# The mortality and cancer experience of New Zealand Vietnam war veterans: a cohort study

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# The mortality and cancer experience of New Zealand Vietnam war veterans: a cohort study

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**Keywords**

Cohort studies; Military Personnel; Vietnam Conflict; Neoplasms; Environmental Exposure.

**Word count**

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# ABSTRACT

**Objectives** The aim was to observe the patterns of mortality and cancer incidence in New Zealand Vietnam veterans. The objectives were to assess if the patterns of disease observed were consistent with those associated with military service in Vietnam, and similar to the patterns found in other groups of Vietnam veterans.

**Design** A historical cohort study.

**Setting** Veterans, identified from service records, with Vietnam service between 1964 and 1972.

**Participants** Of the 3,322 survivors of Vietnam service, we followed up 2,783 (84%).

**Outcome measures** Standardised mortality and incidence ratios (SMRs and SIRs respectively) were calculated based on the numbers of deaths and cancer registrations observed, those expected being based on New Zealand national rates.

**Results** All causes mortality was significantly reduced (SMR 0.85, 95% CI 0.77-0.94) and cancer incidence non significantly increased (SIR 1.06, 95% CI 0.97-1.16). The risk of mortality from cancers of the head and neck (SMR 2.20, 95% CI 1.09-3.93); oral cavity pharynx and larynx (SMR 2.13, 95% CI 1.06-3.81) and the incidence of chronic lymphatic leukaemia (CLL) (SIR 1.91, 95% CI 1.04-3.20) were however significantly increased. Other lymphohaematopoietic disorders, specifically multiple myeloma and Hodgkin disease, showed non significant mortality excesses, reflected by a similar increase in incidence.

**Conclusion**

Service in the Vietnam war was associated with defoliant herbicide exposure, including 2-4-5 trichlorophenoxyacetic acid, 2,4 dichlorophenoxyacetic acid, picloram and cacodylic acid. Subsequent reviews of mechanistic, animal and epidemiological evidence led to certain conditions being deemed compensable. The pattern of mortality and cancer incidence is not at odds with the list of compensable conditions and consistent with that found in Australian veterans serving in the same area of Vietnam, but also consistent with smoking and the healthy soldier effect. In common with the Australian experience, this is the only veterans group to show a significant excess of CLL.

# ARTICLE SUMMARY

## 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. The Institute of Medicine of the US National Academy of Sciences has carried out cumulative reviews of the mechanistic, animal and epidemiological evidence for the relationship between herbicide exposure and health and compiled 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 disease, those on the "limited or suggestive" list being laryngeal cancer; cancer of the lung, bronchus, or trachea; prostate cancer and multiple myeloma.
- This report examines whether the mortality and cancer experience of New Zealand veterans is consistent with Vietnam service and the lists of conditions accepted as being compensable.

## Key Messages

- CLL is on the "sufficient" list largely because of an increased incidence in the farming occupation and a similarity to non Hodgkin lymphoma in that both are due to malignant transformation of B progenitor cells.
- Our results, along with those of an earlier Australian study, provide epidemiological evidence of an increased risk of CLL in veterans.

## Strengths and Limitations.

- The follow up of 83% would tend to minimise bias in the direction of under-estimating disease risks.
- In common with other studies, we do not have exposure data, but the similarity to the Australian veterans experience suggests an ecological effect.
- We also have no information concerning confounding by smoking and alcohol consumption, known to be associated with head and neck cancers.

# INTRODUCTION.

Between 1964 and 1975 nearly 3,400 New Zealand military personnel served in the Republic of Vietnam. The majority of the force was involved in combat operations, from 1966 onwards integrated with an ANZAC (Australian New Zealand Army Corps) Battalion deployed to the East of Hanoi, now Ho Chi Minh City, in the Nui Dat area of Phuoc Tuy province, now Bà Rịa city in Bà Rịa–Vũng Tàu province. At its peak in 1968 it represented a force of 543 personnel. Smaller numbers served in the New Zealand Medical Services team based in Binh Dinh province and with a New Zealand Special Air Services group.

Chemical exposure was a particular feature of this war. Tactical defoliant herbicide sprays, distributed in 55 gallon drums with a colour stripe classification, led to the hallmark "rainbow agent" exposure in this war. Agents Pink and Green contained esters of 2-4-5 trichlorophenoxyacetic acid (2,4,5-T); Agents Purple and Orange esters of 2,4,5-T and 2,4 dichlorophenoxyacetic acid (2,4-D). 2,4,5-T was contaminated, to a greater or lesser extent, with 2,3,7,8 tetrachlorodibenzo-para-dioxin (TCDD or simply "dioxin"). Those herbicides not contaminated with dioxin included Agent White, a mixture of 2,4-D and picloram and finally Agent Blue, a formulation of cacodylic acid (dimethyl arsenic acid or DMA) and its salts. Agent Orange, with an estimated 45,677,937 litres sprayed,[1] has come to epitomise the environmental worries of Vietnam veterans regarding their service.

Subsequent concerns about the toxicity of these substances and the relationship with health effects led the US Department of Veterans Affairs and The Institute of Medicine of the US National Academy of Sciences (IOM) to carry out a biennial and cumulative epidemiological review of herbicide exposure. The evidence is not based on causality but on the strength of epidemiological evidence associating herbicide exposure with health. The IOM report classifies the evidence in support of a relationship as "sufficient", "limited or suggestive", or "inadequate or insufficient". Those in the cancer "sufficient evidence" list in the 2010 update[2] 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 disease. Those on the "limited or suggestive" list are laryngeal cancer; cancer of the lung, bronchus, or trachea; prostate cancer and multiple myeloma. The evidence reviewed comes from biological plausibility, animal studies, studies of the incidence of cancer in people with occupational exposure to herbicides and a number of Vietnam veterans studies. The latter studies have been based on cohorts of American, Australian and Korean Veterans. 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.

# METHODS

## Design

This is a cohort study of New Zealand Vietnam veterans who served in Vietnam between 1964 and 1975.

## Cohort enumeration

The original nominal roll for the cohort was compiled in 1972 from pay records and formed the basis of the Veterans Affairs New Zealand (VANZ) Vietnam veterans database, a cohort of 3,394 men and women. VANZ administers all aspects of war service entitlements, including war pensions, and the service list is now regarded as being complete.

Of this cohort of 3,394 service people, 37 died during the war. The remaining 3,357 were followed up through searches based on the National Health Index (NHI) number linking individuals to health data maintained by the New Zealand Ministry of Health (MoH). No match was found for 791 veterans, but searches on the electoral rolls from 1993 to 2009 provided details of 252. 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 MoH collections and the 32 women who formed too small a sub-group for analysis. Follow up started on the first of January 1988, the first date that data is held electronically on the Mortality Collection database. The end of follow up was the 31st December 2008, the last date that mortality data were available. The Mortality Collection provided the underlying cause of death for all deaths identified. Prior to coding and entry on the Mortality Collection database all the deaths registered by Births Deaths and Marriages New Zealand are subject to verification. The official underlying cause of death recorded is determined after compiling data from a number of additional sources including traffic accident reports, Coroners' inquiries, hospital diagnoses, pathology records and cancer registry entries. The mortality statistics are compiled according to the year the death is registered: deaths before 2000 are recorded in ICD-9-CM-A and have not been mapped forward to ICD-10-AM.

## Exposure information

Methodologically, the weakest aspect of the epidemiological studies of Vietnam veterans has been exposure assessment. The simplest approach is ecological, based on Vietnam service, geographical area and branch of service [3] (page 270). As regards service, the New Zealand records are regarded as complete. Defoliation missions are recorded as being flown in the geographical area[3] (page 98) and by far the largest New Zealand contribution was of combat troops, artillerymen and infantry soldiers, acknowledged to be at greater risk of herbicide exposure. The anti-malarial drug of choice was Dapsone, with aerial spraying of organochlorine pesticides to control mosquitoes, but unfortunately the exposure doses of both cannot easily be determined.

**Statistical Analysis.**

We used the cohort analysis methods described by Breslow and Day,[4] calculating the person-years of follow up for the cohort through each 5-year age category from 30 or more years of age for each of the five time periods, 1988-90, 1991-95, 1996-2000, 2001-05, and 2006-08. Standardised mortality ratios (SMRs) and incidence ratios (SIRs) were then computed based on the number of deaths and cancer registrations observed, the expected numbers being based on New Zealand national rates. The 95% confidence intervals (95% CIs) were estimated using the Poisson distribution.

Ethical approval was given by the New Zealand Multi-regional Ethics Committee: the Ngāi Tahu Research Consultation Committee also gave us a perspective on the Māori health aspects of our proposal.

**Results**

The cohort status is shown in table 1.

Table 1. Cohort information and follow-up.

| | Male | | Female | |
|---|---|---|---|---|
| Available information | Number | Percentage | Number | Percentage |
| Surname | 3361 | 100.0% | 33 | 100.0% |
| An additional surname | 2 | 0.1% | 2 | 0.1% |
| Forename initials only | 7 | 2.3% | 0 | 0.0% |
| An alias available | 25 | 0.7% | 2 | 6.1% |
| Date of birth not available | 52 | 1.6% | 0 | 0.0% |
| Alternative date of birth | 5 | 0.1% | 0 | 0.0% |
| No address | 1205 | 35.9% | 12 | 36.4% |
| Overseas address | 336 | 10.0% | 3 | 9.1% |
| Died in Vietnam service | 36 | 1.1% | 1 | 3.0% |
| Died after Vietnam war and before 1988 | 3 | 0.1% | 0 | 0.0% |
| Male survivors of Vietnam service | 3322 | 98.8% | | |
| Men matched by Ministry of Health | 2531 | | | |
| Men matched with electoral roll | 252 | | | |
| Men followed up | 2783 | 83.8% | | |
| Not matched | 539 | 16.2% | | |
| Unconfirmed date of death | 34 | 6.3% | | |

Of the 3,322 men of the original cohort of survivors of the Vietnam War, 2,783 men (83.8%) were matched and considered to be alive at the beginning of 1988. Of the 539 records not matched, 57.1% had no address and 29.7% had an overseas address listed by VANZ. In addition, VANZ listed a date of death for 34 men (6.3%) whose death was not confirmed by the MoH. As these deaths were unconfirmed by the official New Zealand records, and no cause of death was listed, the death information recorded by VANZ was not used. Of those without an overseas address 89% were traced, either by the MoH or by the research team using electoral rolls from 1993 to 2009.

The deaths of 407 members of the cohort were recorded in New Zealand during this period. The SMRs for various causes of death are shown in Table 2. The SMR for all causes of death was 0.85 (95% CI 0.77-0.94) suggesting lower overall mortality in the cohort. There were 159 (39.1%) "all cancer" deaths with a significantly higher SMR for cancers of the head and neck (SMR 2.20, 95% CI 1.09 - 3.93), in particular cancers of the oral cavity, pharynx and larynx (SMR 2.13, 95% CI 1.06-3.81). There were more deaths from multiple myeloma and Hodgkin disease than expected, but based on small numbers and the SMRs were not significantly raised.

Table 2. Standardised mortality ratios for the 1988-2008 time period.

| Cause of death | Observed | Expected | SMR | 95%CI* |
|---|---|---|---|---|
| All deaths | 407 | 478.1 | 0.85 | 0.77 - 0.94 |
| Coronary heart disease | 104 | 123.7 | 0.84 | 0.69 - 1.02 |
| Respiratory disease (not COPD) | 12 | 29.8 | 0.40 | 0.21 - 0.70 |
| COPD | 18 | 23.2 | 0.78 | 0.46 - 1.23 |
| Infectious disease (excl AIDS) | 3 | 4.0 | 0.75 | 0.15 - 2.22 |
| Accidents and suicide | 27 | 31.9 | 0.85 | 0.56 - 1.23 |
| Accidents | 11 | 20.8 | 0.53 | 0.26 - 0.95 |
| Suicide | 16 | 11.2 | 1.43 | 0.82 - 2.33 |
| All cancer deaths | 159 | 173.5 | 0.92 | 0.78 - 1.07 |
| All other causes of death | 84 | 92.0 | 0.91 | 0.73 - 1.13 |
| | | | | |
| Select cancer sites | | | | |
| Prostate cancer | 13 | 12.6 | 1.03 | 0.55 - 1.76 |
| Lung cancer | 50 | 43.6 | 1.15 | 0.85 - 1.51 |
| Stomach | 9 | 7.1 | 1.27 | 0.58 - 2.42 |
| Pancreas | 5 | 7.5 | 0.67 | 0.22 - 1.56 |
| Colorectal cancer | 20 | 19.2 | 1.04 | 0.64 - 1.61 |
| Head and neck** | 11 | 5.0 | 2.20 | 1.09 - 3.93 |
| Oral cavity, pharynx & larynx† | 11 | 5.2 | 2.13 | 1.06 - 3.81 |
| Larynx | 2 | 1.0 | 2.00 | 0.23 - 7.39 |
| Melanoma | 4 | 7.2 | 0.56 | 0.15 - 1.42 |
| Multiple myeloma | 5 | 3.2 | 1.58 | 0.51 - 3.69 |
| Hodgkin Disease | 1 | 0.4 | 2.30 | 0.03 - 12.8 |
| NHL | 3 | 7.0 | 0.43 | 0.09 - 1.25 |
| All leukaemia | 4 | 5.6 | 0.71 | 0.19 - 1.83 |
| Non - lymphoid leukaemia | 3 | 3.8 | 0.78 | 0.16 - 2.28 |
| Lymphoid leukaemia | 1 | 1.8 | 0.57 | 0.01 - 3.16 |
| All other cancers†† | 34 | 54.9 | 0.62 | 0.43 - 0.87 |

* 95% confidence interval

** Excludes cancer of the larynx or oesophagus

† Head and neck without cancer of the lip, sinus cavities, or salivary glands, but includes cancer of the larynx

†† All cancer except; lung, prostate, stomach, pancreas, colon and rectum, oral cavity, pharynx, larynx, melanoma, multiple myeloma, Hodgkin disease, non-Hodgkin lymphoma, and all leukaemia

The SIRs for cancer incidence over the period are shown in table 3. We found no statistically significant excess of cancer incidence for the 1988-2008 time period (SIR=1.06, 95% CI 0.97-1.16). The incidence of CLL was however significantly higher. The SIRs for cancer of the prostate, lung, larynx, multiple myeloma, non-lymphoid leukaemia and bone and cartilage were increased, but not significantly so.

Table 3. Standardised incidence ratios of cancer for the 1988-2008 time period.

| Cancer site | Observed | Expected | SIR | 95%CI* |
|---|---|---|---|---|
| All cancer | 458 | 431 | 1.06 | 0.97-1.16 |
| Prostate cancer | 136 | 116.2 | 1.17 | 0.98-1.39 |
| Lung cancer | 58 | 51.1 | 1.13 | 0.86-1.47 |
| Stomach | 9 | 10.9 | 0.82 | 0.38-1.56 |
| Pancreas | 6 | 8.3 | 0.72 | 0.26-1.57 |
| Colorectal cancer | 63 | 66.6 | 0.95 | 0.73-1.21 |
| Head and neck** | 19 | 14.2 | 1.34 | 0.81-2.09 |
| Oral cavity, pharynx & larynx† | 18 | 13.7 | 1.32 | 0.78-2.08 |
| Larynx | 5 | 4.2 | 1.18 | 0.38-2.77 |
| Melanoma | 33 | 44.8 | 0.74 | 0.51-1.04 |
| Multiple myeloma | 9 | 6 | 1.51 | 0.69-2.86 |
| Hodgkin Disease | 3 | 1.4 | 2.08 | 0.42-6.09 |
| NHL | 14 | 16.6 | 0.85 | 0.46-1.42 |
| All leukaemia | 21 | 12.8 | 1.64 | 1.02-2.51 |
| Non-lymphoid leukaemia | 7 | 5.4 | 1.29 | 0.52-2.66 |
| Lymphoid leukaemia | 14 | 7.3 | 1.91 | 1.04-3.20 |
| Connective & soft tissue | 3 | 2.9 | 1.04 | 0.21-3.04 |
| Bone and cartilage | 2 | 0.7 | 2.78 | 0.31-10.0 |
| All other cancers†† | 82 | 78.6 | 1.04 | 0.83-1.29 |

* 95% confidence interval
** Excludes cancer of the larynx or oesophagus
† Head and neck without cancer of the lip, sinus cavities, or salivary glands but includes cancer of the larynx
†† All cancer except; lung, prostate, stomach, pancreas, colon and rectum, oral cavity, pharynx, larynx, melanoma, multiple myeloma, Hodgkin disease, non-Hodgkin lymphoma, and all leukaemia (includes connective and soft tissue).

# DISCUSSION

All causes mortality was significantly reduced by 15% in this group, with a lesser and non significant deficit in all cancer deaths and no decrease in all cancer incidence. Specific cancer sites demonstrated an increase in risk, with twice the risk of mortality from head and neck cancers. There was also a twofold and significantly increased incidence of CLL. Other lymphohaematopoietic disorders, specifically multiple myeloma and Hodgkins disease, showed non significant mortality excesses, reflected by a similar increase in incidence.

One of the strengths of the study was that the New Zealand forces served with the Australian Army in one geographical area, in contrast to United States cohorts which have proved more difficult to enumerate and locate geographically.[3] A further strength was the excellent follow up in terms of the 84% of the cohort that we are able to trace, which would tend to minimise bias (in the direction of under-estimating disease risks) in the results. We did have weaknesses in that we were only able to trace deaths in the decades from 1988 onwards, however we would in any case have lagged exposure by 10-20 years to account for the latent period of cancer, thus excluding earlier deaths.

The relatively small size of the cohort limited the power of the study, the other main weaknesses being the absence of information on confounders including ethnicity, alcohol consumption, smoking status and environmental exposure. 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. Māori are known to have poorer health than those of European origin[5] however there was little evidence of poorer overall health in Vietnam veterans during the follow-up period, at least in terms of increased mortality and cancer incidence. Smoking would be expected to cause (in those sites presented here) an increased risk of oral and lung cancers, with alcohol being an additional cause of cancers of the oral cavity, pharynx and larynx.

We are of course limited by the fact that we do not have data on environmental exposures. 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 more likely to be exposed because they more often engaged with the enemy and were therefore more likely to enter sprayed areas. They were also potentially exposed to other agents such as dapsone and insecticides. The clustering of troops by geographic area and combat experience may reduce misclassification bias to environmental exposures, but the potential for such bias remains high.

Interpretation of the results requires consideration of bias in terms of the healthy worker effect, in this case the "healthy soldier effect."[6] The application and selection process for military service, and further selection prior to operational deployment, results in a cohort which has lower disease incidence and mortality than the general population. The effect is evident in this cohort and would be reduced by the selection of a serving but non-deployed

comparison group. At the time of the study this would have required manual selection from paper files, a process which was not logistically possible.

The most comprehensive body of comparative evidence comes from American Vietnam veterans studies, the largest of which is the "Vietnam Experiences Study" (VES).[7] The base for this cohort was 48,513 individuals randomly selected from service records. After applying inclusion criteria and excluding those who had died in-service, it yielded 9,324 Vietnam veterans and 8,989 in a non-Vietnam cohort. There was no overall increase in mortality when comparing these two groups, and both groups of veterans showed the healthy soldier effect in SMR analyses.

The other relevant epidemiological study is the Air Force Health Study of United States Air Force personnel who took part in operation "Ranch Hand" and deployed herbicides including Agent Orange. This group originally consisted of 1,261 Ranch Hand veterans who were initially matched to 19,080 comparison Air Force personnel who were followed up for mortality and morbidity.[8] The mortality follow up ceased in 2002, by which time there was a statistically increased risk of all causes mortality for all participants (relative risk (RR) 1.3, 95%CI 1.0-1.3) but a statistically increased risk of death from circulatory diseases (RR=1.7, 95% CI 1.2-2.4).[9]

The most similar comparison group is the Australian Vietnam veterans cohort, a much larger group of 59,179 individuals, consisting of 23% Navy, 69% Army and 8% Air Force personnel.[10-11] (http://www.dva.gov.au/aboutDVA/publications/health_research/vietnam_vets/Pages/index.aspx) The main points of comparison 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. There are proportionately, though not significantly, more deaths from suicide in New Zealand veterans. Lung cancer contributed the greatest burden of deaths in the New Zealand and Australian cohorts, with excesses of 15% and 18% respectively, only the latter being significant. Other significant causes of cancer related deaths in the Australian cohort, all head and neck along with oral cavity, pharyngeal, and laryngeal cancers, were similar to those found in New Zealand veterans. Cancer incidence showed a non-significant overall excess of 6% in the New Zealand cohort, the excess of 15% being significant for Australian veterans. The SIR for CLL was 1.68, 95% CI 1.18-2.19 in Australian Army Vietnam veterans,[11] (page 91) less than the SIR of 1.91, 95% CI 1.04-3.20 which we found.

As they operated in the same area, the exposures of New Zealand and Australian veterans would have been the same, and the patterns of disease are similar. The mortality and morbidity experience in these cohorts are neither at odds with the IOM classification nor the "presumptive list" adopted as being compensable by VANZ. Further work should include the selection a serving, but non-deployed, comparison group, which will reduce the healthy soldier

effect. We hope to do this and also to collect information on possible confounders (ethnicity, smoking and alcohol consumption) in the surviving cohort members.

In summary, we have identified a risk of CLL that is significantly higher in New Zealand Vietnam veterans than the general population, confirming the similar result found for Australian veterans. CLL was first classified on the "sufficient" list by the IOM in 2002,[12] (page 377) on the basis of an increased risk in farming populations exposed to herbicides and a mechanistic similarity to non Hodgkin lymphoma in that both are due to malignant transformation of B progenitor cells. The Australian and New Zealand veterans groups are however the only ones to show this increased risk.

## ACKNOWLEDGEMENTS

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## FUNDING STATEMENT

The study was funded by the New Zealand War Pensions Medical Research Trust Fund.

## COMPETING INTERESTS

None

## CONTRIBUTORSHIP

Dr David McBride developed the study proposal, wrote the grant application, assisted in interpreting the results and wrote the drafts.

Dr Brian Cox analysed the data and wrote the initial report.

Dr John Broughton advised on the cultural aspects of the proposal, assisted in study design, with the interpretation of the results and helped to write the drafts.

Dr Darryl Tong assisted in study design and interpretation of the results and helped to write the drafts.

## DATA SHARING

Additional tables can be requested from the corresponding author.

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# MORTALITY AND CANCER EXPERIENCE OF NEW ZEALAND VIETNAM WAR VETERANS

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# ABSTRACT

**Objective**

To study the mortality of, and incidence of cancer in, in New Zealand Vietnam veterans.

**Methods**

A historical cohort study

**Results**

All causes mortality was significantly reduced by 15%, with a non significant deficit in "all cancer" deaths and no decrease in "all cancer" incidence. There was an increased risk of mortality from cancers of the head and neck (SMR 2.20, 95% CI 1.09-3.93) and oral cavity pharynx and larynx (SMR 2.13, 95% CI 1.06-3.81), with significantly increased incidence of chronic lymphatic leukaemia (CLL), (SIR 1.91, 95% CI 1.04-3.20). Other lymphohaematopoietic disorders, specifically multiple myeloma and Hodgkins disease, showed non significant mortality excesses, reflected by a similar increase in incidence.

**Conclusion**

Service in the Vietnam war was associated with defoliant herbicide exposure, including 2-4-5 trichlorophenoxyacetic acid, 2,4 dichlorophenoxyacetic acid, picloram and cacodylic acid. Subsequent reviews of mechanistic, animal and epidemiological evidence led to certain conditions being deemed compensable. The pattern of mortality and cancer incidence is consistent with that found in Australian veterans serving in the same area of Vietnam, and not at odds with the list of compensable conditions, but also consistent with smoking and the healthy soldier effect. In common with the Australian experience, this is the only veterans group to show a significant excess of CLL.

**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 r~~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.

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.

**Key Messages**

CLL is on the "sufficient" list largely because of an increased incidence in the farming occupation and a similarity to non Hodgkins lymphoma in that both are due to malignant transformation of B progenitor cells

Our results, along with those of an earlier Australian study, provide epidemiological evidence of an increased risk of CLL in veterans.

**Strengths and Limitations.**

The follow up of 83% would tend to minimise bias in the direction of under-estimating disease risks

In common with other studies, we do not have exposure data, but the similarity to the Australian veterans experience suggests an ecological effect.

We also have no information concerning confounding by smoking and alcohol consumption, known to be associated with head and neck cancers.

## ~~OBJECTIVE~~INTRODUCTION.

Between June 1964 and December 1972 nearly 3,400 New Zealand military personnel served in South Vietnam. The majority of the force was involved in combat, from 1966 onwards integrated with an ANZAC (Australian New Zealand Army Corps) Battalion deployed to the East of Hanoi (now Ho Chi Minh City) in the Nui Dat area of Phuoc Tuy province, now Bà Rịa city in Bà Rịa–Vũng Tàu province. A~~a~~t its peak in 1968 it represented ~~representing~~ a force of 543 personnel. Smaller numbers served in the New Zealand Medical Services team who served in Binh Dinh province and a New Zealand Special Air Services group.

Vietnam veterans were exposed to a number of agents during the war, including Dapsone, an antimalarial drug with haematological effects. Chemical exposure was a particular feature of this war. T~~t~~actical defoliant herbicide sprays, distributed in 55 gallon drums with a colour stripe classification, led to the hallmark 'rainbow agent' exposure in this War. Agents Pink and Green contained esters of 2-4-5 trichlorophenoxyacetic acid (2,4,5-T); Agents Purple and Orange esters of 2,4,5-T and 2,4 dichlorophenoxyacetic acid (2,4-D). 2,4,5-T was contaminated, to a greater or lesser extent, with 2,3,7,8 tetrachlorodibenzo-p-dioxin ~~2,3,7,8 tetrachlorodibenzodioxin~~ (TCDD or simply "dioxin"). Those herbicides not contaminated with dioxin included Agent White, a mixture of 2,4-D and picloram and finally Agent Blue, a formulation of cacodylic acid (dimethyl arsenic acid or DMA) and its salts. Agent Orange, with an estimated 45,677,937 litres sprayed,[1]~~[1]~~ has come to epitomise the environmental worries of -Vietnam veterans about their service.

Subsequent concerns about the toxicity of these substances and the relationship with health effects led t~~T~~he US Department of Veterans Affairs and The Institute of Medicine of the US National Academy of Sciences (IOM) to carry ~~carries~~ out a biennial and cumulative epidemiological review of herbicide exposure and health. The evidence is not based on causality but on the strength of epidemiological evidence associating herbicide exposure with health. The IOM report classifies ~~, classifying~~ the evidence in support of a relationship as "sufficient", "limited or suggestive", or "inadequate or insufficient". Those in the cancer "sufficient evidence" list in the 2010 update[2] 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 are laryngeal cancer; cancer of the lung, bronchus, or trachea; prostate cancer and multiple myeloma. The evidence reviewed comes from biological plausibility, animal studies, studies of the incidence of cancer in people with occupational exposure to herbicides and a number of Vietnam veterans studies. The latter studies have been based on cohorts of American, Australian and Korean Veterans. 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.~~ether there was evidence of long-term health effects in this group.~~

## ~~DESIGN~~METHODS

Design

This is a cohort study of New Zealand Vietnam veterans who served in Vietnam between 1962 and 1971.

**Cohort enumeration**

The cohort consisted of the 3,394 men and women, identified from service records and recorded on the database of Veterans Affairs New Zealand (VANZ), ~~who served in Vietnam between 1962 and 1971.~~ VANZ administers all aspects of war service entitlements, including war pensions, and the service list is regarded as being complete. Of these, 37 died during the war. The remaining 3,357 were followed up through searches based on the National Health Index (NHI) number linking individuals to health data maintained by the New Zealand Ministry of Health (MoH). No match was found for 791 veterans, but searches on the electoral rolls from 1993 to 2009 provided details of 252. We had to exclude ~~Of the~~ 539 individuals who we could not match~~records not matched,~~. Of these, 336 had an overseas address and ~~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 MoH mortality database and the 32 women who formed too small a sub-group for analysis. Follow up started on the first of January 1988, the first date that data is held electronically on the Mortality Collection. The end of follow up was the 31st December 2008, the last date that data were available. The NZHIS Mortality Collection provided the underlying cause of death for all deaths identified. All the deaths registered by Births, Deaths, and Marriages in New Zealand are subject to verification. The official underlying cause of death recorded by NZHIS is determined after compiling data from a number of additional sources including traffic accident reports, Coroners' inquiries, hospital diagnoses, pathology records, and cancer registry entries. The mortality statistics are compiled according to the year the death is registered: deaths before 2000 are recorded in ICD-9-CM-A and have not been mapped forward to ICD-10-AM.

**Exposure information**

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. The exposure doses of both cannot easily be calculated

**Statistical Analysis.**

We used the cohort analysis methods described by Breslow and Day.[3] We calculated the person-years of follow up for the cohort through each 5-year age category from 30 or more years of age for each of the five time periods,

1988-90, 1991-95, 1996-2000, 2001-05, and 2006-08 for mortality and cancer incidence. ~~We calculated s~~Standardised mortality ratios (SMRs) and incidence ratios (SIRs) were calculated based on the number of deaths and cancer registrations observed, the expected numbers being based on New Zealand national rates. The 95% confidence intervals (95% CIs) were calculated using the Poisson distribution.[4]~~[3]~~

Ethical approval was given by the New Zealand Multi-regional Ethics Committee. The Ngāi Tahu Research Consultation Committee also gave us suggestions and advice on the Māori health implication of our study.

**Results**

The cohort status is shown in table 1.

Table 1. Cohort information and follow-up.

| Available information | Male Number | Male Percentage | Female Number | Female Percentage |
|---|---|---|---|---|
| Surname | 3361 | 100.0% | 33 | 100.0% |
| An additional surname | 2 | 0.1% | 2 | 0.1% |
| Forename initials only | 7 | 2.3% | 0 | 0.0% |
| An alias available | 25 | 0.7% | 2 | 6.1% |
| Date of birth not available | 52 | 1.6% | 0 | 0.0% |
| Alternative date of birth | 5 | 0.1% | 0 | 0.0% |
| No address | 1205 | 35.9% | 12 | 36.4% |
| Overseas address | 336 | 10.0% | 3 | 9.1% |
| Died in Vietnam service | 36 | 1.1% | 1 | 3.0% |
| Died after Vietnam war and before 1988 | 3 | 0.1% | 0 | 0.0% |
| Male survivors of Vietnam service | 3322 | 98.8% | | |
| Men matched by Ministry of Health | 2531 | | | |
| Men matched with electoral roll | 252 | | | |
| Men followed up | 2783 | 83.8% | | |
| Not matched | 539 | 16.2% | | |
| Unconfirmed date of death | 34 | 6.3% | | |

Of the 3,322 men of the original cohort of survivors of the Vietnam War, 2,783 men (83.8%) were matched and considered to be alive at the beginning of 1988. Of the 539 records not matched, 57.1% had no address and 29.7% had an overseas address listed by VANZ. In addition, VANZ listed a date of death for 34 men (6.3%) whose death was not confirmed by the MoH. As these deaths were unconfirmed by the official New Zealand records, and no cause of death was listed, the death information recorded by VANZ was not used. Of those without an overseas address 89% were traced, either by the MoH or, by the research team using electoral rolls from 1993 to 2009

The deaths of 4007 members of the cohort were recorded in New Zealand during this period. The ~~non-cancer~~ SMRs for various causes of death ~~and cancer SIRs~~ are shown in Table 1. The SMR for all causes of death was 0.85 (95% CI 0.77-0.94) suggesting lower overall mortality in the cohort. There were 159 (39.1%) "all cancer" deaths with a significantly higher SMR for cancers of the head and neck (SMR 2.20, 95% CI 1.09 - 3.93), in particular cancers of the oral cavity, pharynx and larynx (SMR 2.13, 95% CI 1.06-3.81). There were more deaths from multiple myeloma and Hodgkins disease than expected, but based on small numbers and the SMRs were not significantly raised.

Table 2. Standardised mortality ratios for the 1988-2008 time period.

| Cause of death | Observed | Expected | SMR | 95%CI* |
|---|---|---|---|---|
| All deaths | 407 | 478.1 | 0.85 | 0.77 - 0.94 |
| Coronary heart disease | 104 | 123.7 | 0.84 | 0.69 - 1.02 |
| Respiratory disease (not COPD) | 12 | 29.8 | 0.40 | 0.21 - 0.70 |
| COPD | 18 | 23.2 | 0.78 | 0.46 - 1.23 |
| Infectious disease (excl AIDS) | 3 | 4.0 | 0.75 | 0.15 - 2.22 |
| Accidents and suicide | 27 | 31.9 | 0.85 | 0.56 - 1.23 |
| Accidents | 11 | 20.8 | 0.53 | 0.26 - 0.95 |
| Suicide | 16 | 11.2 | 1.43 | 0.82 - 2.33 |
| All cancer deaths | 159 | 173.5 | 0.92 | 0.78 - 1.07 |
| All other causes of death | 84 | 92.0 | 0.91 | 0.73 - 1.13 |
| | | | | |
| Select cancer sites | | | | |
| Prostate cancer | 13 | 12.6 | 1.03 | 0.55 - 1.76 |
| Lung cancer | 50 | 43.6 | 1.15 | 0.85 - 1.51 |
| Stomach | 9 | 7.1 | 1.27 | 0.58 - 2.42 |
| Pancreas | 5 | 7.5 | 0.67 | 0.22 - 1.56 |
| Colorectal cancer | 20 | 19.2 | 1.04 | 0.64 - 1.61 |
| Head and neck** | 11 | 5.0 | 2.20 | 1.09 - 3.93 |
| Oral cavity, pharynx & larynx† | 11 | 5.2 | 2.13 | 1.06 - 3.81 |
| Larynx | 2 | 1.0 | 2.00 | 0.23 - 7.39 |
| Melanoma | 4 | 7.2 | 0.56 | 0.15 - 1.42 |
| Multiple myeloma | 5 | 3.2 | 1.58 | 0.51 - 3.69 |
| Hodgkin's Disease | 1 | 0.4 | 2.30 | 0.03 - 12.8 |
| NHL | 3 | 7.0 | 0.43 | 0.09 - 1.25 |
| All leukaemia | 4 | 5.6 | 0.71 | 0.19 - 1.83 |
| Non - lymphoid leukaemia | 3 | 3.8 | 0.78 | 0.16 - 2.28 |
| Lymphoid leukaemia | 1 | 1.8 | 0.57 | 0.01 - 3.16 |
| All other cancers†† | 34 | 54.9 | 0.62 | 0.43 - 0.87 |

* 95% confidence interval

** Excludes cancer of the larynx or oesophagus

† Head and neck without cancer of the lip, sinus cavities, or salivary glands, but includes cancer of the larynx

†† All cancer except; lung, prostate, stomach, pancreas, colon and rectum, oral cavity, pharynx, larynx, melanoma, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, and all leukaemia

The SIRs for cancer incidence over the period are shown in table 3. We found no statistically significant excess of cancer incidence for the 1988-2007 time period (SIR=1.06, 95% CI 0.97-1.16). The incidence of CLL was however significantly higher. The SIRs for cancer of the prostate, lung, larynx, multiple myeloma, non-lymphoid leukaemia and bone and cartilage were increased, but not significantly so.

Table 3. Standardised incidence ratios of cancer for the 1988-2008 time period.

| Cancer site | Observed | Expected | SIR | 95%CI* |
|---|---|---|---|---|
| All cancer | 458 | 431 | 1.06 | 0.97-1.16 |
| Prostate cancer | 136 | 116.2 | 1.17 | 0.98-1.39 |
| Lung cancer | 58 | 51.1 | 1.13 | 0.86-1.47 |
| Stomach | 9 | 10.9 | 0.82 | 0.38-1.56 |
| Pancreas | 6 | 8.3 | 0.72 | 0.26-1.57 |
| Colorectal cancer | 63 | 66.6 | 0.95 | 0.73-1.21 |
| Head and neck** | 19 | 14.2 | 1.34 | 0.81-2.09 |
| Oral cavity, pharynx & larynx† | 18 | 13.7 | 1.32 | 0.78-2.08 |
| Larynx | 5 | 4.2 | 1.18 | 0.38-2.77 |
| Melanoma | 33 | 44.8 | 0.74 | 0.51-1.04 |
| Multiple myeloma | 9 | 6 | 1.51 | 0.69-2.86 |
| Hodgkin's Disease | 3 | 1.4 | 2.08 | 0.42-6.09 |
| NHL | 14 | 16.6 | 0.85 | 0.46-1.42 |
| All leukaemia | 21 | 12.8 | 1.64 | 1.02-2.51 |
| Non-lymphoid leukaemia | 7 | 5.4 | 1.29 | 0.52-2.66 |
| Lymphoid leukaemia | 14 | 7.3 | 1.91 | 1.04-3.20 |
| Connective & soft tissue | 3 | 2.9 | 1.04 | 0.21-3.04 |
| Bone and cartilage | 2 | 0.7 | 2.78 | 0.31-10.0 |
| All other cancers†† | 82 | 78.6 | 1.04 | 0.83-1.29 |

* 95% confidence interval
** Excludes cancer of the larynx or oesophagus
† Head and neck without cancer of the lip, sinus cavities, or salivary glands but includes cancer of the larynx
†† All cancer except; lung, prostate, stomach, pancreas, colon and rectum, oral cavity, pharynx, larynx, melanoma, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, and all leukaemia (includes connective and soft tissue).

~~ConclusionWe found no statistically significant excess of cancer for the 1988-2007 time period (SIR=1.06, 95% CI 0.97-1.16). The incidence of CLL was however significantly higher. The SIRs for cancer of the prostate, lung, larynx, multiple myeloma, non-lymphoid leukaemia and bone and cartilage were increased, but not significantly so.~~

## DISCUSSION

All causes mortality was significantly reduced by 15% in this group, with a lesser and non significant deficit in all cancer deaths and no decrease in all cancer incidence. Specific cancer sites demonstrated an increase in risk, with twice the risk of mortality from head and neck cancers. There was also a twofold and significantly increased incidence of CLL. Other lymphohaemopoietic disorders, specifically multiple myeloma and Hodgkins disease, showed non significant mortality excesses, reflected by a similar increase in incidence.

One of the strengths of the study was that the New Zealand forces served with the Australian Army in one geographical area, in contrast to United States which have proved more difficult to enumerate and locate geographically.[2] A further strength was the excellent follow up in terms of the 84% of the cohort that we are able to trace, which would tend to minimise bias (in the direction of under-estimating disease risks) in the results. We did have weaknesses in that we were only able to trace deaths in the decades from 1988 onwards. We would in any case have lagged exposure by 10-20 years to account for the latent period of cancer, thus excluding earlier deaths.

The relatively small size of the cohort limited the power of the study, the other main weaknesses being the absence of information of confounders including ethnicity, alcohol consumption and smoking status. 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. ~~the proportion is likely to be higher than the general population and~~ Māori are however known to have poorer health than those of European origin.[5]~~[4]~~ 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, ~~in veterans during the follow-up period~~. Smoking would be expected to cause (in those sites presented here) an increased risk of oral and lung cancers, with alcohol being an additional cause of cancers of the oral cavity, pharynx and larynx.

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[6] Infantry soldiers were also more likely to be exposed because thy 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.

~~We do not have data on herbicide exposure, but know that that the majority of our veterans were combat soldiers, likely to have been exposed to a similar "toxic environment".~~

Interpretation of the results requires consideration of bias in terms of the healthy worker effect, in this case the "healthy soldier effect." The application and selection process for military service, and further selection prior to operational deployment, results in a cohort which has lower disease incidence and mortality than the general population. The effect is evident in this cohort and would be reduced by the selection of a serving but non-deployed comparison group. ~~.~~ At the time of the study this would have required manual selection from paper files, a process which was not logistically possible.

The most comprehensive body of comparative evidence comes from American Vietnam veterans studies, the largest of which is the "Vietnam Experiences Study" (VES).[7] The base for this cohort was 48,513 individuals randomly selected from service records. After applying inclusion criteria and excluding those who had died in-service, it yielded 9,324 Vietnam veterans and 8,989 in a non-Vietnam cohort. There was no overall increase in mortality when comparing these two groups, and both groups of veterans showed the healthy soldier effect in SMR analyses.

The other relevant epidemiological study is the Air Force Health Study of United States Air Force personnel who took part in operation "Ranch Hand" and actually deployed Agent Orange. This group originally consisted of 1,261 Ranch Hand veterans who were initially matched to 19,080 comparison Air Force personnel who were followed up for mortality and morbidity. The mortality follow up ceased in 2002,[8] by which time there was a statistically increased risk of all causes mortality for all participants (relative risk (RR) 1.3, 95%CI 1.0-1.3) but a statistically increased risk of death from circulatory diseases (RR=1.7, 95%CI 1.2-2.4). The follow-up component, which included regular examinations, did however fail to show significant health effects.

The most similar comparison group is the Australian Vietnam veterans cohort.[9-10] 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. There were proportionately, though not significantly, more deaths from suicide in New Zealand veterans ~~(data not shown)~~. 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. Other significant causes of cancer related deaths in the Australian cohort, all head and neck along with oral cavity, pharyngeal, and laryngeal cancers, were similar to those found in New Zealand veterans. Cancer incidence showed a non-significant overall excess of 6% in the New Zealand cohort, the excess of 15% being significant for Australian veterans. The SIR for CLL was 1.68, 95% CI 1.18-2.19 in Australian Army Vietnam veterans,[6] less than the SIR of 1.91, 95% CI 1.04-3.20 which we found.

As they operated in the same area, t~~T~~he exposures of New Zealand and Australian veterans would have been the same, and the patterns of disease are similar. The mortality and morbidity experience in these cohorts are neither at odds with the IOM classification nor the "presumptive list" adopted as being compensable by VANZ.

Further work should include the selection a serving, but non-deployed, comparison group, which will reduce the healthy soldier effect. We hope to do this and also to collect information on possible confounders (ethnicity, smoking and alcohol consumption) in the surviving cohort members.

In summary, we have identified a risk of CLL that is significantly higher in New Zealand Vietnam veterans than the general population, confirming the similar result found for Australian veterans. CLL was first classified on the "sufficient" list by the IOM in 2002,[11][7] on the basis of an increased risk in farming populations exposed to herbicides and a mechanistic similarity to non Hodgkins lymphoma in that both are due to malignant transformation of B progenitor cells. The Australian and New Zealand veterans groups are however the only ones to show this increased risk.

## ACKNOWLEDGEMENTS

We are grateful to the staff of Veterans Affairs New Zealand, particularly Corina Herewini, for their invaluable help in updating and formatting the service records. We also acknowledge the assistance of the analytical services staff at the Ministry of Health.

## FUNDING

The study was funded by the War Pensions Medical Research Trust Fund.

## COMPETING INTEREST

None

## CONTRIBUTORSHIP

Dr David McBride developed the study proposal, wrote the grant application, assisted in interpreting the results and wrote the drafts.

Dr Brian Cox analysed the data and wrote the initial report.

Dr John Broughton advised on the cultural aspects of the proposal, assisted in study design, with the interpretation of the results and helped to write the drafts.

Dr Darryl Tong assisted in study design and interpretation of the results and helped to write the drafts.

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STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract ☑ |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ☑ |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported ☑ |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses ☑ |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper ☑ |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ☑ |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ☑ |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ☑ |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group N/A |
| Bias | 9 | Describe any efforts to address potential sources of bias ☑ |
| Study size | 10 | Explain how the study size was arrived at N/A |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why N/A |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding ☑ |
| | | (*b*) Describe any methods used to examine subgroups and interactions N/A |
| | | (*c*) Explain how missing data were addressed ☑ |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed N/A |
| | | (*e*) Describe any sensitivity analyses N/A |

Continued on next page

| | | |
|---|---|---|
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ☑ |
| | | (b) Give reasons for non-participation at each stage N/A |
| | | (c) Consider use of a flow diagram ☑ |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ☑ |
| | | (b) Indicate number of participants with missing data for each variable of interest N/A |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) ☑ |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time ☑ |
| | | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ☑ |
| | | (*b*) Report category boundaries when continuous variables were categorized N/A |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses N/A |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives ☑ |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ☑ |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ☑ |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ☑ |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.