

SYSTEMATIC REVIEW OF HOSPITALISATION IN GULF WAR VETERANS

Abstract

Context

There has been great concern over whether Gulf War Veterans have endured long term ill-health effects .

Objective

To identify and summarise the findings from studies that have assessed morbidity using hospitalisation data as an outcome in Gulf War Veterans when compared with an appropriate control group.

Data Sources

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

Study selection

Studies were included which examined hospitalisation rates in Gulf War Veterans who were deployed or present in the Persian Gulf arena on either military, medical or peace-keeping grounds and which had used a comparison group who had not been deployed to the Persian Gulf. 2296 abstracts were independently reviewed by two reviewers.

Data extraction

Data extraction was performed independently by two reviewers with disagreements resolved by consensus.

Data synthesis

Eight primary studies which assessed hospitalisation rates fulfilled the inclusion criteria. There was no consistent pattern of increased risks among Gulf War Veterans. There was evidence of an initial increased risk of testicular cancer but this was no longer significant with a longer follow-up period. There was no evidence for an increased risk of hospitalisation for an unknown illness and no consistent pattern for mental illness.

Conclusions

These studies do not support the hypothesis that Gulf War Veterans are at increased risk of hospitalisation though there is some evidence of a healthy warrior effect, which could mask a relatively small adverse effect.

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 problems³ and unexplained fatigue⁴. Many of these have been assessed by self-reported symptoms; one measure of the extent of health problems which is possibly more objective is the amount of hospitalisation.

Our aim was to systematically review studies which have investigated these problems. Here we report on those which have considered hospitalisation in Gulf War Veterans. We included only those studies that compared hospitalisation in Gulf War Veterans with an appropriate comparison sample, usually of other contemporaneous military personnel who were not deployed to the Gulf.

Methods

The methods used in this systematic review were described in detail in another publication⁵ and are summarised here. 5387 studies were identified for possible inclusion after a search through relevant databases and websites; individual researchers in the field were also contacted. For inclusion a study had to contain data on military, medical or peace-keeping personnel who were deployed to the Gulf. The study also had to involve an appropriate control group of personnel who were not deployed to the Gulf. For the purposes of this paper the outcome of the study was hospitalisation. Reviews for other outcomes are the subject of separate papers.

Data from studies which met the inclusion criteria were extracted independently by two reviewers; these data included the results relevant to the main hypotheses but also aspects of study design used to assess the quality of the study. These included potential bias in the selection of subjects or controls, the completeness of the hospitalisation data, the corrections made for confounding variables and whether the analysis had made appropriate allowances for changes in procedure in hospital admissions.

This last part is particularly important in studies which extend beyond June 1994, when the Comprehensive Clinical Evaluation program (CCEP) was introduced. This offered clinical examinations and evaluations to GWVs and it is likely that it increased the rate of hospitalisation for GWVs after that date; allowance must therefore be made for it.

Statistical Analysis

Point estimates and confidence intervals were extracted where possible. The intention was to perform meta-analyses if there were sufficient independent studies with similar outcome measures.

Results

We identified eight studies⁶⁻¹³ that met our inclusion criteria, though Coate's paper⁶ is an early analysis of that given in Gray⁸ and will be discussed separately. Table 1 shows a summary of the most important results, together with some comments on the methodology employed. Essentially all the studies were on the cohort of US military

Gulf War Veterans (GWVs), comparing them with non-deployed veterans (NDVs). There were no studies from other countries. The studies differ in aspects such as the length of follow-up and the cause of hospitalisation, with some looking at a range of general causes while others looked at specific causes such as testicular cancer, mental disorders and unexplained symptoms. This means that the studies are not independent ones, since the same subjects are involved, and so a meta-analysis of the results is not appropriate.

Two studies (Gray⁸, Bell¹⁴) considered pre-war hospitalisation among veterans and concluded that those who were deployed tended to have a lower risk of hospitalisation from all causes or from a cause specifically related to a Gulf War type illness, although Bell's study suggested an increased risk of hospitalisation from injury. This gives strength to the idea of a healthy warrior effect, proposed by Haley¹⁵ among others, indicating a selection bias towards better health in the choice of personnel for deployment. As a result in most studies an indicator variable corresponding to pre-war hospitalisation was included, where possible, in the analysis of post war hospitalisation.

Gray⁸ considered all-cause hospitalisation and, without quoting details, stated that the GWVs had a similar risk of hospitalisation as the NDVs after the war. For specific ICD categories 42 comparisons were made, using 14 categories of reasons for admission in three time periods, and there was no consistent pattern. There was some evidence of an increased risk of neoplasms and genito-urinary disease in the first year and of blood-related disease in the second year, together with mental illness in the first two years, but this made no allowance for the multiple testing. Rather more categories showed a significantly reduced risk of disease, including infections, digestive, endocrine, musculo-skeletal and ill-defined symptoms. This probably reflects the selection bias in deployment referred to above. Specific areas with some evidence of increased risk were infertility in women, alcohol and drug dependence and testicular cancer.

Knoke et al¹¹ looked specifically at testicular cancer, taking a similar study group as in the above one, but including more controls. The outcome was hospitalisation with a primary diagnosis of a new incident case of testicular cancer. Over the period of follow-up to March 1996 the adjusted rate ratio was 1.05 with 95% confidence interval (0.86 – 1.29). A plot of the hazard function suggested that an early increased risk before the difference between the GWVs and NDVs became non-significant with a longer follow-up period; further investigation of the data from January 1990, before deployment, suggested that this early apparent effect might be a case of regression to the mean, following the selection bias, and that it could also be due to cases which occurred during deployment being deferred until after the war was over.

Knoke and Gray¹² considered hospitalisation with symptoms consistent with an unexplained illness, with a follow up until April 1996. For each subject they considered up to 8 ICD codes for reasons for hospitalisation and checked for one of 77 diagnoses. They differentiated between those whose primary ICD code referred to the unexplained illness and those for whom any of the codes referred to this. The adjusted risk ratio, taking any of the 8 ICD codes as defining the illness, was 1.06 with 95% confidence interval (1.03 – 1.09), while taking only the primary ICD code the risk ratio was 0.99 (0.95 – 1.03). The follow-up period extended beyond the introduction of the CCEP referred to earlier. By plotting the hazard functions over time Knoke and Gray

argued that the data were consistent with an increase in the rate of hospitalisation following the introduction of the CCEP. Censoring participants in the program at its introduction gave new rate ratios of 0.93 (0.91 – 0.96) using 8 ICD codes and 0.93 (0.89 – 0.97) using the primary ICD code only; thus there would seem to be evidence that the risk is actually reduced among GWVs.

A similar study group was chosen by Smith et al¹³ to investigate hospitalisation due to systemic lupus erythematosus (SLE), amyotrophic lateral sclerosis (ALS) or fibromyalgia, with a followup until July 1997. There was no evidence of an effect of deployment on the risk of either SLE, with an adjusted rate ratio of 0.94 (0.65 – 1.35) or of ALS, with an adjusted rate ratio of 1.66 (0.62 – 4.4). There appeared to be an effect on fibromyalgia with a significantly raised rate ratio of 1.23. The CCEP appeared to have an effect on hospitalisation rates, however, with the rate ratio increasing from 0.92 in the period before June 1994 to 1.76 in the subsequent period. Introducing a covariate for participation in the program had a major impact, reducing the rate ratio to 0.56 (0.41 – 0.78) in this second period.

Dlugosz⁷ considered hospitalisation in the army for 10 mental disorder categories in the period up to September 1993. The GWVs were divided into those involved in combat, those in support units and those not involved in the ground war, comparing all of these with NDVs. There were few consistent patterns. Among the men the GWVs were less likely to have had hospitalisation for mood or personality disorders but had an increased risk due to acute stress reactions; those involved in combat had an increased risk due to alcohol-related disorders. The women also had a reduced risk for mood disorders and those in support units an increased risk for drug-related causes. The much smaller number of women deployed affects the levels of significance attained in the comparisons.

In all of these studies deployment was taken as a surrogate for exposure. Gray⁹ considered a specific exposure, to a munitions destruction site which was found to contain nerve gas. Plume analysis was used to estimate the levels of exposure which were divided into three categories. Hospitalisations due to all causes and also 15 specific causes were considered and the three levels of exposure, together with those who had been deployed elsewhere in the Gulf, were compared to non-deployed controls. The risk ratios for all causes were 0.95 (0.93 – 0.97), 0.96 (0.92 – 0.99) and 0.93 (0.90 – 0.96) in the three exposed groups, while for those not exposed the risk ratio was 1.02 (0.96 – 1.08). There is therefore no evidence for an increased risk, but rather more supporting evidence for a healthy warrior effect. Looking at specific causes, of the 60 comparisons made only three showed an increased risk compared to non-exposed and so there is no real evidence of an effect due to exposure.

All of the above studies used hospitalisation data from hospitals of the Department of Defense; this excludes those who left the service, together with reservists and the National Guard. Gray¹⁰ attempted to include these by considering different hospital systems, namely those of the Veterans Affairs and the California system. Unfortunately these turned out to be inadequate for providing suitable denominator data and instead the proportional morbidity ratios in each system were calculated for 14 categories of disease. There was no consistent pattern; of 42 comparisons made only 5 showed an increased risk in the GWVs; there was some evidence of an increased risk of injuries and of mental illness. The disease rates varied greatly between different hospital

systems; for example in the Veterans' System over 31% were affected, compared with 14.1 in the California system and 9.4 in the Department of Defense. Thus there is no real evidence for the claim that GWVs are at increased risk of hospitalisation.

Discussion

Overall there appears to be little evidence for an increased risk of hospitalisation, both from all causes and also from specific diagnoses. The studies carried out on pre-war hospitalisation suggest that the deployed troops were less likely to have been hospitalised, giving credence to the idea of a healthy warrior effect. Studies carried out on post-war hospitalisation generally show no overall effect once adjustments for confounders have been made. Several studies made a large number of comparisons and inevitably some positive results occurred. These were relatively few in number, little more than would be expected by chance, and with no consistent pattern. Indeed they are outnumbered by significant results suggesting that the deployed troops were less likely to have been hospitalised for a variety of illnesses – again the healthy warrior effect.

Almost all of the studies simply equated deployment with exposure and this is obviously a limitation. One study attempted to measure the extent of exposure to potential hazards, using knowledge of deployment positions and estimating the movement in the air of the hazardous substances, and in that study there was no evidence of a dose-related effect.

Quality of the primary studies

Ascertainment and bias

The lack of a national system in the United States for recording hospitalisation means that most of the studies relied on records from the Department of Defense hospitals. Consequently only those veterans who remained in service until the end of the study period were included in such studies. Presumably those who leave the service are more likely to be in poor health, and liable for hospitalisation, than those who remain in the service and hence the hospitalisation rates are likely to be biased downwards. This should affect both the Gulf War and non-deployed veterans and so a differential bias seems unlikely. Use of these hospitals also excludes reservists and members of the National Guard. Gray¹¹ attempted to include these other groups by taking databases from the Veterans' Administration and the California hospital system but found almost insuperable difficulties due to the lack of denominator data.

A more serious source of bias arises from the introduction in June 1994 of the Comprehensive Clinical Evaluation Program (CCEP), which offered thorough clinical examinations and evaluations to Gulf War Veterans who sought them. Knoke and Gray¹³ attempted to investigate the effect of this program and concluded that it increased the hospitalisation rates among the GWVs substantially; adjustment is therefore required to take account of this if the follow-up period extends beyond the introduction of the CCEP. In the two studies which looked at this, an apparent effect was removed by this adjustment.

Outcome measure

Hospitalisation is a clearly defined outcome but there are no universal criteria for admission. Clearly hospitalisation will only identify the more serious cases and cannot be completely equated with morbidity, but it is perhaps a more objective measure than self-reported symptoms which are commonly used in other types of study. The media attention given to the alleged problems of veterans may have increased the rate of hospitalisation. This would have acted to increase the rate in the GWVs, however, and allowing for this, if it were possible, would reduce even further their rates, weakening the case for an effect. Looking at hospitalisation for a variety of different illnesses leads to a multiple comparison problem and studies made no allowance for this, even though some made a very large number of comparisons. By chance we would expect some positive and some negative associations and would hope that there was a consistent pattern before reaching any firm conclusions. It is also worth noting that inevitably these studies look at causes of hospitalisation in the fairly short term. Diseases which may have an effect on a longer time scale, such as most forms of cancer, could not be included as causes of hospitalisation in these studies.

Confounding and interactions

The studies controlled for a variety of demographic variables, principally sex, age, race, marital status, branch of service, occupation, rank, pay grade and length of active military service. Where possible an indicator variables based on pre-war hospitalisation was also included as an important predictor; this acted essentially as an indicator of health status at the time when decisions were made about deployment.

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 little evidence for an increased risk of hospitalisation among the troops deployed to the Gulf. There is some evidence that the troops deployed were in better health at the time of deployment and therefore it is possible that a healthy warrior effect could mask an increased risk, but these studies suggest that this effect could not be large. The lack of complete data outside the Department of Defense hospitals is a serious limitation and the introduction of the CCEP causes design problems for further studies which might look at admissions related to diseases with a much longer period of incubation.

ACKNOWLEDGMENTS

This project was funded by the MOD through the Medical Research Council.

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Hospitalisation

First author	Study design	Sample	Study period	Main outcomes	Main results	Confounding	Comments
Bell 2000	Retrospective cohort	675,626 active duty US Army soldiers	Jan1980 – August 1990	Deployment to the Gulf War	Deployers less likely to have been hospitalised prewar 1989 OR 0.97 (0.95, 0.98) 1990 OR 0.93 (0.91, 0.95) Less likely to be depressed or suicidal	Age Sex Race Education Rank Time in service	Gives information about the health of those deployed compared to those not-deployed but gives no results on the effect of deployment
Coate 1995	Retrospective cohort	578,492 GWVs 699,792 NDVs	Oct 1 1988 – Sept 30 1992	Total hospitalisation	Standardised rate ratios 1989 0.93 (0.92, 0.94) 1991 1.02 (1.00, 1.03) 1992 0.98 (0.97, 0.99) In 1992 SRR was 1.15 (1.07, 1.23) for mental disorders	age sex occupation race time in service branch of service home of record	Essentially the same study as Gray (1996)
Dlugosz 1999	Retrospective cohort	567,671 GWVs 1,417,325 NDVs	June 1991- Sept 1993	Hospitalisation for mental disorders GWVS divided into combat and support, by period of fighting and remaining period	HRs Alcohol-related 1.04 (1.00 – 1.08) Drug-related 1.29 (1.10 – 1.52) Organic disorders 0.96 (0.76 – 1.22) Mood disorders 0.77 (0.69 – 0.87) Schizophrenia 0.94 (0.75 – 1.17) Neurotic disorders 0.69 (0.59 – 0.82) Personality disorders	Age Gender Service branch	Various differences between results for different categories of GWVs e.g. in male combat troops organic disorders showed a significant effect of NDVs But many comparisons made

					0.82 (0.74 – 0.90) Adjustment disorders 0.90 (0.85 – 0.95) Acute reaction to stress 1.45 (1.08 – 1.94) Others 0.95 (0.84 – 1.07)		
Gray 1996	Retrospective cohort	547076 vets 618335 non-deployed vets (random sample)	Oct 1 1988 – July 31 1990 Aug 1 1991- Dec 31 1991 Jan 1 1992 – Dec 31 1992 Jan 1 1993 – Sept 30 1993	Hospitalisation in facilities operated by Defense dept Only covers those who stayed on active service until Sept 1993	Stated that no difference in risk after war (no figures given) 42 comparisons (14 ICDs, 3 periods) 16 sig differences, 5 had vets at greater risk These include neoplasms in 1991 & mental disorders in 1992 & 1993 esp to do with drug & alcohol use	Sex Age group ethnic group pre-war hospitalisation marital status rank occupation salary branch of service length of service	Tries to control for selection bias i.e. fittest deployed Overall little evidence for an effect
Gray 1999	Retrospective cohort	Deployed veterans classified by exposure to a munitions destruction site 224,804 not exposed 75,717 low dose 48,770 subclinical exposure (subdivided into	March 10 1991 – Sept 30 1995	Hospitalisation in facilities operated by Defense dept I presume it only covers those who stayed on active service until Sept 1995 but not sure	All causes – little effect Risk ratios: uncertain low vs not exposed 0.95 (0.93, 0.97) level 1 vs non-exp 0.96 (0.92, 0.99) Level 2 vs non-exp 0.93 (0.90, 0.96) level 3 vs non-exp 1.02 (0.96, 1.08)	Sex Age group ethnic group pre-war hospitalisation marital status rank occupation branch of service	Exposure estimated by plume analysis Broad conclusion is that there is no evidence that exposure to the nerve agent plumes affected post-war morbidity

		3)			Analysis repeated for 15 subgroups 19/60 comparisons sig no obvious pattern		
Gray 2000	Retrospective cohort	Similar to Gray 1996 but extended to cover those who left the service 652,979 vets 652,922 NDV	Aug 1 1991 – Dec 31 1994	used proportional morbidity ratios for 14 categories in each of 3 records systems	16/42 sig 5 intervals suggested vets at greater risk Lower risk for infection & parasitic disease in all 3 systems Some evidence of higher risk for injury & poisoning & mental disorders	age sex race	Wanted to do full analysis of all vets But hospital records systems not good enough Used 3 databases – DoD, VA and California Not convinced of data quality outside DoD data
Knoke 1998	Retrospective cohort	717,223 GWVs 1,291,323 NDVs	Aug 1 1991 – 31 – 3 1996	Hospitalisation for testicular cancer	Hazard ratio 1.05 (0.86 – 1.29) Some limited evidence of an initial increase consistent with Gray 1996	race/ethnicity age occupation rank salary marital status length of service branch of service	DoD hospitals only prompted by findings of Gray 1996 showing an early increase Attributed here to regression to the mean, not very convincingly
Knoke 1998	Retrospective cohort	552,111 GWV 1,479,751 NDV Active duty personnel only (for DoD hospitals) Not clear if they had to be in the service until the end	Aug 1 1991 – Mar 31 1996 Sub-analysis to May 31 1994	Hospitalisation in which one of the diagnostic categories was 'unexplained illness' – 10 most common of these were selected Most common	Risk ratio 1.06 (1.03 – 1.09) Plots of prob of hospitalisation by deployment status follow near-identical pattern until mid 1994 & then GWV prob increases	race rank branch of service salary Other considered e.g. age, marital status	CCEP effect investigated Suggestion that apparent increased risk is due to vets using this for evaluation – not for real hospitalisation Censoring those who took part

				– unspecified viral infection			reduce risk ratio to 0.93 (0.91 – 0.96) Possibly under-estimates true value
Smith 2000	Retrospective cohort	551,841 GWV 1,478,704 NDV	Aug 1 1991 – July 31 1997	Hospitalisation for systemic lupus erythomatosus, amyotrophic lateral sclerosis, fibromyalgia	SLE RR 0.94 (0.65, 1.35) ALS RR 1.66 (0.62, 4.44) RR 1.23 (1.05, 1.43)	Sex Age Service pre-war hospitalisation marital status race	Analysis by survival analysis to allow for those who left service as hospitalisation data reliable only in DoD Risk of fibromyalgia slightly greater in GWV Risks changed with start of Comprehensive Clinical Evaluation program

Not included:

Bell EA, Wartime stressors and health outcomes: women in the Persian Gulf War, *J. Psychosocial Nursing*, 1998; **36**: 19-25

It contains no data and the cases were self-selected

Notes

By hospitalisation is meant whether hospitalised or not – not length of stay