ARTICLE DETAILS

TITLE (PROVISIONAL)	Transformation of mortality in a remote Australian Aboriginal community: a retrospective observational study
AUTHORS	Hoy, Wendy; Mott, Susan; McLeod, Beverly

VERSION 1 - REVIEW

REVIEWER	Laurence Gruer University of Edinburgh
REVIEW RETURNED	27-Mar-2017

GENERAL COMMENTS	This is one of the most interesting papers I have reviewed for some time, providing a unique overview of the evolving patterns of mortality in an isolated community over a 50 year period. With access to data over such a long period of time it shows considerable improvements which would not be evident with shorter periods of follow-up and comparison to the majority population. Specific points Strengths and Limitations Given that doctors were at best only intermittently present in the community and latterly multiple pathologies seemed common, the authors should state that cause of death was potentially inaccurate, as they note in the Discussion.. Methods More detail should be given about how cause of death was ascertained. 5.11 It would be helpful to give the rough date when medically ascertained cause of death became usual. Discussion 7.40 Particularly as no supportive data are presented in this paper, the authors, in my opinion, are making too much of the "Barker hypothesis" by saying the "improving rates are in large part a representation of the Barker hypothesis." It's debatable whether data can "represent" a hypothesis rather than "support" it but it is also not possible to be confident from the data presented here to what extent low birth-weight per se actually drives the patterns seen here. For example, low-birth weight might be confounded by other risk factors such as on-going malnutrition, parental smoking or alcohol abuse etc. I also think that the prominence given to the Barker hypothesis in the abstract is unwarranted. 7.49 This sentence lacks a phrase such as "those with low birth-weight".

	8.6 Given the remarkable incidence of renal failure, the authors could usefully consider what might be the underlying causal factors. Is any evidence available from renal biopsy or post-mortem histology?
	Figures 5 A-D For all the space they take up, I don't find the population pyramids particularly helpful. If they are included each figure needs to have the year it refers to clearly indicated.
	Figure 6 The upper two lines should be labelled Aboriginal Northern Territory; Non-Aboriginal Northern Territory

REVIEWER	Neophytos Stylianou University of Bath, UK
REVIEW RETURNED	13-Apr-2017

GENERAL COMMENTS	Overall I would like to thank the editor/authors for providing me with the opportunity of reviewing the manuscript. I would like to congratulate the authors for the work they have done. It is good to see that people work on remote communities and they try to increase our understanding of them. Overall the paper tries to describe the trends in deaths over a time period for different age groups of a remote Australian community. The paper lacks specific aims and objectives and needs to be tighten for publication. Results will need to be further discussed in discussions ection to suggest possible explanations. Limitations needs more work. Further clarification and specific comments are shown below: Introduction 1. Overall the aims and objectives of the paper need to be clear in the Introduction section of the paper, which at the moment they are not. 2. On p3, line 8, the authors state that deaths are associated with non-communicable disease. This statement is referenced and generally holds but this paper looks more specifically at remote populations so I would prefer if they added something here describing trends in disease and mortality for specifically remote populations (if this exists). 3. On p3, line 28, is there evidence of cigarette introduction at that time? It is anecdotal evidence? 4. On p4, line 40, is there any speculation/justification for six fold death rates? 5. On p4, line 43is there any reason behind the highest rates of renal failure for Tiwai people? Methods 6. Please comment on the precautionary measures taken to avoid duplication on the number of deaths. On p4, line 51-54 the authors mention written logs of death by clinicians, dialysis units and records kept by parish priests. For example if a patient died in a clinic and then had a funeral was this death duplicated? 7. On p5, lines 6-8, the authors mention that dialysis patients is considered as natural death. How long do usually patients needing dialysis live with it? Could this be a bias source? If they live for many years then assigning them to die in a specific one, overestimates the deaths in that year. 8. Adding to the previous comment (comment number 8) it was

never clear before that the authors had a special interest in dialysis patients. Why dialysis and not any other chronic comorbidity i.e. Diabetes and the introduction of HBa1C monitoring?

9. P5, line 21 what do the authors mean by accident? Car accidents? As the ones mentioned after accidents (drownings, burns) can also be considered accidents.

10. On p5, lines31-34 it is unclear what happened to the uncertain deaths. Was there an unknown category? Were they excluded for analyses?

Patient involvement

11. Is this intended to be an ethics approval statement, justifying that there was no need for an ethics approval? If this is the case then this should not be here but at the appropriate ethics statement section during paper submission.

12. I believe this could go before the description of analyses in methods section and it does not need its own section.

13. This is a bit controversial as the authors state that no patients were asked to advice and this is expected as the paper is investigating deaths! Also in methods section p 5, line 33 the authors mentioned that they seek advice for community members.

Results

14. Overall it is not bad to use crude numbers but if we want to show a true increase or decrease in deaths it would be good to standardise the numbers according to population and some form of standard population e.g. SMR or DSR. It could be difficult in this case as there are complexities with the census and being in a remote area but it is something that could act as a limitation.

15. On p6, line 5 can you please mention on how many records the age was documented and on how many it was inferred? How were they inferred? Please make this clear either here or in methods section.

16. Please be consistent throughout the paper regarding numbers presentation. For example when crude numbers are given it is advisable to be followed by the percentage in brackets.

17. A well-presented table would be beneficial in describing the deaths and percentages in different age groups and give some summary statistics such as men(SD) over the time period.

18. Can the authors please provide the mean (SD numbers of deaths or median (IQR)?

19. On p6, line 25 what the authors state there is inevitable. As the number of children dying decreases the number of adults dying will increase if they do not migrate.

20. Can the authors please clarify the "now" on p6 line 33. When?

21. From figure 2 it looks like this is the case since mid 70s.

22. Overall is better to change figure 2 to percentage and not frequency if in the results section referring to the image the authors state % and not crude numbers.

23. When describing figure 3 please do not ignore the obvious peaks and troughs. Please describe them as suggestions why those are occurring will be needed in the discussion part.

24. Can you please clarify what figures 4 show? Age sex standardised deaths? Mortality rates/100,000 population?

25. On p6,line 56 the authors say early 1990s but form figure it can be see that it is mid 1990s.

26. Please mention which of the figure 4 you are referring. There are 3 figures and it would be good to be clearly stated that in this section you are talking about $C or 4b. It makes it easier for the reader.

27. Where the authors refer to table, the table has a CI of a negative value. Please set that to 0.

28. I did not understand the value of figures 5 in this paper. I do not

	believe they add to the paper. You could just mention it somewhere in the discussion point where you make your arguments on increase or decrease of deaths.
	29. Overall the presentation of figures need to be improved. The legend is always the same when more than one is used under the same figure number and is very difficult to understand what they illustrate
	Discussion
	30. Could you introduce the Barker Hypothesis earlier in the introduction section? Also a brief explanation is needed as not everybody is aware of it.
	31. On p8, lines 9-23 not enough was said earlier on renal failure. If this was one of the aims of the paper it was needed to be stated in introduction.
	32. P8, line 34 the authors state one of the limitation…18% fewer deaths… Can you suggest possible reasons why this is?
	33. I do not believe that Figures 8 and 9 add to the paper. Just mentioning them and citing them is enough. Otherwise the paper gets heavy on figures that are not produced with data from this research but citing other work using them.
	34. Did any of the MDGs play any part in the reduction of early life mortality? No mention of that.
	35. On p9, line 22-23 the authors sate that changes in various sectors should be celebrated. Are there any specific policies which can be cited here?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Specific points

Strengths and Limitations
Given that doctors were at best only intermittently present in the community and latterly multiple pathologies seemed common, the authors should state that cause of death was potentially inaccurate, as they note in the Discussion.

Response: insertion of the following at the Strengths and Limitations and the Methods sections:
'In some recorded natural deaths the assignments were approximate and the contribution of multiple causes was underestimated.'

Methods
More detail should be given about how cause of death was ascertained.
5.11 It would be helpful to give the rough date when medically ascertained cause of death became usual.

Response: insertions in the 4th para of the Methods section:

"In some recorded natural deaths the assignments were approximate and the contribution of multiple causes was underestimated."

"Cause of death was assigned by clinic directors and always took into account the previous health profile of each deceased person."

Discussion

7.40 Particularly as no supportive data are presented in this paper, the authors, in my opinion, are making too much of the "Barker hypothesis" by saying the "improving rates are in large part a representation of the Barker hypothesis." It's debatable whether data can "represent" a hypothesis rather than "support" it but it is also not possible to be confident from the data presented here to what extent low birth-weight per se actually drives the patterns seen here. For example, low-birth weight might be confounded by other risk factors such as on-going malnutrition, parental smoking or alcohol abuse etc. I also think that the prominence given to the Barker hypothesis in the abstract is unwarranted.

Response: we have published evidence of the association of lower birthweight with natural death in this same community, in infants, children and young adults (15 reference inserted, 3rd para of the Discussion section) and have recently, again in the same setting, confirmed it amongst a supplemented number of deaths amongst adults more recently (references 16 inserted in the 3rd para of the Discussion section). These deaths are included among those described in this manuscript

However, we have modified reference to the Barker hypothesis. We have taken out the word representation, but left in reference to the Baker hypothesis as Reviewer 2 wanted it to be more fully explained. Please see the beginning of the 3rd paragraph of the Discussion.

7.49 This sentence lacks a phrase such as "those with low birth-weight".

Response: thank you. The phrase has been inserted in the 3rd para of the Discussion section.

8.6 Given the remarkable incidence of renal failure, the authors could usefully consider what might be the underlying causal factors. Is any evidence available from renal biopsy or post-mortem histology?

Response: We have inserted additional text and references (12, 23,24) in para 4 of the Discussion in order to address this important point.

"We have published extensively on the expression, course and biopsy representation of the underlying renal disease.12 It is clearly multideterminant with risk enhanced by low birthweights, inflammation and infection, episodes of post-streptococcal glomerulo nephritis and higher BMIs and diabetes in adult life.23,24"

Figures 5 A-D
For all the space they take up, I don't find the population pyramids particularly helpful. If they are included each figure needs to have the year it refers to clearly indicated.

Response: We apologise for the lack of clarity in these figures. 5 A-D are intended to sit against each other in a small 2x2 panel, but needed to be uploaded separately. The instructions for extra labelling that includes their years and population size are attached but not adjacent to the figures. The figures have now been reworked and submitted with the extra labelling. These figures are very important to the telling of this story. Among other things, they refute the common misapprehension that remote-living Aboriginal people are a disappearing race.

Figure 6 The upper two lines should be labelled Aboriginal Northern Territory; Non-Aboriginal Northern Territory
Response: the figure has been modified accordingly.

Reviewer: 2

Overall I would like to thank the editor/authors for providing me with the opportunity of reviewing the

manuscript. I would like to congratulate the authors for the work they have done. It is good to see that people work on remote communities and they try to increase our understanding of them. Overall the paper tries to describe the trends in deaths over a time period for different age groups of a remote Australian community. The paper lacks specific aims and objectives and needs to be tighten for publication. Results will need to be further discussed in discussions section to suggest possible explanations. Limitations needs more work. Further clarification and specific comments are shown below:

Introduction
1. Overall the aims and objectives of the paper need to be clear in the Introduction section of the paper, which at the moment they are not.

Response: the aims and objectives are to describe the change in rates of mortality over the time period. This has been inserted under a new heading called "Aims and objectives", placed before the former heading "Introduction". The heading "Introduction" has been changed to "Background".

2. On p3, line 8, the authors state that deaths are associated with non-communicable disease. This statement is referenced and generally holds but this paper looks more specifically at remote populations so I would prefer if they added something here describing trends in disease and mortality for specifically remote populations (if this exists).

Response: long-term trends in mortality and specifically remote populations have not been described before.

3. On p3, line 28, is there evidence of cigarette introduction at that time? It is anecdotal evidence?
Response: it is anecdotal evidence. A text insertion to explain this has been added (third paragraph of the Background section).

4. On p4, line 40, is there any speculation/justification for six fold death rates?
Response: the following sentence has been inserted into the last paragraph of the Background section:
"This reflects generally the much younger age of Tiwi people at death."

5. On p4, line 43is there any reason behind the highest rates of renal failure for Tiwai people?
Methods

Response: the following has been inserted into the last paragraph of the Background section: High renal failure rates have followed in other remote communities. The characteristics and speculative causes of the renal disease have been described extensively 12,13,14.

5. Please comment on the precautionary measures taken to avoid duplication on the number of deaths. On p4, line 51-54 the authors mention written logs of death by clinicians, dialysis units and records kept by parish priests. For example if a patient died in a clinic and then had a funeral was this death duplicated?
Response: there was no duplication in deaths. Each subject was unique and ascertained by first name, second name, date of birth, date to death and personal knowledge of the project's field staff. There was no duplication in dialysis records.

7. On p5, lines 6-8, the authors mention that dialysis patients is considered as natural death. How long do usually patients needing dialysis live with it? Could this be a bias source? If they live for many years then assigning them to die in a specific one, overestimates the deaths in that year.

Response: the start of dialysis is considered a natural death because without the institution of dialysis a person with terminal renal failure would die within a few weeks. The other chronic morbidities, such as diabetes, are not direct causes of death. Patients who start dialysis are recorded as a renal death on that date. They are not recounted when they finally expire.

Patients live on average 3 1/2 years after the institution of dialysis. They are assigned a renal cause of death on the day that dialysis is begun and no other cause of death assignment is given when they finally expire.

To further clarify, the following sentence has been inserted in-text:

"There was no additional assignment of date or cause of death when they finally expired."

8. Adding to the previous comment (comment number 8) it was never clear before that the authors had a special interest in dialysis patients. Why dialysis and not any other chronic comorbidity i.e. Diabetes and the introduction of HBa1C monitoring?

Response: please see the comment above

9. P5, line 21 what do the authors mean by accident? Car accidents? As the ones mentioned after accidents (drownings, burns) can also be considered accidents.

Response: they are vehicular accidents and this clarification has been inserted in-text.

10. On p5, lines31-34 it is unclear what happened to the uncertain deaths. Was there an unknown category? Were they excluded for analyses?

Response:

34 ascertained deaths occurring between 1960 and 2010 did not have either a cause of death/date of birth or date of death. They were excluded from the analyses.

Of the 1,156 deaths analysed 85 adult (>=15 years of age) natural deaths (8.4% of all 1,017 natural deaths) did not have a precise cause of death. They are presented in Figure 3 as Unknown Cause of Death.

All adult non-natural deaths had a precise cause of death and were included in analyses, although they were not presented by precise cause.

All deaths in those <15 years had a natural or non-natural death assignment and were included in analyses. They were not analysed by exact cause of death.

Numbers of all deaths by major cause group (natural and non-natural/misadventure) are shown in Figure 2.

Patient involvement
11. Is this intended to be an ethics approval statement, justifying that there was no need for an ethics approval? If this is the case then this should not be here but at the appropriate ethics statement section during paper submission.

Response: The paragraph was not intended as an ethics statement. There were no interactions with individual patients for this manuscript. The paragraph has been deleted.

12. I believe this could go before the description of analyses in methods section and it does not need its own section.

Response: please see above response

13. This is a bit controversial as the authors state that no patients were asked to advice and this is expected as the paper is investigating deaths! Also in methods section p 5, line 33 the authors mentioned that they seek advice for community members.
Results

Response: Data combine a series of studies. Particular elements had their own approvals. The Tiwi Land Council (representing the Tiwi community) have approved the review of deaths and dialysis and have reviewed and approved this and all other manuscripts using Tiwi data.
It is unclear how to respond to the query. In-text we have commented:
"When there was uncertainty about deaths or persons, data were checked with several senior community members, who had lived through much of the study interval and had known most community members."

14. Overall it is not bad to use crude numbers but if we want to show a true increase or decrease in deaths it would be good to standardise the numbers according to population and some form of standard population e.g. SMR or DSR. It could be difficult in this case as there are complexities with the census and being in a remote area but it is something that could act as a limitation.

Response: The data was age-standardised (stated in-text) and this adjusts for the earlier stage of death among adults.
We have used crude numbers to describe the deaths as clearly explained. As also explained we could only estimate rates where population figures were available.

15. On p6, line 5 can you please mention on how many records the age was documented and on how many it was inferred? How were they inferred? Please make this clear either here or in methods section.

Response: Analyses were conducted for broad age-groups and not by year of age. 1,190 deaths were identified and 1,156 were included in analyses. The following classifications were made for deaths that had a degree of missing information.

34 had no date of birth, date of death or cause of death – they were not included in analyses.

16 did not have date of birth but did have date of death and cause of death – based on cause of death, clinical judgement and local knowledge they were assigned an age of 50 years which puts them into the category of the oldest adults (≥45 years).

5 did not have date of birth but did have date of death and cause of death. Their cause of death was old age – based on cause of death, clinical judgement, and local knowledge they were assigned an age of 60 which puts them into the category of the oldest adults (≥45 years).

16. Please be consistent throughout the paper regarding numbers presentation. For example when crude numbers are given it is advisable to be followed by the percentage in brackets.

Response: Thank you for this advice. Missing crude numbers or percentages have been added to the text.

17. A well-presented table would be beneficial in describing the deaths and percentages in different age groups and give some summary statistics such as men(SD) over the time period.

Response: We have created a new table of numbers and percentages of deaths by age-group and 5-year time interval and suggest it that it become a supplement as it reflects what is given in Figure 2.

18. Can the authors please provide the mean (SD numbers of deaths or median (IQR)?

Response: We are not sure how to respond to this question.

19. On p6, line 25 what the authors state there is inevitable. As the number of children dying decreases the number of adults dying will increase if they do not migrate.

Response: We agree.

20. Can the authors please clarify the "now" on p6 line 33. When?

Response: the following change has been made in-text for clarification:

Most deaths are now Since 1975 most deaths are in people of >45 years, and most of these are of natural causes. The numbers have not perceptibly increased since the early 1990s. Only 13 (2.5%) of these older adult deaths were due to misadventure.
21. From figure 2 it looks like this is the case since mid 70s.
Response: thank you for this correction. Please see above response

22. Overall is better to change figure 2 to percentage and not frequency if in the results section referring to the image the authors state % and not crude numbers.

Response: we appreciate this point. The numbers of deaths have been inserted into the results section.

23. When describing figure 3 please do not ignore the obvious peaks and troughs. Please describe them as suggestions why those are occurring will be needed in the discussion part.

Response: Owing to the small size of this community, deaths are presentation as a frequency. The natural fluctuations in deaths have already been smoothed over 5-year periods in order to visualise trends. Interpretation is of overall trends.

24. Can you please clarify what figures 4 show? Age sex standardised deaths? Mortality rates/100,000 population?

Response: the y-axis of the figure is labelled "Rates of natural deaths per 100,000 population" and natural death rates are presented by age-group. For further clarity the Figure title has been modified as below:
Figures 4 A-C. Tiwi rates of natural death per 100,000 population rates by age-group, 1986-2010
Additionally, the Figure legend has been expanded to improve clarity.
25. On p6,line 56 the authors say early 1990s but form figure it can be see that it is mid 1990s.

Response: thank you for this point, the time estimate has been corrected in-text as below:

"Figures 4 A-C show the smoothed estimated rates of natural deaths by age-group since 1986.15 Rates of death in infants and children have fallen remarkably (4A). There was an early increase in death rates among young adults (4A), followed by a progressive decline since the early mid-1990s. Death rates of people age ≥45 years have markedly declined, at least (4B)."

26. Please mention which of the figure 4 you are referring. There are 3 figures and it would be good to be clearly stated that in this section you are talking about $C or 4b. It makes it easier for the reader.

Response: insertions indicating which figure 4 graph is referred to have been made. Please see the in-text changes shown at the above response.

27. Where the authors refer to table, the table has a CI of a negative value. Please set that to 0.

Response: thank you for pointing this out. The negative value has been replace with 0.

28. I did not understand the value of figures 5 in this paper. I do not believe they add to the paper. You could just mention it somewhere in the discussion point where you make your arguments on increase or decrease of deaths.

Response: please see response given to Reviewer 1 re Figures 5.

29. Overall the presentation of figures need to be improved. The legend is always the same when more than one is used under the same figure number and is very difficult to understand what they illustrate

Response: The figure legends have been updated and individual graph numbers have been inserted into the legend text to improve their presentation where a figure includes multiple graphs.

Discussion
30. Could you introduce the Barker Hypothesis earlier in the introduction section? Also a brief explanation is needed as not everybody is aware of it.

Response: please see the modified text as a combined response at Reviewer one's query at 7.4

31. On p8, lines 9-23 not enough was said earlier on renal failure. If this was one of the aims of the paper it was needed to be stated in introduction.

Response: Please see the expanded description of the excess of kidney disease, as a combined response at Reviewer 1's query at 8.6.

32. P8, line 34 the authors state one of the limitation…18% fewer deaths… Can you suggest possible reasons why this is?

Response: Government agencies do not always have available specific community assignment for Aboriginal people who have died.

33. I do not believe that Figures 8 and 9 add to the paper. Just mentioning them and citing them is enough. Otherwise the paper gets heavy on figures that are not produced with data from this research but citing other work using them.

Response: It is very important for Australian agencies to see that Tiwi (remote Aboriginal) changes in mortality and life expectancy are mirrored in all other transitional populations.

34. Did any of the MDGs play any part in the reduction of early life mortality? No mention of that.

Response: The MDGs were formulated late in this observation period. However the reductions in

early life mortality are compatible with achievement of this MDG.

35. On p9, line 22-23 the authors sate that changes in various sectors should be celebrated. Are there any specific policies which can be cited here?

Response: The longitudinal perspective is not widely appreciated in Australia. Health care providers tend to focus on, and are discouraged by, the burden of disease they currently see, especially in adults. However, there is continued effort to offer standards of best care to Aboriginal people where possible across all age groups.

VERSION 2 – REVIEW

REVIEWER	Prof Laurence Gruer University of Edinburgh UK
REVIEW RETURNED	19-Jun-2017

GENERAL COMMENTS	I am happy that the authors have made satisfactory changes in response to my comments, along with other useful amendments, and I thus consider this very interesting paper is now suitable for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Neophytos Stylianou
Institution and Country: University of Bath Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below I would like to thank the authors for addressing most of my comments, and hope they agree that the paper is now a lot clearer.

Recommendations:

1. I would add the aims and objectives at the end of the Background section; definitely not at the beginning of the paper.

Response:
The Aims and objectives have been moved to the end of the Background section.

2. Can you please add in the methods section, the exclusions that you have responded to my comments number 10 & comment number 15.

Response:
These paragraphs have been inserted into the Methods section as suggested:

One thousand, one hundred and ninety deaths were ascertained, and with exclusion of 34 who lacked a recorded cause of death, date of birth or date of death, 1,156 were included in analyses. Amongst them, some details were sometimes still lacking. Eighty five of 1,017 people (8.4%) who died as adults (at >15 years of age) of natural causes, did not have a precise cause of death recorded: they were described as natural deaths of unknown cause. Deaths of misadventure had been clearly documented. Deaths in those age <15 years had clear natural or non-natural death assignments.

Age was documented or age group was inferred for the 1,156 deaths. Analyses were conducted using broad age-groups, rather than a single year of age. Sixteen death records lacked a date of birth but did have date of death and cause of death – based on cause of death, clinical judgement and local knowledge they were assigned an age of 50 years, which put them into the category of the oldest adults (≥45 years). Five did not have date of birth but did have date of death and cause of death had been recorded as old age. They were assigned an age of death of 60 years, which also put them into the category of the oldest adults (≥45 years).

3. At the end of the discussion section I would like to see any policy implications/recommendations to decision makers this paper can have.

Response:
Policy implications and recommendations are included in the last two paragraphs of the Discussion. Please see the modified text.

Reviewer: 1
Reviewer Name: Prof Laurence Gruer
Institution and Country: University of Edinburgh, UK Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below I am happy that the authors have made satisfactory changes in response to my comments, along with other useful amendments, and I thus consider this very interesting paper is now suitable for publication.

VERSION 3 – REVIEW

REVIEWER	Neophytos Stylianou University of Bath, UK
REVIEW RETURNED	28-Jun-2017

GENERAL COMMENTS	I am happy that the authors have made satisfactory changes in response to reviewers comments and recommend that this paper is now suitable for publication