PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quantifying the role of modifiable risk factors in the differences in cardiovascular disease mortality rates between metropolitan and rural populations in Australia: A macrosimulation modelling study.
AUTHORS	Alston, Laura; Peterson, Karen; Jacobs, Jane; Allender, Steven; Nichols, Melanie

VERSION 1 – REVIEW

REVIEWER	Mikiko Terashima Assistant Professor School of Planning/Department of Community Health & Epidemiology Dalhousie University Canada
REVIEW RETURNED	11-Jul-2017

GENERAL COMMENTS	Comments for the authors Overall, this paper addresses an important question and employs an approach which is very helpful in providing policy makers with an intuitive and easily interpretable findings. It is clearly written for the most part and I quite enjoyed reading this paper. Since the writing has little problem, my comments are primarily on macro-level points that I believe would further strengthen this paper. 1. About the 'counterfactual scenario' As I understand it, the dietary factors the paper investigated performed better in rural areas than urban areas. Policy makers do not aim to create policies for rural areas to necessarily have the same levels of risk factors as the urban counterpart when they perform worse, but rather to 'catch up' with the high level of performances for the factors the urban areas are good at, while maintaining (or even further improving if possible) what rural areas are currently good at. Therefore, it would make more sense if the paper compared avoidable deaths between current and under the 'best case scenario', rather than current and the scenario in which the rural performed exactly the same as the urban counterpart. Having said so, performing like the urban area on dietary factors would actually increase deaths is an interesting observation and I feel that it should be kept. While I put 'major revision' because of this point, I do not think it will take much time for recalculation and representation of the comparison (the paper essentially has the values figured out).

2. List of risk factors
The readers would like to see the list of risk factors investigated earlier in the paper. Perhaps it would also be beneficial to present the parameters involved in the PRIME model. The authors could do either. Additionally, the authors should clearly state that the factors examined are individual factors. Perhaps the authors might have avoided the word 'behavioural' or 'individual' in explaining the risk factors included in the analysis for some reason. If not these exact words, I still feel that it is important to articulate that the risk factors of the authors' interest are related to what individuals do, especially as the discussion of policy is one of the tenet of this study—the study alludes to policies that are more program-based intervention for change in behavioural factors rather than changes in the environment.

3. Use of three data as a strength
It would benefit the readers if a brief sentence were added to further explain the reason why using the three data is a strength. I assume that the study could not use all the parameters involved in the PRIME model otherwise.

4. On uncertainty analysis
The paper did not really elaborate about the uncertainty analysis. Some description would be necessary on what it is, how it was done and why it was important.

5. Description for Table 3
The second paragraph that starts with "Table 3 shows…" (page 13, line 25) does not quite explain Table 3. I wonder if this is a mistake (for instance, there was Table 4 and it was taken out?).

REVIEWER	Leigh Kinsman Joint appointment, University of Tasmania and Tasmanian Health Service.
REVIEW RETURNED	12-Jul-2017

GENERAL COMMENTS	This well written and important paper adds evidence to explaining the unacceptable gap in CVD outcomes between rural and urban Australians. Historically, explanations for the gap are hypothesised as a combination of access to health services, lifestyle, social determinants and ethnicity (e.g. aboriginal status). To my knowledge, this is the first attempt to measure and quantify the impact of one of these dimensions on the rural/urban gap. The design and methods are sound. Rurality is defined by populations not classified as a major city; the PRIME risk model has been derived from multiple studies and tested on large datasets; and the data sources (Australian census, Australian Institute of Health and Welfare and Australian Health Survey) are highly credible. Comments: 1. While the relative contribution of risk factors to the rural/urban gap is an important outcome, rural Australia cannot be considered a single homogeneous group.

There are several levels of remoteness, and health outcomes generally worsen as remoteness increases. There are also various types of rural communities, including agricultural, mining, tourist and aboriginal communities. While incorporation of the research methods described across different levels of remoteness and types of communities would be beyond the scope of this study, the results need to be interpreted carefully and not accepted as a blanket statement for all rural Australia.

2. Lines 83-4. "…reduced access to evidence-based treatments in rural hospitals" is an over-generalisation. There is ample evidence of high quality, timely access to best practice in rural hospitals, so perhaps this statement meant to reflect lack of access to interventions such as angioplasty.

Suggested revisions:
1. Line 185+: Differences in risk factors between rural and metropolitan areas
• Smoking needs to be included in this section.

2. Page 10, Table 1: Differences in dietary intakes, rural compared with metropolitan areas, females and males 2011-12.
Line 32: Fibre, females – the mean difference should be 0.1, not 0.4.
Line 34: Sodium, females – delete the decimal points (.25) for mean intake.
Page 11, Line 7: % energy from fat – for consistency, include decimal points in this row. Recheck the mean intakes, as the reported mean difference for females of 0.3 is not consistent with the numbers. For males, the mean difference of 0.7 is also not consistent with the mean intakes.
Line 13: % energy from monounsaturated fat – for consistency, insert decimal points in this row.
Line 19: % energy from polyunsaturated fat – for consistency, insert decimal points in this row. Recheck the calculations for males, as the reported mean difference of 0.8 does not reflect the mean intakes (4.6 v 4.7).
Lines 25-30: Why are "Current smokers" and "Physical activity" reported in this table of dietary intakes? These should be separate.

3. Page 13, Table 3: Preventable deaths from CVD and IHD attributable to individual risk factors if rural populations had the same risk factor levels as populations in major cities.
Line 56: The reported result for alcohol consumption does not seem to make sense. Table 1 appeared to reflect that alcohol intake was more damaging in rural areas, yet the result in table 3 suggests that if rural and metropolitan alcohol consumption were the same that there would be an increase in rural CVD deaths. Please recheck this calculation, including whether this affects the overall reported reduction in deaths.
Page 14, Line 3: Obesity – it looks like the reported number of -955 for IHD deaths should be 955 (not minus).

4. Ensure consistency in reporting number of deaths averted. The abstract (page 2, line 35) reports a reduction of 1458, whereas the results (page 12, line 11 and table 2) report 1461 deaths.

Reviewer 1
Question: As I understand it, the dietary factors the paper investigated performed better in rural areas than urban areas. Policy makers do not aim to create policies for rural areas to necessarily have the same levels of risk factors as the urban counterpart when they perform worse, but rather to 'catch up' with the high level of performances for the factors the urban areas are good at, while maintaining (or even further improving if possible) what rural areas are currently good at. Therefore, it would make more sense if the paper compared avoidable deaths between current and under the 'best case scenario', rather than current and the scenario in which the rural performed exactly the same as the urban counterpart. Having said so, performing like the urban area on dietary factors would actually increase deaths is an interesting observation and I feel that it should be kept. While I put 'major revision' because of this point, I do not think it will take much time for recalculation and representation of the comparison (the paper essentially has the values figured out).

Response: This is a very valuable point to consider from reviewer 1, thank you. Vegetable intakes were significantly higher in rural areas, resulting in slightly higher fibre intakes also. These two dietary factors were the only risk factors that were better in rural areas in the baseline scenario. Therefore, we have added an additional 'best case' scenario, in which we have recalculated the model analysis, leaving vegetable and fibre intakes unchanged, as recommended. We agree that this analysis is relevant to policy development and recommendations. We believe the new calculations have greatly strengthened this paper.Please see results section, page 15, lines 59-69.

2. List of risk factors
Question: The readers would like to see the list of risk factors investigated earlier in the paper. Perhaps it would also be beneficial to present the parameters involved in the PRIME model. The authors could do either.

Response: We have inserted a new table detailing the risk factors in the model for clarity. Please see the new table 1 titled 'Summary of risk factor data entered into the PRIME model' on page 7 in the methodology section.

Question: Additionally, the authors should clearly state that the factors examined are individual factors. Perhaps the authors might have avoided the word 'behavioural' or 'individual' in explaining the risk factors included in the analysis for some reason. If not these exact words, I still feel that it is important to articulate that the risk factors of the authors' interest are related to what individuals do, especially as the discussion of policy is one of the tenet of this study—the study alludes to policies that are more program-based intervention for change in behavioural factors rather than changes in the environment

Response: Thank you for this suggestion. We have avoided using 'behavioural' to describe these risk factors as Body Mass Index (BMI) was one of the risk factors analysed, which of course doesn't quite fit. For clarity, we have now added the term individual modifiable risk factors throughout the text, as per the reviewer's suggestion. Please see changes in the terminology used to describe risk factors throughout the manuscript.

3. Use of three data as a strength
Question: It would benefit the readers if a brief sentence were added to further explain the reason why using the three data is a strength. I assume that the study could not use all the parameters involved in the PRIME model otherwise.

Response: Thank you for the comment. The reviewer is correct that these data sources are required to populate the PRIME model, however data of varying quality could potentially be used. The strengths sections has been amended to more clearly highlight that it is the availability and use of high quality, comprehensive, nationally representative data as inputs that strengthens the results. Currently population, mortality and risk factor data are collected separately in Australia, and not kept as one dataset, therefore we required the use of these three, high quality datasets. Please see added text in strengths section, page 18.

4. On uncertainty analysis
Question: The paper did not really elaborate about the uncertainty analysis. Some description would be necessary on what it is, how it was done and why it was important.

Response: Thank you for this suggestion, additional detail has now been included on the Monte Carlo analysis, and its purpose within this study. Please see expansion in methods section on page 9, and related citation.

5. Description for Table 3
Question: The second paragraph that starts with "Table 3 shows…" (Page 13, line 25) does not quite explain Table 3. I wonder if this is a mistake (for instance, there was Table 4 and it was taken out?).

Response: Thank you for noticing this error. This has been corrected and removed as it was an error. This has been removed and all table numbering has been updated in the manuscript.

Reviewer 2 Comments
Question: While the relative contribution of risk factors to the rural/urban gap is an important outcome, rural Australia cannot be considered a single homogeneous group. There are several levels of remoteness, and health outcomes generally worsen as remoteness increases. There are also various types of rural communities, including agricultural, mining, tourist and aboriginal communities. While incorporation of the research methods described across different levels of remoteness and types of communities would be beyond the scope of this study, the results need to be interpreted carefully and not accepted as a blanket statement for all rural Australia.

Response: Thank you for this very important point, which had not been adequately addressed in our discussion. We have now included this as a limitation of the study. In addition to being beyond the scope of these analyses, it was unfortunately not possible, due to small population size, and sample size in the raw data, to conduct separate analyses by level of remoteness. We acknowledge that research into different rural communities and their needs is paramount to improving rural health outcomes for the future. Added to limitations, on page 18-19, lines 151-157.

Question: Lines 83-4. "…reduced access to evidence-based treatments in rural hospitals" is an over-generalisation. There is ample evidence of high quality, timely access to best practice in rural hospitals, so perhaps this statement meant to reflect lack of access to interventions such as angioplasty.

Response: Thank you for highlighting this, the text has been changed to reflect that we are talking about surgical interventions to reduce the over-generalisation of this statement See page 4, line 90.
Suggested revisions:
Comment: Line 185+: Differences in risk factors between rural and metropolitan areas- Smoking needs to be included in this section.

Response: Amended, Page 10, line 263.
Table 1 edits

Comment: Line 32: Fibre, females – the mean difference should be 0.1, not 0.4.

Response: Amended Please see table 2, pages 11-12

Comment: Line 34: Sodium, females – delete the decimal points (.25) for mean intake.

Response: Amended Please see table 2, pages 11-12

Comment: Page 11, Line 7: % energy from fat – for consistency, include decimal points in this row. Recheck the mean intakes, as the reported mean difference for females of 0.3 is not consistent with the numbers. For males, the mean difference of 0.7 is also not consistent with the mean intakes.

Response: Amended Please see table 2, pages 11-12

Comment: Line 13: % energy from monounsaturated fat – for consistency, insert decimal points in this row.

Response: Amended Please see table 2, pages 11-12

Comment: Line 19: % energy from polyunsaturated fat – for consistency, insert decimal points in this row.

Response: Amended Please see table 2, pages 11-12

Comment: Recheck the calculations for males, as the reported mean difference of 0.8 does not reflect the mean intakes (4.6 v 4.7).

Response: Amended Please see table 2, pages 11-12

Comment: Lines 25-30: Why are "Current smokers" and "Physical activity" reported in this table of dietary intakes? These should be separate.

Response: Thank you for this observation. We have changed the title of the table to "risk factors" instead of "dietary factors" to better represent the data presented as suggested by the reviewer. See table 2 title, page 11.

Page 13, Table 3: Preventable deaths from CVD and IHD attributable to individual risk factors if rural populations had the same risk factor levels as populations in major cities.

Question: Line 56: The reported result for alcohol consumption does not seem to make sense. Table 1 appeared to reflect that alcohol intake was more damaging in rural areas, yet the result in table 3 suggests that if rural and metropolitan alcohol consumption were the same that there would be an increase in rural CVD deaths. Please recheck this calculation, including whether this affects the overall reported reduction in deaths.

Answer: Thank you for the comment. Although overall alcohol intakes were higher in rural areas, as the model calculates deaths based on inputs by 5 year age group and sex, Males over 75 years in rural areas had slightly lower alcohol intakes than metropolitan males, which resulted in more deaths under the counterfactual scenario.We have now included a paragraph on the alcohol results in the discussion section of the paper, page 17, line 109-115.

Comment: Page 14, Line 3: Obesity – it looks like the reported number of -955 for IHD deaths should be 955 (not minus).

This is an error that has been fixed. See Page 15.
Thank you for reviewing our manuscript. Please see attached documentation, and this response in table form.

VERSION 2 – REVIEW

REVIEWER	Mikiko Terashima Dalhousie University Canada
REVIEW RETURNED	22-Aug-2017

GENERAL COMMENTS	The paper reads much more clearly with clear explanation of the research process (methods) and substantial discussions. The list of risk factors very much strengthened the paper as well. My comments focus on two points, which are relatively minor.

1. The organization of Table 3 (and 5)
This table is somewhat difficult to follow, partly because interpretation of this requires some numbers that are not in the table. It might be worthwhile reformatting it. For instance, the last column shows % of total deaths from condition—say in overall CVD death counts were 1,461 out of 13,600=about 11% (I would put 10.7% in the table to be consistent throughout). The sex differentiated % of averted or delayed deaths are not described. May I suggest something like below.

	Deaths	Averted or delayed death (% of total death in the category)
CVD all		
Both sex	13,600	1,461 (10.7)
Male	6,846	629 (9.2)
Female	6754	828 (12.3)
CVD under 75 years of age		
Both sex	3,137	420 (13.4)
Male	2,200	343 (15.6)
Female	915	78 (8.5)
IHD all		
Both sex	7,560	793 (10.5)
Male	Add	418 (add)
Female	Add	374 (add)
IHD under 75 years of age		
Both sex	2,089	304 (14.6)
Male	1,636	266 [267?] (16.3)
Female	452	37 (8.2)

Once these numbers are laid out, it is easy for the readers to figure out the values the authors are highlighting in the text (for example, Line 10 says Premature IHD deaths [75 years and under] would account for 38.3% of the IHD deaths that would be delayed or averted, or 4% of all rural IDH deaths" The former would be 304/793, and the latter 304/7560 [which you do not have to explain in the text]).

	Lines 13-16. This short paragraph may be put after the table, because it is not directly relevant to Table 3. Is 'excess death' the same thing as 'premature death' here? At the end of the second sentence, the authors might like to add "data not shown" to be clear. Table 5 might be organized in the same way, or modified to be a simpler table (because it reads as a more of secondary analysis) showing only averted or delayed deaths for both sexes and their percentage out of total. But please also see the second point below. 2. The 'best case' scenario analysis in discussion The best case scenario analysis in the result section is a good addition, but it is not followed up in the discussion, leaving it in isolation. Perhaps the authors might like to consider commenting at least % of total deaths in IHD averted or delayed if rural folks keep eating fruits and vegetables, which is about 5% higher than the counterfactual scenario while others are not as different. Or, it may also work if the authors include some observation of the best case scenario in the discussion without making it as a formal part of the analysis (and omit Table 5). But not mentioning the best case scenario at all would seem odd, since (as I elaborated previously), policy is interested in improving the risk factors and not worsening it for the sake of being the same with the cities.

REVIEWER	Leigh Kinsman University of Tasmania and Tasmanian Health Service
REVIEW RETURNED	09-Aug-2017

GENERAL COMMENTS	Congratulations to the authors on a worth-while, well-written paper. The revisions have added value to a high quality study. Good luck with your future work to understand and address inequitable outcomes from CVD.

VERSION 2 – AUTHOR RESPONSE

VERSION 3 – REVIEW

REVIEWER	Mikiko Terashima Dalhousie University Canada
REVIEW RETURNED	21-Sep-2017

GENERAL COMMENTS	The previous comments were addressed sufficiently, and I think the paper is ready to be accepted.