

SYSTEMATIC REVIEW OF MORTALITY IN GULF WAR VETERANS

Abstract

Objective - To identify and summarise the findings from studies that have assessed mortality as an outcome in Gulf War veterans when compared with an appropriate control group.

Design - Systematic review.

Data Sources - Studies published between 1990 and 2001 were identified from a range of electronic databases including; EMBASE, MEDLINE, ASSIA, SIGLE and PsycINFO. Reference lists and websites were searched and key researchers in the field were contacted.

Study selection - Studies were included which examined mortality in Gulf War veterans who were deployed or present in the Persian Gulf arena on either military, medical or peacekeeping grounds and which had used a comparison group who had not been deployed to the Persian Gulf. 2296 abstracts were independently reviewed by two authors.

Results - Three primary studies which assessed mortality fulfilled the inclusion criteria. Results were quite consistent across studies, in spite of different periods of follow-up, suggesting an increase of risk in deaths from external causes, with an odds ratio of approximately 1.18, and a lower rate of mortality from disease-related causes.

Conclusions - These studies suggest there is an increased risk of mortality from accidental causes in Gulf War veterans but they do not support the hypothesis that Gulf War veterans are at increased risk of mortality from disease.

Introduction

Veterans who served in the Persian Gulf War of 1991 have reported a range of health complaints, including joint and limb pain 1,2 respiratory problems 3 and unexplained fatigue 4. Media reports of increased mortality rates also aroused concern and a number of studies were commissioned to investigate the matter 5-7.

Our aim was to systematically review studies which have investigated these problems. Here we report on those which have estimated mortality rates in Gulf War veterans. We excluded deaths resulting from combat related injury and only included studies that compared rates in Gulf War veterans with an appropriate comparison sample.

Methods

Searching

Studies between 1990-2001 were identified from a range of electronic databases including EMBASE. MEDLINE. ASSIA, STGLP, PsycINFO, CancerLit, HealthStar, Dissertation Abstracts, Current Contents, Health and Psychosocial Instruments, CINAHHL and Biological abstracts. Keywords used to identify the studies were as follows:

'desert storm' OR 'desert shield' OR 'desertshield' OR 'Gulf war' OR 'Gulf syndrome' OR 'Gulf war syndrome' OR 'Persian Gulf war' OR 'Persian Gulf syndrome'

References of identified studies were searched for further studies. Specialist Gulf Veterans' Illnesses research websites (the DoD Center for Deployment Health Research site 9 and the Walter Reed Army Medical Center Gulf War database¹⁰) and more general Gulf websites were also searched for any additional references. Researchers who had expressed an interest in Gulf Veterans' Illnesses research were contacted for any non-published information. There were no restrictions on the identification of studies in terms of publication status or language. This search strategy identified a total of 5387 studies.

Study Selection

Inclusion criteria

Studies were included if they contained data on Gulf War veterans who had been deployed to the Gulf War on either military, medical or peace-keeping grounds (i.e. those persons involved in either Desert Shield, Desert Storm/ Operation GRANBY or Desert Peace). Any study design was eligible for inclusion provided an appropriate control or comparison group was included to compare risk or rates of mortality.

Exclusion criteria

Studies were excluded if the subjects were indigenous to the Persian Gulf arena. Combat related death that was not specific to the Gulf War was excluded.

Health outcomes

This review summarises the findings from the studies that have assessed mortality risks or rates in Gulf War Veterans as compared to a control group at any time period after the beginning of the Gulf War. Other reports on different health outcomes are the subject of separate reports.

Adherence to inclusion / exclusion criteria

A flowchart of progress through the systematic review is shown in Figure 1. Since the search strategy was developed to be highly sensitive, the 5387 references identified were initially assessed by one of the authors to exclude those which were very obviously not relevant. Each of the 2296 studies which remained under review were then independently assessed by two members of the research team. If the abstract indicated that the study might achieve the inclusion criteria, the full article was obtained for further inspection. If the abstract provided enough information to fulfill one of our a priori exclusion criteria, it was excluded. If the abstract was unclear, or if the raters disagreed, the full article was sought for further review. The level of agreement between the raters was good, with Kappa values ranging from 0.42 to 0.73. A total of 409 full articles were sought for further review.

Data extraction

The studies that fulfilled the inclusion criteria were then categorised by health outcome; three studies which investigated mortality were identified. Data relating to the studies' main aim and to methodological quality were extracted independently by two members of the research team on to pre-designed data extraction forms. The assessment of the methodological quality of the individual studies was based on the response or follow-up rate, the potential of selection bias in the sampling of subjects, the potential bias in the measurement of outcomes, the availability of data on confounders and the controlling for such variables, and the statistical power of each study.

Quantitative data and its synthesis

We have estimated the absolute mortality rate difference, expressed as the difference in the number of deaths per year per 100,000 servicemen between those deployed and those not deployed. These are unadjusted rates since the published data do not allow these to be adjusted for the effects of confounders, nor do they allow a proper calculation of confidence limits. It was not appropriate to perform a quantitative meta-analysis of the data due to differences in the time periods and rates of follow-up in the primary studies.

Results

We identified three studies that met our inclusion criteria. One of these⁷ has since been updated with a longer period of follow-up⁸. Table 1 shows a summary of the most important results, together with some comments on the methodology employed.

All three studies investigated mortality in all US^{5,6} and UK^{7,8} service personnel deployed to the Gulf. All studies selected a comparison sample from other military personnel. Kang selected from all those on active duty, in the National Guard or in the military reserves who served during the same period as the Gulf War but who were never deployed to the Gulf. They were sampled to have approximately the same mix of type of service unit. Writer took as controls the entire set of military personnel on active duty between August 1st 1990 and July 31st 1991 who were not deployed to the Gulf. Macfarlane used a matched sample of military personnel who were in service on January

1st, 1991 but who were not deployed to the Gulf.

All of the studies presented results for all-cause mortality, mortality from illness and external causes, largely accidents, but including homicides and suicides. However the follow-up periods differed, ranging from 1 to 9 years and so it is not appropriate to combine the results. For the Macfarlane study 7 we have taken the figures published in Hansard 8 after 9½ years follow-up rather than those in the original publication.

Kang 5 used an odds ratio as the summary measure, controlling for confounders in a logistic regression, while Writer 6 used indirect standardization, with age and sex specific mortality rates from the controls. Macfarlane 7 used a matched design, thereby controlling for confounders, and calculated a mortality rate ratio. These are different measures but they have broadly similar interpretations and the results were very consistent.

All cause mortality

Kang's study found a significant increase in all-cause mortality with an odds ratio of 1.09. The other studies, with fewer deaths, had similar results which were not significant. Table 2 shows the estimated unadjusted rate differences for all three studies. Kang's study suggests that for every 100,000 servicemen deployed, in each year 8 more will die on average compared to the non-deployed. An approximate 95% confidence interval is given, based on raw data unadjusted for confounders. The excess risk seems to decrease with the length of follow-up period, though standard errors of the estimates are large.

Deaths due to external causes

All studies found an increased mortality rate from external causes in Gulf War veterans. The result for the smaller British study was not quite significant at 8 years but was after 9½ years follow-up. Table 3 shows the estimated excess risks per 100,000 person-years of follow-up. Within this category of death, all studies showed a significant increase in the risk of death from an accident. The longer studies suggested (that this risk was increased by 25%.

Deaths due to illness

All three studies found a reduced mortality rate for illness, though this was only statistically significant in the Macfarlane study. The rate ratio varied between 0.81 and 0.94. There is no evidence for a substantial increase in the risk of death from disease. Table 4 shows the mortality rate difference. Thus the British study suggests that on average there will be about 9 fewer deaths from disease per year for every 100,000 service personnel deployed compared to those not deployed.

Death from specific diseases

There was no evidence for a difference in mortality rates between those serving in the Gulf and the controls, though the power for comparing rates was low due to the small numbers of deaths from specific diseases.

Exposures

There was no information on exposure to potential risk factors in the Gulf.

Discussion

An increase in the risk of death from accidents was found in all three studies identified. Since Kang and Writer both used all US deployed service personnel, though with different follow-up periods, these results are not completely independent, Writer's study found an increased risk of suicide during the war but this was not found in the other studies. It might be an effect of the conflict itself rather than of exposure to some harmful agent. Added evidence on the increased risk of accidents comes from a study by Zwerling 12 which found an increased risk of hospitalization due to self-reported injuries in Gulf War veterans compared to non-deployed military personnel.

All three studies suggested a reduction in the mortality rate from illness for those who were deployed, though only in the study with the longest follow-up was the result statistically significant.

The validity of the estimates of mortality rely upon the comparability of the non-deployed veterans with the Gulf War veterans. It is probable that deployment depended, in part, upon the characteristics of the service personnel, in other words deployment was not random. This has led Haley to propose a "healthy warrior" effect, essentially claiming that those deployed were fitter and in better health than those not deployed and therefore less liable to suffer a fatal illness. He argued that this effect has obscured an increase in mortality in Gulf War veterans. There is no convincing way to quantify such potential biases. The results suggest a reduction in mortality from illness in the deployed group of around 10%, indicative of a health selection bias. A larger effect seems somewhat unlikely given the requirement of good health to remain in the armed forces. Bell 13 examined members of the US forces in the decade before the Gulf War and found that those deployed were less likely to have been hospitalized than those not deployed, particularly in the years immediately before the Gulf War, adding credence to a difference in health status between those deployed and those not deployed. The observed effect was fairly small, however, and it seems unlikely that this would mask even a moderate increase in the risk of illness-related deaths. While the studies controlled for a number of confounders, none accounted for marital status. This is a potential confounding variable as deployed personnel were less likely to be married.

Any effect on the rates of a disease like cancer would not be identified until a much longer period of follow-up has elapsed. It will also be impossible to carry out adequately powered studies to investigate cancer deaths. For example, a study of all US veterans after 8 years would only have 50% power for identifying the rate ratio of 1.1 found in Macfarlane's study. For a cancer with a rate of 10% of the overall cancer rate, a similar study would only have 10% power. To achieve 80% power then the expected rate ratio would need to be as large as 1.6. There are two hypotheses to explain the increased rate of accidental death. The first is that those deployed are more disposed to risk-taking. The second possibility is that deployment led to an increase in risk-taking, as a result of physical or psychological exposures during the Gulf War. The studies reported here cannot shed light on which, if either, of these hypotheses is true but the first received some support from Bell's study 13 which suggested that troops deployed to the Gulf had

shown a greater propensity for risk taking, both within their military service and in other activities.

Haley has also suggested that a finite population correction should be applied to these data, since all troops deployed to the Gulf were studied. This would lead to narrower confidence intervals. A number of arguments against this approach have already been aired however we would additionally argue that the Gulf War veterans are a subset of a hypothetical infinite population who could have been exposed to such situations then or in the future. This is analogous to a clinical trial in which those who have been allocated a new treatment are regarded as a sample, not as the entire population.

Quality of the primary studies

Ascertainment

The method of ascertainment varied between studies. Kang used a database of the Department of Veterans Affairs and checked a sample of 15000 deployed and 15000 controls with the National Death Index, with complete agreement. A quite separate study checked deaths of Vietnam veterans from this veteran's database against the Social Security Administration database with 97% agreement. Writer's follow-up period did not extend beyond the period of military service of the study population and so military records could be used. There was no estimate of any errors involved in this or in ascertaining deployment status. Macfarlane's study had a much longer follow-up period and about 3.5% were lost to follow-up and another 1% emigrated. Since the study was reported relatively soon after the end of the follow-up period, complete mortality data, especially on the cause of death, were not always available.

Confounding and interactions

Kang adjusted the odds ratios for age, sex, race and unspecified military variables. Writer used indirect standardization, presumably adjusting for age and sex. Macfarlane, on the other hand, chose the controls to be matched for age, sex, service, rank and fitness — though it is not made entirely clear how fitness was assessed or indeed how the matching was performed. Marital status is a potential confounder particularly for mortality from external causes but none of the studies adjusted for this.

Selection of controls

The choice of other military personnel who were deployed elsewhere in the same era is a sensible and practical one. Some of those controls served in the Balkans. The recent publicity concerning the possible exposure of troops who served there to some of the same potential hazards as the Gulf veterans highlights the difficulties in choosing suitable controls; the inclusion of those troops will tend to reduce the apparent magnitude of any effect of exposure.

Conclusion

There is evidence that the risk of accidental death is higher in veterans of the Gulf War than in the control population of military personnel not deployed there. There are several hypotheses to explain this but none can be tested from the data available. In a review of studies on mortality following military service in the Vietnam War, Boyle 15 showed that the risk of death from these causes was raised in those who served in Vietnam compared to controls who served in the armed forces but were not deployed to Vietnam. Thus this

might be a common experience of those deployed to war zones rather than a specific effect of the Gulf War.

The evidence points towards a lower disease mortality rate among those deployed; this may possibly be explained by a 'healthy warrior' effect. The low mortality rate ratios for certain diseases support this idea, as argued by Haley, but too few details of the criteria for deployment are available to investigate this, though Bell's study gives it some support. Such an effect, if real, could mask an adverse effect of deployment to the Gulf. Only by a very detailed investigation of the health of those deployed, compared to that of those not deployed, could the existence of such an effect be determined or ruled out.

There is, and will remain, a considerable uncertainty about the possibility of an increased (or reduced) risk of diseases such as cancer which present many years after exposure, or for relatively uncommon illnesses. There is insufficient statistical power to investigate this question.

Overall, Gulf War Veterans can be relatively reassured by the results of these studies. While findings from both the US and UK give a consistent pattern of a moderate increase in deaths from accidents, there is no evidence of an increased overall rate of death from illness, though there will remain uncertainty about specific causes of death.

Acknowledgments

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Figure 1 Progress through the stages of the Gulf systematic review

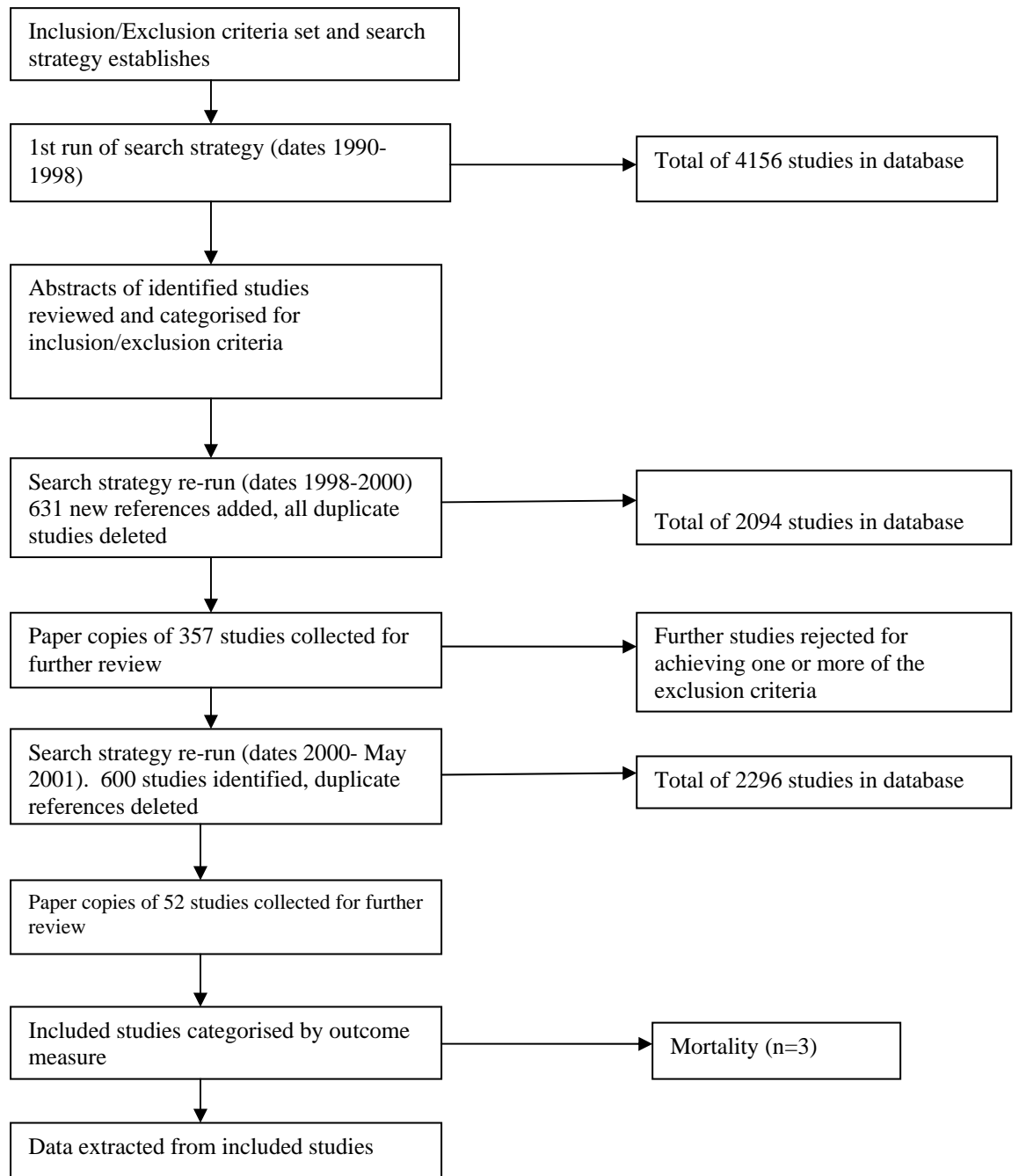


Table 1 Studies that have investigated the association between deployment to the Gulf War and mortality

First author	Study design	Sample	Study period	Main outcomes	Main results	Case ascertainment	Confounding
Kangl	Retrospective cohort study	695516 US Gulf veterans 746291 other US veterans	Start: Gulf veterans day of leaving Gulf Other veterans 1 May 1991 End: 30 Sept 1993	Death from all causes and also from accidents and illness	All causes OR 1.09 (1.01,1.16) External causes OR 1.17 (1.08,1.27) Accidents OR 1.25 (1.13,1.39) Illness OR 0.88 (0.77,1.02)	Mortality was determined from the Dept of Veteran affairs A sample of 15000 deployed and 15000 controls was checked with the National Death Index with 100% agreement	Odds ratios were controlled for age, sex, race and military variables
Writer 2	Retrospective cohort study	US service personnel on active duty between 1 August 1990 and 31 July 1991 688702 Gulf veterans and 1901491 controls	1 August 1990 to 31 July 1991	Death from combat, non-combat injury and illness	All causes* SMR 1.12 (0.97,1.26) All injuries SMR 1.18 (1.01,1.34) Accidents SMR 1.54 (1.32,1.77) Illness SMR 0.94 (0.63,1.34)	Deaths obtained from Department of Defense based on casualty report forms. No validation of the deployment status of individuals was possible. The follow-up period coincided with military service reducing follow-up errors.	Controlled for age and sex using indirect standardization with comparison group as source of standard rates
Macfarlane 3	Retrospective cohort study	British veterans. 53462 Gulf veterans and 53462 non-deployed personnel	1 April 1991 to 31 March 1999 with follow-up in additional report to 31 December 2000	Death from all causes and also from external causes and illness	To March 1999 All causes MRR 1.05 (0.91,1.22) External causes MRR 1.18 (0.98,1.42) Accidents MRR 1.25 (1.01,1.53) Illness MRR 0.87 (0.67,1.11) To Dec 2000 All causes MRR 1.02 (0.90,1.16) External causes MRR 1.20 (1.02, 1.42) Accidents MRR 1.29 (1.05, 1.58) Illness MRR 0.81 (0.66, 0.99)	By Office for National Statistics 0.8% emigrated and survival status not known. 3.5% lost to follow up	Comparison Sample were frequency matched for age, sex, rank, service and level of fitness

* In the Writer study, whose follow-up period included the conflict, all-cause mortality excludes battle deaths

Table 2 Unadjusted excess deaths from all causes due to deployment, expressed as the number of deaths per 100,000 person-years at risk, together with 95% confidence intervals

Study	Excess deaths from all causes	Confidence limits
Writer	11.4	(-0.2, 23.3)
Kang	8.0	(1.4, 14.6)
Macfarlane	2.6	(-11.4, 16.6)

Table 3 Unadjusted excess deaths from external causes due to deployment, expressed as the number of deaths per 100,000 person-years at risk, together with 95% confidence intervals.

Study	Excess deaths from external causes	Confidence limits
Writer	27.9	(17.5, 38.3)
Kang	17.6	(12.1, 23.1)
Macfarlane	11.9	(1.2, 22.6)

Table 4 Unadjusted excess deaths from disease due to deployment, expressed as the number of deaths per 100,000 person-years at risk, together with 95% confidence intervals.

Study	Excess deaths from disease	Confidence limits
Writer	-2.5	(-6.9, 1.8)
Kang	-9.8	(-13.1, -6.5)
Macfarlane	-9.4	(-18.2, -0.5)

What is already known on this topic

- There has been great concern over whether Gulf War veterans have endured long term ill effects in both morbidity and mortality

What this study adds

- This systematic review examines all the available evidence on the effect of the Gulf War on mortality
- It suggests that there is no evidence for an increase in all-cause mortality but that there is an increased risk of accidental death
- The apparent decrease in risk in mortality from disease suggests that there is a selection bias affecting studies, with troops deployed to the Gulf being healthier than those deployed elsewhere