PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis
AUTHORS	Sullivan, Michael; Rankin, Alastair; Jani, Bhautesh; Mair, Frances; Mark, Patrick

VERSION 1 – REVIEW

REVIEWER	Catherine McCarty University of Minnesota Medical School, Duluth campus
REVIEW RETURNED	20-Mar-2020

GENERAL COMMENTS	I was asked top review this manuscript for the statistics. I find the methods appropriate and clearly presented. One small comment related to the abstract. Abbreviations were used without being previously defined.

REVIEWER	Abolfazl Akbari Colorectal Research Center, Iran University of Medical Sciences, Tehran, Iran
REVIEW RETURNED	21-Mar-2020

GENERAL COMMENTS	The abstract should be checked for revising based on requested journal format. Notably, the results/findings should be revised according the statistical analyses in both the abstract section and main results. It seems that results have not been presented corresponding the right analysis method. It is suggested that authors check the significanc and other statistical indecis for presenting the results.

REVIEWER	Daniel Edmonston Duke University, Durham, NC, USA
REVIEW RETURNED	22-Mar-2020

GENERAL COMMENTS	In this study, Sullivan and colleagues perform a systematic review and meta-analysis of available data to determine the association between multimorbidity and clinical outcomes in patients with CKD. As expected, the significant amount of heterogeneity in the included studies diminishes the power of the meta-analyses. However, the data are consistent with the prevailing theory that increasing multimorbidity increases the risk of mortality, heart failure hospitalization, and progression of kidney disease. Of special interest, increasing multimorbidity associates with increased risk of kidney disease progression in kidney transplant recipients. The methodological approach is thorough and transparent. The presentation of the results is at times difficult to

	follow. However, the discussion presents a concise and thoughtful contextualization of the study. Below I present a few comments on the manuscript, each of which I consider minor. - In the first line of abstract, the abbreviation “LTC” is introduced without first defining the meaning. - Also, it may be worth clarifying the abstract that CKD is not considered one of the comorbidities to qualify for multimorbidity in this study. - Under the “Main Findings” header, I do not understand the following sentence: “Unadjusted HRs were quoted as adjusted HRs were not available for all studies.” Please clarify. - Consider changing references of “HD patients” to “patients receiving HD.” - Under the discussion, it may be more accurate to say that the study investigated the association of multimorbidity with outcomes in CKD rather than the effects of multimorbidity.

REVIEWER	Yang Cao Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Sweden
REVIEW RETURNED	23-Mar-2020

GENERAL COMMENTS	1. Inclusion criteria and exclusion criteria should be specified in a separate section. 2. Why random-effects model was not used to synthesize the effects? 3. Lines 27-32, page 7: The authors said “Where necessary and possible, we calculated RRs for studies, comparing patients with multimorbidity to those without multimorbidity. HRs could not be calculated as there were no individual time-to-event data.” But in the figures and tables, the authors used HRs. 4. Line 20, page 8: I don’t understand what the authors mean “each increase in CCI”. Please specify. 5. Some studies have more than one HRs corresponding to different quartile, quantile, or CCI categorical groups. It’s not clear how the authors synthesize them. 6. Why risk ratio instead of HR used in Figure 3? 7. Why Generic Inverse Variance Method was used in Figure 2, but Mantel-Haenszel Method was used in Figure 3? 8. The authors said that they followed the PRISMA-R guidelines, but why a MOOSE checklist was provided? The statistical analyses are confusing and were not described clearly. Major revision is needed.

REVIEWER	Maarten Taal University of Nottingham, UK
REVIEW RETURNED	28-Mar-2020

GENERAL COMMENTS	This manuscript presents an excellent systematic review and meta-analysis of published observational studies that have investigated the association between multimorbidity and adverse outcomes in persons with chronic kidney disease. Despite substantial heterogeneity between studies there was a clear association between multimorbidity and increased risk of death as well as associations with progression of CKD, hospitalisation and cardiovascular events in a smaller number of studies. The authors highlight important knowledge gaps to inform the design of future studies.

	Comments: 1. Methods: the authors should explain why CKD was not counted as a long term condition in their analysis. 2. As CKD is a heterogenous condition is would be interesting to see subgroup analyses that focus on persons a) on dialysis or conservative care b) with mild to moderate CKD c) with a renal transplant, or the authors should explain why this was not possible. 3. Figure 2: Please spell out “Charlson Comorbidity Index” in the legend. 4. Supplementary File 3: Please define abbreviations in a footnote. 5. Supplementary File 4: Please spell out “Newcastle Ottawa Scale”.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1. Abbreviations in the abstract have now been defined.

Reviewer 2. The abstract has been revised to fit the format requested by the journal. Clarifications about the statistical analyses have been added to the Methods (Data synthesis and analysis) and Results (Meta-analysis) sections.

Reviewer 3. Abbreviations in the abstract have now been defined. Clarification has been added to the abstract and Methods section that CKD has not been counted as an LTC. In Results (Main Findings), clarification has been provided as to why unadjusted effect sizes have been quoted. As suggested, "HD patients" has been changed to "patients receiving HD". As suggested, in the Discussion, "the effects of multimorbidity" has been changed to "the associations between multimorbidity and outcomes".

Reviewer 4. In the Methods section, Inclusion and Exclusion criteria have now been clearly separated. In the Methods section (Data synthesis and analysis), clarification has been provided as to why fixed effects meta-analysis were used, and the rationale for Generic Variance and Mantel-Haenszel methods in each meta-analysis has been described. Clarification has been provided that RRs were calculated for meta-analysis only and that this was instead of HRs because time-to-event data were not available. Clarification is present that "each increase in CCI" references CCI being considered as a continuous variable. There is reference to the MOOSE checklist in the acknowledgements section: this is requested when submitting a systematic review to the journal.

Reviewer 5. Clarification has been provided as to why CKD was not considered as a co-morbid LTC. Clarification has been provided that sub-group analyses were not possible because there were insufficient data on sub-groups like mild to moderate CKD. "Charlson Comorbidity Index" and other abbreviations have been spelled out, as suggested.

VERSION 2 – REVIEW

REVIEWER	Yang Cao Örebro University, Sweden
REVIEW RETURNED	22-Apr-2020

GENERAL COMMENTS	1. The authors assumed the direction of effect of multimorbidity on mortality would be consistent across the studies and heterogeneity would not contribute to the effect estimates. However, I’m not convinced unless the author may provide I-square and relevant test in the manuscript.

	2. In Figure 2, the risk was presented using HR. Did all the studies have HR? Otherwise, the authors should use RR instead of HR in the figure.

REVIEWER	Maarten Taal University of Nottingham, UK
REVIEW RETURNED	07-May-2020

GENERAL COMMENTS	The authors have adequately addressed the Reviewers' initial comments. I have no further comments or recommendations.

VERSION 2 – AUTHOR RESPONSE

We thank reviewer 4 for their comments about our meta-analysis. In response to these:

1. The comment about heterogeneity between studies is valid, and there are indeed advantages and disadvantages to the use of fixed effects and random effects models. We used fixed effects models from the outset because previous literature has demonstrated consistent associations between multimorbidity and mortality and we assumed the direction of effect of multimorbidity on mortality would be consistent in our studies, barring sampling errors and differences in sample size. We acknowledge that random effects models would also be helpful if the participants in the included studies were inherently different. We have therefore added meta-analyses using random effects models, which demonstrate similar results to when fixed effects models were used. The results from these analyses are now available in the supplemental data and we have further described the rationale for our approach in the main text.

2. All the studies used in figure 2 had HRs available. A statement has been added to the manuscript, clarifying this.