Author’s response to reviews

Title: Estimating the total prevalence and incidence of End-Stage Kidney Disease among Aboriginal and non-Aboriginal populations in the Northern Territory of Australia, using multiple data sources

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Response to Editor’s Comments:

Editor comment 1: Per reviewer 1's comments, a sensitivity analysis examining those with a lower eGFR could be warranted, and a note in the limitations section that not all patients with eGFR < 15 may need RRT may be appropriate. However, I do think that the definition of ESKD with eGFR < 15 is consistent with literature and is okay to keep as the main analysis, particularly if the objective is to estimate the incidence of ESKD (and not just RRT).

Response: Agreed, we have added a sensitivity analysis with a cut off of eGFR<=7, which generates a smaller number of undiagnosed cases. With this alternate definition, there is a small change in the diagnosed cases, and substantial reduction in the undiagnosed cases. We now describe the sensitivity analysis in the definition section of Methods, describe the Results section and have added a new table as Appendix Table 6.

We confirm the editors’ comment, the definition of ESKD that we have used is based on the Australian standard. We have added that “not all patients with eGFR < 15 may need RRT” in the limitations section.
Editor comment 2: More information is needed in the methods section about the capture/recapture method, the specific denominators used, and information about the different data sets. For example, it is unclear which dataset was the primary source of information about race/ethnicity, age, and sex. In addition, the years of each dataset should be clarified. The details of how some of data in the tables/figures is not clearly described in the methods section. All results should have a corresponding description in the methods.

Response: Agreed, as suggested we have amended the method section.

Editor comment 3: In the introduction of the paper it would be helpful to have the context for previous incidence estimates (the actual numbers) for both Aboriginal and non-Aboriginal patients. This could help set up the need for these methods, as well as the need for this race/ethnicity stratification.

Response: Agreed, we have added further details in the Introduction

Editor comment 4: Other minor comments: the abstract should include the years of the data sources in the methods section; would refer to "patients" rather than "clients".

Response: Agreed, as suggested, we have added the years of the data sources in the methods section of the abstract and changed all "clients" to "patients".

Response to Reviewers’ Comments:

James Heaf (Reviewer 1):

Reviewer 1, comment 1: The main problem with this paper is the definition of ESKD. The normal definition is progressive CKD requiring permanent RRT. This will occur at an eGFR of about 7 ml/min. Patients not receiving therapy can be expected to die within months. This study has included all patients with CKD stage 5. Many patients with an eGFR of 15 ml/min are virtually asymptomatic, and the recent IDEAL study suggests that RRT is not indicated for them. These patients should, of course, be under nephrological care, but this issue is not addressed in the current study. Thus, the undiagnosed group combines patients with CKD not requiring RRT with the much more interesting group of patients requiring, but not receiving, therapy, either due to patient wish, physician decision, poor referral patterns or patient non-compliance.

Response: While we are in agreement with the reviewer’s central point (and have added a sensitivity analysis examining only those with an eGFR<=7ml/min/1.73m2), we feel that the issue of the definition of ESKD is considerably more complex than the reviewer has outlined,
should not only be defined by the need for renal replacement therapy (as the reviewer implies), and is a topic of ongoing debate in the literature. The latest ANZDATA report does indeed suggest that non-Indigenous patients in Australia start renal replacement therapy at a median of around 7ml/min/1.73m² (with Indigenous patients starting at a median of around 6ml/min/1.73m²), but we note a very large interquartile range around these medians. Given that rates of “late referral” in the NT during the study period are similar to national levels (between 20-25%), we suggest that the majority of patients with an eGFR <15ml/min/1.73m² who are intending renal replacement therapy should be reflected in available hospital administrative or primary care clinical data. While we think that it is worthwhile noting the issue of varying definitions of ESKD by varying eGFR threshold in the paper, we feel that the KDIGO definition for ESKD (<15ml/min/1.73m²) aligns with ICD-10AM coding and ICPC-2R codes and is best used for work that incorporates these different data sources.

We also think that the statement “Patients not receiving therapy can be expected to die within months” may be true for the elderly with substantial comorbidity, but is not necessarily true for a much younger Indigenous population with ESKD.

Reviewer 1, comment 2: The AIHW definition of ESKD is similarly controversial. A patient has ESKD if one of various CKD diagnoses is given as associated cause of death. Since mortality, particularly cardiovascular, increases with falling eGFR, it would be perfectly rational to include this as an associated diagnosis e.g. for a patient with hypertensive nephropathy, CKD stage 4, who died of a cerebral hemorrhage. The reliability and comprehensiveness of associate diagnoses should be documented.

Response: While we agree that the AIHW definition of ESKD is controversial, we have used this in order to allow comparisons with the only available national data.

Reviewer 1, comment 3: Since the databases are essentially measuring different things, a table is therefore required describing how many patients were captured by each of the capture techniques, both alone and in combination.

Response: Agreed, as suggested we have added Appendix 2,3,4,5 for the number of patients picked up by one dataset, and the number of patients found in additional datasets.

Reviewer 1, comment 4: I do not quite follow the argument that underestimation is due to the fact that Aboriginals do not currently access the services for social, geographic or cultural reasons.
1) The prevalence underestimation was similar between Aboriginals and non-Aboriginals (Table 2). The statement "Estimated undiagnosed ESKD prevalent and incident cases who were Aboriginal people accounted for a much larger proportion (81% and 82% respectively) than their population proportion (30%)" (page 6 line 10) could be mainly due to their much higher incidence of CKD.

2) In order to be included in the study, all patients had to have had at least one contact with the health services. The question, as to whether the subsequent follow-up treatment was inadequate was due to patient- or system-related causes, is not addressed by this study.

Response:

1) Agreed, this paragraph has been rewritten for clarity.

2) By using capture-recapture method, we estimated undiagnosed patients (people have no contact with the health services for ESKD) that are not caught by any of the 4 datasets in our study. The general observation of poor access has now been included in the subsequent paragraph of the Discussion, with the addition of several references.

Reviewer 1, comment 5: Fig 1 could be improved. The absolute number of patients is uninteresting. Consider four figures showing incidence and prevalence rates proportional to population for both Aboriginal and non-Aboriginal patients.

Response: Figure 1 has been included to demonstrate the relative contributions of treated, untreated and undiagnosed cases across age groups. A similar graph, based on case numbers, has been published previously (Australian Institute of Health and Welfare. End-stage kidney disease in Australia: total incidence, 2003–2007 (AIHW Cat. No. PHE 143). Canberra: AIHW, 2011. http://www.aihw.gov.au/publication-detail/?id=10737419269 (accessed July 2015), (with the contribution of treated and untreated cases) and is regularly presented as a demonstration of unmet need.

The four graphs suggested by the Reviewer repeats information that is available in Tables 2 and 3.

We consider that the existing figure is the most relevant option and our preference is to retain this original figure. We are happy to accept the guidance of the editor, and if appropriate can remove the figure from the article.
Reviewer 1, comment 6: Page 4 line 8 (4-8) "with a previous eGFR <60 mL/min/1.73m2" Why? Many patients only have their first creatinine measured at a late stage in their kidney disease.

Response: This part of the definition was used to restrict to those with chronic kidney disease. As noted above, “late referral” rates for maintenance renal replacement therapy are at low national rates in the Northern Territory.

Susan M Samuel (Reviewer 2):

Reviewer 2, comment 1: 1. Were the ESRD codes used to identify cases from these datasets previously evaluated for case ascertainment (formal or informal validation)? Provide some more detail in the case definition section, in addition to citation 10.

Response: All the definitions for ESKD, used in manuscript, follow standards used in Australia, notably by the Australian Institute of Health and Welfare or otherwise by consensus national guidelines. We have added Appendix Table 1 for the Definition of ESKD cases for the four datasets and have added a further three references.

Reviewer 2, comment 2: 2. It would be good to provide some information regarding the context of health insurance and access to services in Northern Territory, in particular for Aboriginal and highlight any differences between Non-Aboriginals.

Response: Agreed, we have added additional information in the fourth paragraph of the Discussion.

Reviewer 2, comment 3: 3. As a general question, is the term Aboriginal still in use in Australia. Canada has moved to using the term Indigenous. This is a minor point to clarify.

Response: ‘Indigenous’ is disliked by many Aboriginal and Torres Strait Islander Australians and is falling from favour. We follow the convention of the preferred use of “Aboriginal” recommended by the National Institute for Aboriginal and Torres Strait Islander Health Research (Lowitja Institute) (Source: https://www.lowitja.org.au/sites/default/files/TLI-style-guide-v13.pdf)

Reviewer 2, comment 4: The capture re-capture methods can be described in more detail in the methods section. It says the 'incidence was calculate using all new diagnoses recorded in any of the data sources during 2013'....'ESKD cases in death registration data who died during 2013 but
not found in the other three clinical datasets were included in the incidence model.’ However, no
details are given regarding how 'the capture recapture' methods were carried out using all the
datasets. The results of how many of the patients were found between all the datasets or in
single datasets will be interesting (proportion picked up by one dataset, and proportion found in
additional datasets etc).

Response: Agreed, as suggested we have added Appendix Tables 2,3,4,5 for the proportion
selected from each single dataset, and additional datasets.

Reviewer 2, comment 5: Following from this, what is the definition of diagnosed (known) cases
and similarly the definition of unknown cases.

Response: Agreed, as suggested we have added Appendix1 for the Definition of ESKD cases for
the 4 datasets. The undiagnosed cases are generated from capture –recapture method: A log-
linear capture recapture model was used to estimate the number of ESKD cases not reported at
all based on the number of patients in the HSD, ANZDATA, PCIS and BDM.

Reviewer 2, comment 6: How was the proportion of 'underdiagnosis' and 'underestimation'
calculated. These should be clearly described in the methods section.

Response: The underdiagnosis and underestimation are calculated by the diagnosed cases
divided by diagnosed plus undiagnosed cases. To keep the consistency, we have changed all the
underdiagnosis to underestimation. We have added this sentence in the method section.

Reviewer 2, comment 7: For the discussion, it is best to give a headline summary of your study
results in the first paragraph. Then compare and contrast with other studies in the subsequent
paragraphs.

Response: Agreed, as suggested we have added a headline summary of our study results in the
first paragraph.