PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Chronic kidney disease as a risk factor for acute community-acquired infections in high income countries: a systematic review
AUTHORS	McDonald, Helen; Thomas, Sara; Nitsch, Dorothea

VERSION 1 - REVIEW

REVIEWER	Sreejith Parameswaran Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Pondicherry, India
REVIEW RETURNED	11-Nov-2013

GENERAL COMMENTS	In the 'methods' section (page 9, line 20), while describing the search strategy, the authors have mentioned 'elevated creatinine or creatinine clearance' as a search term used to identify CKD. I believe the authors meant 'elevated serum creatinine or REDUCED creatinine clearance' and not really 'elevated creatinine clearance' (which do not qualify as CKD by itself). The same error is repeated on page 45, line 23, in supplementary table 4, under the subheading 'Exposure of interest'. Please see the attached file, with these words highlighted in yellow colour, in the respective pages.

REVIEWER	Vivek Jha PGIMER, Chandigarh, India
REVIEW RETURNED	13-Nov-2013

GENERAL COMMENTS	This review addresses an important issue for clinicians managing patients with chronic kidney disease. The authors do well to point out the major limitations in interpretation of the evidence and suggest that available data suggest a graded increase in the infection risk with increasing severity of CKD. I would request a few clarifications: 1. Why was the search restricted to reports from high income countries? This necessarily restricts the global generalisability of the study. 2. Did the authors consider looking for risk of tuberculosis, an important community acquired infection in large parts of the world. 3. Although the authors have excluded studies that only had patients with ESRD, they do note that 7 of 11 did include an unspecified number of these patients. This is important when making an assessment of graded increase in risk. If these were the studies that showed such an increase (page 13, last para), and if this was unduly modified by the presence of ESRD, the authors conclusion that pre dialysis CKD increased infection risk would be in jeopardy.

	4. Can the analysis be repeated to include ref #27?

REVIEWER	Andrew Elders University of Aberdeen, UK
REVIEW RETURNED	20-Dec-2013

GENERAL COMMENTS	The investigators have conducted a systematic review of studies investigating CKD as a risk factor of community-acquired infections. Their methods are set out clearly and they demonstrate a sound approach to screening potential studies and assessing the quality of included studies, for example their use of the kappa statistic in describing agreement in study selection. The investigators identify two studies which fail to report confidence intervals or standard errors (or other statistics from which these could be derived). Was there any attempt to contact the authors of these primary studies so that the data could be requested? If so, then this should be reported and, if not, then this should be considered. Moderate to high heterogeneity was identified and no meta-analysis was performed as a result. Whilst this level of heterogeneity does preclude a fixed effect meta-analysis from being conducted, it does not necessarily mean that there should have been no meta-analysis. The study would be greatly improved with some appropriate pooled estimate of effect size and the investigators should consider carrying out a random-effects analysis. It may, however, be worth attempting to eliminate identified sources of heterogeneity before carrying out a meta-analysis. The study report does include a good discussion of heterogeneity in which potential sources are identified, particularly the effect of age as described by James (2009). Discussion of the effect of the inclusion of the study by Campbell (2011) in the context of a flu pandemic should also be included.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Sreejith Parameswaran
Institution and Country Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Pondicherry, India

Reviewer's comment: In the 'methods' section (page 9, line 20), while describing the search strategy, the authors have mentioned 'elevated creatinine or creatinine clearance' as a search term used to identify CKD. I believe the authors meant 'elevated serum creatinine or REDUCED creatinine clearance' and not really 'elevated creatinine clearance' (which do not qualify as CKD by itself). The same error is repeated on page 45, line 23, in supplementary table 4, under the subheading 'Exposure of interest'. Please see the attached file, with these words highlighted in yellow colour, in the respective pages.

Response: Thank you for spotting this typing error which we have corrected in both the Methods (paragraph 2 page 9 with tracked changes) and supplementary table 4.

Reviewer Name Vivek Jha

Institution and Country PGIMER, Chandigarh, India

Reviewer's comment: This review addresses an important issue for clinicians managing patients with chronic kidney disease. The authors do well to point out the major limitations in interpretation of the evidence and suggest that available data suggest a graded increase in the infection risk with increasing severity of CKD.

Response: Thank you.

Reviewer's comment: I would request a few clarifications:
Reviewer's comment: 1. Why was the search restricted to reports from high income countries? This necessarily restricts the global generalisability of the study.

Response: We restricted our search to high income countries as we felt that the relationship between CKD and infections in low and middle income countries would be different, requiring a separate search and encountering different issues. For example, as CKD is a silent disease, under-ascertainment would be a greater problem in countries with lower levels of monitoring. In addition, the epidemiology and ascertainment of community-acquired infections would be different in these countries; thus we believe that the association between CKD and infections in these settings in an interesting but separate research question.

Reviewer's comment: 2. Did the authors consider looking for risk of tuberculosis, an important community acquired infection in large parts of the world.

Response: We agree that tuberculosis is a very important infection, both in the general population in large parts of the world, and particularly as a serious complication of end-stage renal disease. We did not include it in this review, as the relationship between CKD and chronic infections from slow-replicating intracellular pathogens such as Mycobacterium tuberculosis is very likely to differ from that between CKD and acute infections, which were our focus in this review.

Reviewer's comment: 3. Although the authors have excluded studies that only had patients with ESRD, they do note that 7 of 11 did include an unspecified number of these patients. This is important when making an assessment of graded increase in risk. If these were the studies that showed such an increase (page 13, last para), and if this was unduly modified by the presence of ESRD, the authors conclusion that pre dialysis CKD increased infection risk would be in jeopardy.

Response: Thank you for pointing out that this was unclear. We have clarified in the Results and Discussion that the four studies which found a graded association of increased risk of infection with more severe CKD all excluded patients with end-stage renal disease, and we have redrawn Figure 2 to present all estimates stratified by inclusion or exclusion of patients with ESRD, as described above in the response to the Editor’s comments.

Reviewer's comment: 4. Can the analysis be repeated to include ref #27?

Response: We have updated the search to 16 January 2014, and repeated the analysis to include reference 27 and also two newly identified studies, as discussed above.

Reviewer Name Andrew Elders
Institution and Country University of Aberdeen, UK

Reviewer's comment: The investigators have conducted a systematic review of studies investigating CKD as a risk factor of community-acquired infections. Their methods are set out clearly and they

demonstrate a sound approach to screening potential studies and assessing the quality of included studies, for example their use of the kappa statistic in describing agreement in study selection.

Response: Thank you for your comments.

Reviewer's comment: The investigators identify two studies which fail to report confidence intervals or standard errors (or other statistics from which these could be derived). Was there any attempt to contact the authors of these primary studies so that the data could be requested? If so, then this should be reported and, if not, then this should be considered.

Response: We calculated the rate ratios for these two studies from rates that were presented without standard errors or denominators. Due to the heterogeneity we encountered we do not believe that these standard errors would facilitate meta-analysis. However, we have updated the Forest plot to include these estimates, without confidence intervals, to allow the reader to assess how they fit in to the context of other results, and hope this avoids any negative consequences of the missing confidence intervals (Figure 2).

Reviewer's comment: Moderate to high heterogeneity was identified and no meta-analysis was performed as a result. Whilst this level of heterogeneity does preclude a fixed effect meta-analysis from being conducted, it does not necessarily mean that there should have been no meta- analysis. The study would be greatly improved with some appropriate pooled estimate of effect size and the investigators should consider carrying out a random-effects analysis. It may, however, be worth attempting to eliminate identified sources of heterogeneity before carrying out a meta-analysis.

Response: With the increased number of estimates from updating the study, we have re-explored sources of heterogeneity and present these expanded results in Results (page 13 with tracked changes, page 12 without). Unfortunately we were unable to eliminate sources of heterogeneity, as there are too few studies to stratify adequately for the multiple sources of heterogeneity. As a significant source of between-study heterogeneity is likely to be due to the non-comparable study populations (as we highlight in the Discussion), we are reluctant to produce a pooled result through random effects meta-analysis, as we think it could be misleading. We have removed meta-analysis from the title, as suggested by the Editor.

Reviewer's comment: The study report does include a good discussion of heterogeneity in which potential sources are identified, particularly the effect of age as described by James (2009). Discussion of the effect of the inclusion of the study by Campbell (2011) in the context of a flu pandemic should also be included.

Response: Thank you. We have added this helpful suggestion to the Discussion (page 24 with tracked changes).
“In general the risk of ascertainment bias from increased monitoring for infection among patients with CKD is probably low, although one study assessed risk factors for hospitalisation with influenza during an influenza pandemic, in which context patients with influenza-like symptoms may have been more likely to be tested for influenza A(H1N1) if they also had CKD.”

VERSION 2 – REVIEW

REVIEWER	Vivek Jha PGIMER, Chandigarh, India
REVIEW RETURNED	14-Feb-2014

GENERAL COMMENTS	Thank you for addressing the question of better defining the patient population. Since you chose to limit the review to HIC, this needs to be discussed along with reasons in the paper, same with why some infections (e.g. TB) were excluded. Also, the title should include HIC.

VERSION 2 – AUTHOR RESPONSE

Reviewer's comments:
Thank you for addressing the question of better defining the patient population.
Since you chose to limit the review to HIC, this needs to be discussed along with reasons in the paper, same with why some infections (e.g. TB) were excluded.
Also, the title should include HIC.

Response:
We are pleased that our clarification of our patient population was helpful. We have added, as suggested, a discussion of the reason for focusing on acute community-acquired infections in high-income countries, to the Methods section (page 9, paragraph 1), as follows:

"Ascertainment of CKD, as a silent disease, and, to a certain extent, ascertainment of acute community-acquired infections, are dependent on high levels of monitoring and good access to healthcare, so we restricted our search to high-income countries. Chronic infections such as tuberculosis were not included, as the relationship between CKD and chronic infection is very likely to differ from that between CKD and acute infections, which was our focus in this review."

We have also added "in high-income countries" to the title, as suggested.