We have rephrased the last paragraph on Page 13 of the manuscript to better reflect that 'hearing loss' is only one of the ICD-10 codes under the chronic condition 'physical disability'. We do, however, recognize that 'physical disability' does not only include the ICD-10 codes 'hearing loss' and 'congenital malformation of the musculoskeletal system'. However, as we had a fixed number of NHGP ICD-10 codes, this had limited the inclusivity of the chronic condition 'physical disability'. We have incorporated this into our limitations (Page 14). Members of our team are also currently working on a Delphi study in Singapore

using the proposed list of chronic conditions to come to a consensus with an expert panellist of family physicians for the final list of chronic conditions and ICD-10 codes within each category.

Once again, thank you for giving us the opportunity to submit a revised version of our manuscript and we look forward to your reply.

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VERSION 2 – REVIEW

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REVIEWER	Dr Caroline Potter University of Oxford, United Kingdom
REVIEW RETURNED	08-Oct-2020

GENERAL COMMENTS	The authors have responded to all comments raised in the earlier review of this article, for improved clarity on the implications of their findings and the limitations of the study. While all of the points that I raised were addressed to some extent, I would have liked some further clarity on the representativeness of the sample (i.e. whether the demographic characteristics reported in Table 1 are in line with national trends, or if the NHGP sample differs in some way - age, ethnicity, level of economic security, etc.). I would also have liked a clearer acknowledgement from the authors that the choice to draw only on NHGP data was based on pragmatic rather than scientific reasons (this is what I assume based on the authors' affiliations, but it is not explicitly stated). However these points are relatively minor, and in the context of more substantive points that were clarified in the revision and my overall positive assessment of the work at first review, this article is acceptable for publication in its current form.

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VERSION 2 – AUTHOR RESPONSE

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Thank you for giving us the opportunity to submit a revised version of our manuscript "Comparing the prevalence of multimorbidity using different operational definitions in primary care in Singapore based on a cross-sectional study using retrospective, large administrative data" for publication in BMJ Open. We have re-formatted our abstract in accordance to the journal's instructions. We also greatly appreciate the comments and recommendation for publication given to us by Dr Caroline Potter. Please see below for our response to Dr Potter's comments.

1)   While all of the points that I raised were addressed to some extent, I would have liked some further clarity on the representativeness of the sample (i.e. whether the demographic characteristics reported in Table 1 are in line with national trends, or if the NHGP sample differs in some way - age, ethnicity, level of economic security, etc.).

Author Response: Compared to the 2016 Singapore population, the NHGP study population was similar in terms of sex distribution but captured a relatively larger proportion of the Malay, Indian and Others ethnicity as well as the age groups '45 to 64 years' and '65 years and above' (Table 1). We have accounted for these differences by standardizing our study population to the 2016 Singapore population (Page 6, Section 2.5).

Table 1: Demographics of the 2016 Singapore population vs NHGP study population

	Singapore Population		NHGP Study Population	
	Frequency	Percent	Frequency	Percent
Total	3,933,559	100.0	787,446	100.0
Sex				
Female	2,004,033	50.9	400,965	50.9
Male	1,929,526	49.1	386,481	49.1
Ethnicity				
Chinese	2,923,172	74.3	537,234	68.2
Malay	525,888	13.4	127,501	16.2
Indian	356,876	9.1	78,452	10.0
Others	127,623	3.2	44,259	5.6
Age Groups				
0 - 24	1,096,789	27.9	201,839	25.6
25 - 44	1,180,975	30.0	165,212	21.0
45 - 64	1,168,225	29.7	252,206	32.0
65 - 99	487,570	12.4	168,189	21.4

2)   I would also have liked a clearer acknowledgement from the authors that the choice to draw only on NHGP data was based on pragmatic rather than scientific reasons (this is what I assume based on the authors' affiliations, but it is not explicitly stated).

Author Response: We have included into our manuscript that our decision to draw data from only the NHGP was due to pragmatic reasons (Page 5, Section 2.1).

Once again, thank you for giving us the opportunity to submit a revised version of our manuscript for publication.