

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the OEM but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The mortality and cancer experience of New Zealand Vietnam war veterans
AUTHORS	McBride, David; Cox, Brian; Broughton, John; Tong, Darryl

VERSION 1 - REVIEW

REVIEWER	<i>The reviewer wished to publish his review anonymously</i>
REVIEW RETURNED	12-Apr-2013

GENERAL COMMENTS	<p>This manuscript reports a mortality and cancer incidence study of New Zealand Vietnam war veterans and compares their mortality and cancer incidence with that of the general New Zealand population. The authors acknowledge that they hope they will be able to conduct further research in this important group of veterans that will enable important confounders to be considered and other health effects to be assessed in this population.</p> <p>Comments:</p> <ol style="list-style-type: none">1. The main and stated objective of the manuscript was to report the mortality and cancer incidence of New Zealand Vietnam war veterans. Throughout the manuscript however the authors also related the findings to whether this was consistent with exposure to defoliant herbicide exposure that they state was associated with service in the Vietnam war, whether the findings are consistent with overseas studies of Vietnam war veterans in this respect, and whether they are consistent with a list of compensable conditions – as stated in the Conclusions of the abstract. I would think given the prominence of this theme in the manuscript it needed to have been more clearly stated as an objective of the manuscript and there needs to be more information provided on the possible exposure aspect of New Zealand Vietnam war veterans. The manuscript could benefit from a greater balance of detail through the paper.2. What this paper adds should name the source of the presumptive lists and suggestive lists.3. Was the study approved by an ethics committee? I saw no statement to this effect.4. The headings of the body of the paper reflect those of the abstract and would be better set out in a standard way as Introduction, Methods, Results, and Discussion.5. The 'OBJECTIVE' is really an Introduction to the manuscript and describes well the various Agents and classification, although the same phrase "as it was contaminated.....(TCDD or simply "dioxin")" probably does not need to be repeated in paragraph 2 of the Objective.6. The statements about the possible exposure of NZ Vietnam war
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veterans are rather weak and some more supportive evidence or references need to be added if the orientation of this mortality and cancer incidence study back to consistency with herbicide exposure is maintained, e.g. The statement in the last line of paragraph 2 of the Objective that this has come to characterise the toxic environment experienced by Vietnam veterans as a rather statement on exposure assessment. The statement that Australian and NZ soldiers were serving in the same area of Vietnam and their exposures 'would have been the same', in the Conclusions of the Abstract and the Manuscript, does not really say sufficient about possible exposure for the NZ cohort.

7. Consistent with journal style it would be better if Methods were described under that heading.

8. In terms of cohort enumeration, were any other searches conducted, mention is made of date of death listed by VANZ but what about veterans in receipt of pensions etc, was matching with the Australian Electoral Roll considered to attempt to reduce the proportion of unknown status.

9. Results are included under an overall heading of DESIGN

10. There are some aspects that should be described including estimation and number of person years at risk, use of age bands.

11. Table 1 heading should reflect that the Standardised Mortality Ratio is for non cancer SMRs and cancer SIRs.

12. Refer consistently to cancer incidence where appropriate throughout, eg last para of Results and to Vietnam veterans, not just veterans, e.g. last sentence of Abstract.

13. The current CONCLUSION is really a Discussion, through a final concluding paragraph is appropriate.

14. Conclusion, 1st paragraph -, 2nd sentence --- specific cancer sites demonstrated an increase in mortality... Although the opening paragraph states that several haematopoietic disorders showed non significant mortality excesses, these results were not presented in the results. Other factors may have affected mortality from these cancers so that the wording around reflected by a similar increase in incidence might be reconsidered.

15. The authors may have used all sources available to trace veterans and I have asked for clarification on this, but 16% were not able to be traced. It is not clear from my reading of the paper how these unknown veterans were managed, were they included in the cohort or excluded. What was the final number? This should be stated in the Methods. If sensitivity analysis had been conducted on excluding/including them, this should be reported, given a reasonable percentage of veterans have not been located.

16. Why would the proportion of veterans be significantly higher than the general population, were Māori more likely to serve in Vietnam?

17. How do the authors know there was little evidence of poorer overall health in veterans during the follow-up period? Could this statement be substantiated.

18. The statement that the majority of NZ veterans were combat soldiers likely to have been exposed to a similar "toxic environment" is not a scientifically substantiated and some referencing of likely exposure in relation to NZ veterans is warranted.

19. Lung cancer deaths 15% and 18%, need clarity/referencing for which group are Australian and which are NZ.

20. The statement that the cancer incidence is similar in both groups i.e. Australian and NZ with an excess of 15% being significant for Australian veterans is a bit confusing, is it not compared to a non-significant increase of 6% in NZ veterans?

21. The findings in NZ veterans are compared with those of overseas studies of Vietnam veterans other than Australian

	<p>veterans, although no critical findings of overseas studies are reported or cited to allow the reader to assess this as part of this report. Brief reporting of these would add to completeness of the article.</p> <p>22. The reference to the “presumptive list” adopted as being compensable by VANZ comes late in the manuscript and is also included in the abstract conclusions. As is previously suggested if an objective of this manuscript was to consider the findings of this cancer incidence and mortality study in relation to other findings on herbicide exposure and rulings, I would suggest this should be considered as an objective. Also the specific statement around mechanism in the summary paragraph would be better introduced earlier in the article.</p>
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- The manuscript received a second review at the Occupational and Environmental Medicine but the reviewer did not give permission for their comments to be published.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

Review - The mortality and cancer experience of New Zealand Vietnam war veterans

This manuscript reports a mortality and cancer incidence study of New Zealand Vietnam war veterans and compares their mortality and cancer incidence with that of the general New Zealand population. The authors acknowledge that they hope they will be able to conduct further research in this important group of veterans that will enable important confounders to be considered and other health effects to be assessed in this population.

Comments:

1. The main and stated objective of the manuscript was to report the mortality and cancer incidence of New Zealand Vietnam war veterans. Throughout the manuscript however the authors also related the findings to whether this was consistent with exposure to defoliant herbicide exposure that they state was associated with service in the Vietnam war, whether the findings are consistent with overseas studies of Vietnam war veterans in this respect, and whether they are consistent with a list of compensable conditions – as stated in the Conclusions of the abstract. I would think given the prominence of this theme in the manuscript it needed to have been more clearly stated as an objective of the manuscript and there needs to be more information provided on the possible exposure aspect of New Zealand Vietnam war veterans. The manuscript could benefit from a greater balance of detail through the paper.

We tend to agree, see the last bullet point (page 3) of the article focus:

“This report examines whether the mortality and cancer experience of New Zealand veterans is consistent with Vietnam service and the presumptive lists accepted as being compensable.”

and the last sentence of the introduction, page 3 line 1:

“This is the first cohort study of New Zealand Vietnam War Veterans, undertaken to assess whether health outcomes were consistent with those reported by the IOM as being due to Vietnam service”

2. What this paper adds should name the source of the presumptive lists and suggestive lists. Agreed, this now forms the subject of the first two bullet points in article the article focus:

“Service in the Vietnam war was characterized by defoliant herbicide exposure, including 2-4-5 trichlorophenoxyacetic acid, 2,4 dichlorophenoxyacetic acid, picloram and cacodylic acid., Cumulative

with reviews of mechanistic, animal and epidemiological studies by the Institute of Medicine of the US National Academy of Sciences has resulted in lists “presumptive lists” of conditions associated with Vietnam service, adopted as “presumptive lists” compensable by Veterans Affairs New Zealand.

Those in the cancer “sufficient evidence” list are soft-tissue sarcoma (including heart); non Hodgkin lymphoma (NHL); chronic lymphocytic leukemia (CLL) (including hairy cell leukemia and other chronic B-cell leukemias) and Hodgkin’s disease, those on the “limited or suggestive” list being laryngeal cancer; cancer of the lung, bronchus, or trachea; prostate cancer and multiple myeloma”

3. Was the study approved by an ethics committee? I saw no statement to this effect. It was, see first paragraph of the methods, page 3 line 6.

4. The headings of the body of the paper reflect those of the abstract and would be better set out in a standard way as Introduction, Methods, Results, and Discussion. Agreed and amended.

5. The ‘OBJECTIVE’ is really an Introduction to the manuscript and describes well the various Agents and classification, although the same phrase “as it was contaminated.....(TCDD or simply “dioxin”)” probably does not need to be repeated in paragraph 2 of the Objective. Repetition corrected.

6. The statements about the possible exposure of NZ Vietnam war veterans are rather weak and some more supportive evidence or references need to be added if the orientation of this mortality and cancer incidence study back to consistency with herbicide exposure is maintained, e.g. The statement in the last line of paragraph 2 of the Objective that this has come to characterise the toxic environment experienced by Vietnam veterans as a rather statement on exposure assessment. The statement that Australian and NZ soldiers were serving in the same area of Vietnam and their exposures ‘would have been the same’, in the Conclusions of the Abstract and the Manuscript, does not really say sufficient about possible exposure for the NZ cohort.

This sentence may have been misleading. Vietnam veterans now talk about a ‘toxic environment’ which conveys concern. We now state explicitly (page 2 line 16) “has come to epitomise the environmental worries of Vietnam veterans.”

7. Consistent with journal style it would be better if Methods were described under that heading. Agreed, amended.

8. In terms of cohort enumeration, were any other searches conducted, mention is made of date of death listed by VANZ but what about veterans in receipt of pensions etc, was matching with the Australian Electoral Roll considered to attempt to reduce the proportion of unknown status. The VANZ list is regarded as complete, for example as evidence of pensionable service. Page 3 line 10 refers “VANZ administers all aspects of war service entitlements including pensions and the service list is regarded as being complete”

New Zealand researchers do not generally undertake searches in Australia. We attempted to do so on this occasion, but the administrative process for those outside Australia is prohibitively complex. We will say this if necessary but prefer not to upset our Australian cousins.

9. Results are included under an overall heading of DESIGN We prefer to leave these ‘as is’. These results are related to the search algorithm, which we think helps in understanding the cohort enumeration.

10. There are some aspects that should be described including estimation and number of person years at risk, use of age bands. Use of age bands now supplied, first paragraph of statistical analysis, page 4, lines 10-12.

11. Table 1 heading should reflect that the Standardised Mortality Ratio is for non cancer SMRs and cancer SIRs.

The tables have now been reinstated in full, having been abridged as part of the change to a ‘short paper’ for OEM

12. Refer consistently to cancer incidence where appropriate throughout, eg last para of Results and to Vietnam veterans, not just veterans, e.g. last sentence of Abstract.
Now amended throughout.

13. The current CONCLUSION is really a Discussion, through a final concluding paragraph is appropriate.
Now changed to discussion

14. Conclusion, 1st paragraph -, 2nd sentence --- specific cancer sites demonstrated an increase in mortality...Although the opening paragraph states that several haematopoietic disorders showed non significant mortality excesses, these results were not presented in the results. Other factors may have affected mortality from these cancers so that the wording around reflected by a similar increase in incidence might be reconsidered.

This information is now re-instated in table 2, the SIR table, which we trust will be self explanatory to the reader.

15. The authors may have used all sources available to trace veterans and I have asked for clarification on this, but 16% were not able to be traced. It is not clear from my reading of the paper how these unknown veterans were managed, were they included in the cohort or excluded. What was the final number? This should be stated in the Methods. If sensitivity analysis had been conducted on excluding/including them, this should be reported, given a reasonable percentage of veterans have not been located.

They had to be excluded from the study, as stated page 3 lines 15-17:

“We had to exclude 539 individuals who we could not match. Of these, 336 had an overseas address and 203 were lost to follow up. We also had to exclude 34 men who had a date of death listed by VANZ but no official record on the Mortality Collection and the 32 women who formed too small a sub-group for analysis”

16. Why would the proportion of veterans be significantly higher than the general population, were Māori more likely to serve in Vietnam?
Page 9 lines 21-22 explains that the NZDF has traditionally been able to recruit proportionately more Maori.

“We do not know how many cohort members might have identified themselves as being of Māori ethnicity, but the New Zealand Defence force has always been able to recruit proportionately more Maori than are found in the general population”

17. How do the authors know there was little evidence of poorer overall health in veterans during the follow-up period? Could this statement be substantiated.

Our logic was that the SMRs and SIRs were lower, now explicit page 9 lines 23-24:

There was however little evidence of poorer overall health in Vietnam veterans during the follow-up period, at least in terms of increased mortality and cancer incidence

18. The statement that the majority of NZ veterans were combat soldiers likely to have been exposed to a similar “toxic environment” is not a scientifically substantiated and some referencing of likely exposure in relation to NZ veterans is warranted.

We agree to some extent. Page 4 now includes, first paragraph, a statement on exposure.

“Methodologically, the weakest aspect of the epidemiological studies of Vietnam veterans has been exposure assessment, the simplest approach being ecological, being based on Vietnam service, geographical area and branch of service. As regards service, the New Zealand records are regarded as complete. Defoliation missions are recorded in the area [2] and the New Zealand contribution was of combat soldiers, both Artillerymen and Infantry soldiers, acknowledged to be at greater risk of herbicide exposure. [2] The anti-malarial drug of choice was Dapsone, with aerial spraying of organochlorine pesticides to control mosquitoes. Unfortunately, the exposure doses of both cannot easily be calculated”

We also discuss this more specifically in the discussion, page 9. Line 27 et.seq.

“We are of course limited by the fact that we do not have data on herbicide exposure. The Nui Dat area lay in US Military Region 3, and some 20k distant from the Rung Sat special zone, known to have been heavily sprayed[3] Infantry soldiers were also more likely to be exposed because they more often engaged the enemy and were more likely to enter sprayed areas. The clustering of troops by geographic area and combat experience, as here, may reduce misclassification bias, but the potential for such bias remains high, with a tendency to reduce any association..”

19. Lung cancer deaths 15% and 18%, need clarity/referencing for which group are Australian and which are NZ.

Now clarified, page 10 lines 27 et. seq.:

Lung cancer contributed the greatest burden of deaths in the New Zealand and Australian both cohorts, with excesses of 15% and 18% respectively, only the latter being significant.

20. The statement that the cancer incidence is similar in both groups i.e. Australian and NZ with an excess of 15% being significant for Australian veterans is a bit confusing, is it not compared to a non-significant increase of 6% in NZ veterans?

This has been corrected, see p10 lines 23-24:

The important comparisons between the two are a similar healthy soldier effect, with significantly fewer deaths from all causes in both cohorts but a contrast in the 6% significant excess of all cancer deaths in the Australian cohort, cancer also being the single most common cause of death.

21. The findings in NZ veterans are compared with those of overseas studies of Vietnam veterans other than Australian veterans, although no critical findings of overseas studies are reported or cited to allow the reader to assess this as part of this report. Brief reporting of these would add to completeness of the article.

This paragraph was removed from the short report, and is now reinstated. First para page 10 line 11 et. seq.

22. The reference to the “presumptive list” adopted as being compensable by VANZ comes late in the manuscript and is also included in the abstract conclusions. As is previously suggested if an objective of this manuscript was to consider the findings of this cancer incidence and mortality study in relation to other findings on herbicide exposure and rulings, I would suggest this should be considered as an objective. Also the specific statement around mechanism in the summary paragraph would be better introduced earlier in the article.

We have now introduced these concepts in the article focus and key messages section.