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BRIEF COMMUNICATION

Risk factors for continued illness among Gulf War veterans: a cohort study

M. HOTOPF,[1] A. DAVID, L. HULL, V. NIKALAOU, C. UNWIN AND S. WESSELY

From the Gulf War Illness Research Unit, Guy's King's and St Thomas' School of Medicine, King's College, London

ABSTRACT

Background. There are no prospective cohort studies of prognostic factors on the outcome of Gulf War veterans. We aimed to test the hypotheses that Gulf War veterans who were older; had more severe symptoms; had more exposures during deployment; had increased psychological distress and believed they had 'Gulf War syndrome' would experience greater fatigue and poorer physical functioning at follow-up.

Method. Gulf War veterans who responded to an earlier retrospective cohort study were followed with a postal survey. More symptomatic individuals were oversampled. Outcome was measured on the Chalder fatigue questionnaire, the General Health Questionnaire and the Medical Outcome Study Short-Form 36.

Results. Of those surveyed, 73·8% responded. We found some evidence for four of the five hypotheses. More self-reported exposures at baseline were not associated with poorer outcome, but older people, those with more severe symptoms at baseline, those with psychological distress and who believed they were suffering from 'Gulf War syndrome' had more fatigue at follow-up. Officer status was associated with a better outcome. A similar lack of association was found for exposures and physical functioning and GHQ-12 score. 'Gulf War syndrome' attribution was associated with a worse outcome for GHQ-12 and physical functioning even after controlling for severity of symptoms at baseline.

Conclusions. This study suggests that while multiple vaccination and military exposures are important risk factors for the onset of symptoms in Gulf War veterans, these are not important risk factors for persistence of such symptoms. Instead the severity of the initial symptoms; psychological distress and attributions may be more important determinants of outcome.

INTRODUCTION

A number of large epidemiological studies that have followed veterans of the 1990–91 Gulf War have indicated higher rates of physical symptoms and complaints than comparable military comparison groups (Fukuda *et al*. 1998; Proctor *et al*. 1998; Gray *et al*. 1999, 2002; Unwin *et al*. 1999; Cherry *et al*. 2001). Few studies have followed veterans at more than one time point to determine outcome in Gulf War veterans. In a previous paper (Hotopf *et al*. 2003) we reported the results of a cohort study of UK Gulf War veterans who had been followed once in 1997 and again in 2001. We reported that as a group Gulf War veterans continued to experience high levels of fatigue, psychological distress, and physical symptoms. While scores for most symptoms fell modestly over this time period, there was a worsening in physical

[1] Address for correspondence: Dr Matthew Hotopf, Department of Psychological Medicine, Guy's, King's and St Thomas' School of Medicine, 103 Denmark Hill, London SE5 8AZ.
(Email: m.hotopf@iop.kcl.ac.uk)

functioning measured on the Medical Outcomes Study Short-Form 36 (SF-36) (Ware & Sherbourne, 1992). Compared to two comparison groups (veterans of peace-keeping duties in Bosnia and non-deployed UK military personnel) Gulf War veterans remained considerably sicker on all health outcomes except physical functioning. The previous descriptive analyses we performed have not attempted to describe why some Gulf War veterans remained unwell, while others improved: this is the focus of the present paper.

There is no accepted case definition of Gulf War illness. While one uncontrolled study demonstrated a distinct syndrome apparently related to service in the Gulf (Haley *et al.* 1997), most studies that have used this design have failed to demonstrate a set of factors or clusters unique to Gulf War veterans (Ismail, 2001; Wessely, 2001). Fatigue is one of the most commonly reported symptoms in ill Gulf War veterans (Unwin *et al.* 1999). Among civilians with chronic fatigue a number of risk factors have been identified for poor prognosis, including increasing age, more severe illness, psychological distress or depression, and a strong belief that the illness has a physical cause (Joyce *et al.* 1997).

The aim of this paper was to test a series of hypotheses regarding the outcome of fatigue (our primary outcome) in Gulf War veterans. We hypothesized that fatigue at stage 2 would be higher in veterans who were: (*a*) older; (*b*) had higher fatigue scores; (*c*) had psychological distress; (*d*) reported more exposures; and (*e*) reported that they were suffering from Gulf War syndrome, at stage one.

METHOD

Participants

We followed military personnel who participated in our original study on health effects of deployment to the Gulf War ($N=8195$). For the purposes of the present study we focus only on those individuals who served in the Persian Gulf War between 1 September 1990 and 30 June 1991. The original sampling strategy is described in our previous papers (Unwin *et al.* 1999), but essentially consisted of a random sample of all Gulf War veterans, with over-sampling of females. The sampling frame for the present study was composed of all participants who completed stage one. We used a random stratified sampling technique to select participants into the next stage. All females were selected. Because we wanted to determine the outcome of individuals who were significantly symptomatic at baseline, we stratified the sampling on the severity of fatigue at stage one. In the absence of a universally approved case definition of Gulf War illness, fatigue measured at stage one on a validated scale was chosen as the stratifying variable (Chalder *et al.* 1993). The selection process included all male veterans with a fatigue score of $\geqslant 9$ ($N=511$); a 50% sample of veterans with mid-range fatigue scores of 4–8 ($N=484$); and an approximately one in eight sample of veterans with fatigue scores <4 was selected in order to represent asymptomatic individuals ($N=250$). The first mailing of the questionnaire was sent in June 2001. Three further mailings were performed in August and November 2001, and March 2002. We used multiple tracing methods described in our previous paper (Hotopf *et al.* 2003).

Questionnaire

For the present study we focused on three main outcomes – fatigue measured on the Chalder fatigue scale (Chalder *et al.* 1993); psychological distress measured on the 12-item general health questionnaire (GHQ-12) (Goldberg & Williams, 1988); and physical functioning measured on the Medical Outcome Studies Short Form-36 (SF-36) scale (Ware & Sherbourne, 1992; McHorney *et al.* 1993), which give measures of disability. In the absence of an accepted case definition of Gulf War illness, and the absence of a reproducible syndrome, we chose fatigue as the principal outcome for this study.

Analysis

For all three outcomes we assessed the role of variables measured at stage one on the outcome at stage one using multiple regression analysis controlling for baseline scores of the questionnaire. In order to compare the strength of effect sizes for the three outcomes the outcomes were standardized by subtracting the mean score and dividing by the standard deviation. This allows direct comparison between regression coefficients for the three scales. Because both the Chalder Fatigue Scale and the GHQ-12 have

Table 1. *Predictors of fatigue, GHQ-12 score and SF-36 physical functioning*

	Fatigue		GHQ score		Physical functioning	
	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*
			Model 1: sociodemographic variables at stage 1			
Variance explained by model 1	$r^2=0{\cdot}04$		$r^2=0{\cdot}03$		$r^2=0{\cdot}06$	
Male sex	0·11 (−0·04, 0·26)	0·16	0·10 (−0·07, 0·27)	0·24	−0·11 (−0·28, 0·05)	0·18
Age	0·011 (0·001, 0·02)	0·01	0·010 (−0·0002, 0·021)	0·06	−0·03 (−0·04, −0·01)	<0·001
Army *v.* Royal Navy	−0·07 (−0·29, 0·15)	0·5	0·05 (−0·22, 0·32)	0·7	0·08 (−0·14, 0·29)	0·5
Army *v.* RAF	−0·01 (−0·19, 0·16)	0·9	−0·05 (−0·24, 0·13)	0·6	0·09 (−0·08, 0·27)	0·3
Married	−0·09 (−0·24, 0·08)	0·3	−0·15 (−0·30, 0·005)	0·06	0·16 (0·02, 0·30)	0·03
Still serving	0·19 (0·05, 0·32)	0·006	0·14 (0·01, 0·28)	0·03	−0·12 (−0·24, 0·004)	0·06
Officer	−0·40 (−0·55, −0·25)	<0·001	−0·37 (−0·54, −0·20)	<0·001	0·45 (0·28, 0·61)	<0·001
			Model 2: Model 1 variables + severity at stage 1			
Variance explained by model 2	$r^2=0{\cdot}43$		$r^2=0{\cdot}34$		$r^2=0{\cdot}47$	
Score on questionnaire at stage 1	0·12 (0·11, 0·13)	<0·001	0·09 (0·08, 0·10)	<0·001	0·04 (0·03, 0·04)	<0·001
			Model 3: Model 1 & 2 variables + exposure variables at stage 1			
Variance explained by model 3	$r^2=0{\cdot}46$		$r^2=0{\cdot}37$		$r^2=0{\cdot}48$	
Believes has GWS	0·20 (0·03, 0·38)	0·03	0·28 (0·09, 0·48)	0·004	−0·36 (−0·54, −0·18)	<0·001
Total exposures	−0·0012 (−0·01, 0·01)	0·9	−0·0007 (−0·01, 0·01)	0·9	−0·0005 (−0·01, 0·01)	0·9
Vaccines (quintiles)	−0·005 (−0·05, 0·04)	0·8	−0·01 (−0·05, 0·03)	0·5	0·01 (−0·03, 0·05)	0·6
GHQ case	0·13 (−0·01, 0·27)	0·07	NA	NA	−0·11 (−0·23, 0·00)	0·05

RAF, Royal Air Force; GWS, Gulf War syndrome; GHQ, General Health Questionnaire; NA, not applicable.

accepted cut-off scores that define being a 'case' we also performed an analysis where we assessed risk factors for remaining a case between stages 1 and 2 using logistic regression analysis.

Because of the large number of independent variables, we used a hierarchical approach to the regression analyses, where three models were devised. The first (model one) entered all sociodemographic variables together (age, sex, rank, service (e.g. Royal Navy, Army, Royal Air Force), marital status at stage 1). Model 2 entered model 1 variables, plus severity of the symptom under study at stage 1. Model 3 entered model 1 and 2 variables, plus exposure related variables (total exposures reported while in theatre; total vaccinations; belief that the individual suffered from Gulf War syndrome; and being a 'case' on the GHQ-12 at stage 1). In this approach we anticipated that individuals with more severe clinical symptoms at stage 1 would remain ill longer irrespective of exposure status and that any effect of exposure status should be controlled for original illness severity. In order to determine the prognosis of individuals who scored above threshold on the GHQ-12 and fatigue scale, we performed a similar analysis using logistic regression analysis, where the outcome was remaining symptomatic. Finally, for each outcome, we performed stepwise regression or logistic regression analysis entering all the variables included in the full model (i.e. model 3 – sociodemographics, baseline scores and exposure variables) setting alpha at 0·2. All analyses were performed in Stata 6 and used sampling weights and robust standard errors in order to take account of the stratified sampling we used.

In a separate *post hoc* analysis performed in order to determine whether specific deployment related exposures were associated with poor outcome, we entered each exposure variable from a list of 29 deployment related exposures was entered into a regression analysis (logistic or multiple, depending on the outcome) which controlled for demographic variables and stage 1 score. A stepwise regression analysis was performed with *P* set at 0·2, to determine whether any of the exposure variables acted as independent variables.

RESULTS

Our previous paper has described the response rates and patterns of non-response in detail (Hotopf *et al.* 2003). We achieved an overall response rate of 73·8% among the Gulf cohort. Response rates were lower in males, younger participants, and those who were unmarried. Non-responders tended also to have rated their health as poorer at stage 1 in terms of physical functioning, but were slightly less likely to have been cases on the GHQ-12. There were no differences between responders and non-responders according to whether they were still in the military at stage 1, and there were no differences in levels of fatigue.

Table 1 shows the results of regression analyses for fatigue, GHQ-12 score and SF-36 physical functioning scores at stage 2. All predictors were measured at stage 1. The dependent variables in each of these regression analyses were standardized such that the mean value is zero and the standard deviation is 1. This means that a regression coefficient of 0·5 indicates that individuals with the predictor variable in question are predicted to have a mean score 0·5 standard deviations higher than an individual without the attribute. For continuous (or interval) variables such as age, the coefficient refers to the change each unit on that scale (e.g. year) leads to in standard deviations of the outcome variable. For the SF-36 physical functioning score, a higher score indicates better functioning, and therefore positive coefficients are a sign that the variable is associated with improved physical functioning. These results indicate that for all three outcomes, increasing age is associated with poorer health, and officer status is associated with better health. Individuals who had remained in the armed forces at stage 1 tended to have better health at stage 2. In addition, for GHQ-12 score and SF-36 physical functioning, being married appears to have been protective. For all three outcomes, score on the scale at stage 1 was a powerful predictor on stage 2 scores, and including stage 1 scores was responsible for most of the variance explained. For both SF-36 and fatigue, being a 'case' on the GHQ-12 at baseline was associated with worse health at stage 2, although the effect was modest. Finally, individuals who thought they had Gulf War syndrome at stage 1 tended to have poorer health. Total exposures and vaccines reported at stage one were not predictors of any of these outcomes.

Table 2. *Predictors of remaining fatigued*

Variable	*N* exposed (% cases)	OR (95% CI)
Model 1: Demographic variables		
Age (years: 23–67)		1·02 (0·99–1·04)
Gender		
Female	92 (66·3)	
Male	717 (72·3)	1·2 (0·66–2·0)
Rank		
Other ranks	690 (72·0)	
Officers	90 (64·4)	0·68 (0·38–1·2)
Service		
Army	657 (73·7)	1·0
Royal Navy	62 (54·8)	0·37 (0·20–0·69)
Royal Air Force	90 (67·8)	0·84 (0·49–1·4)
Serving status		
Still serving	413 (70·2)	1·0
Left armed forces	379 (73·6)	1·0 (0·74–1·5)
Marital status		
Single/ex-married	207 (70·5)	
Married/cohabiting	597 (71·7)	1·1 (0·73–1·6)
Model 2: Model 1 variables plus severity at stage 1		
Fatigue at stage 1 (0–39)		1·23 (1·17–1·29)
Model 3: Models 1 & 2 variables, plus exposures at stage 1		
GHQ case		
Non-case	232 (57·3)	
Case	564 (77·7)	1·6 (1·0–2·5)
Total exposures (0–29)		1·01 (0·98–1·07)
Self-report Gulf War syndrome		
No	394 (64·5)	
Yes	238 (85·3)	2·0 (1·2–3·4)
Quintiles of vaccines (1–5)		1·03 (0·90–1·2)

Tables 2 and 3 show the risk factors for remaining a case on the fatigue scale and GHQ-12 respectively. For fatigue, the demographic variables did not greatly predict persistence, however individuals from the Royal Navy had a better outcome than those serving in the Army or RAF. Baseline fatigue was a strong predictor of fatigue at stage 2. Being a 'case' on the GHQ-12 at baseline was also a predictor, as was believing that one suffered from Gulf War syndrome. For persistence of GHQ-12 status, the pattern was slightly different. We found that older individuals were more likely to remain cases, as were men. There was no effect of branch of the armed forces. Baseline GHQ-12 status remained predictive. Self-reported Gulf War syndrome was the only exposure risk factor which was predictive.

In the *post hoc* analysis for fatigue, seven of the 29 exposures (smoke from oil-well fires

Table 3. *Predictors of remaining a case on GHQ-12*

Variable	*N* exposed (% cases)	OR (95% CI)
Model 1: Demographic variables		
Age (years: 23–67)		1·04 (1·00–1·07)
Gender		
Female	519 (68·6)	
Male	84 (54·8)	2·0 (1·1–3·6)
Rank		
Other ranks	502 (67·5)	
Officers	75 (57·3)	0·56 (0·29–1·1)
Service		
Army	497 (67·6)	1·00
Royal Navy	38 (68·4)	0·83 (0·34–2·0)
Royal Air Force	68 (58·8)	0·74 (0·40–1·3)
Serving status		
Still serving	294 (63·3)	1·0
Left armed forces	300 (70·0)	1·3 (0·87, 2·0)
Marital status		
Single/ex-married	170 (69·4)	
Married/cohabiting	429 (65·5)	0·64 (0·39–1·04)
Model 2: Model 1 variables plus severity at stage 1		
GHQ at stage 1 (0–36)		1·12 (1·07–1·17)
Model 3: Models 1 & 2 variables, plus exposures at stage 1		
Total exposures (0–29)		0·99 (0·94–1·04)
Self-report Gulf War syndrome		
No	267 (59·2)	
Yes	197 (76·1)	1·8 (1·1–3·1)
Quintiles of vaccines (1–5)		0·95 (0·81–1·1)

(OR = 1·3); burning rubbish or faeces (OR = 1·6); chemical agent resistant paints (OR = 1·4); seeing dead animals (OR = 1·3); seeing dismembered, burnt or disfigured bodies (OR = 1·3); wearing NBC suits other than during training (OR = 1·4); and hearing chemical weapons alarms (OR = 1·5)) were associated with symptom persistence at $P < 0{\cdot}05$. Four of the 29 exposures were associated with persistence on the GHQ-12: smoke from oil-well fires (OR = 1·4); burning rubbish or faeces (OR = 1·4); paints and solvents (OR = 1·4) and consuming local food other than food provided by the Armed Forces (OR = 1·4). For none of the statistically non-significant exposures were the odds ratios $> 1{\cdot}5$, suggesting that it is unlikely that we missed powerful effects of rare exposures we were under-powered to detect.

Table 4 summarizes the results of stepwise regression and logistic regression analyses. For each outcome, all the variables in model 3 described in Tables 1–3 were entered. We set the level of statistical significance at 0·2, and report associations if $P < 0{\cdot}1$. As expected, outcome at stage 2 is most strongly predicted by the score on the same questionnaire at stage one. There is a weak association between increasing age and fatigue and physical functioning. There was a tendency for officers to have lower scores on the fatigue questionnaire and GHQ. The pattern for male gender was inconsistent – with men generally having lower scores on the fatigue scale, but a worse outcome if they were cases on the GHQ-12 at stage one. For fatigue score, physical functioning score and fatigue persistence being a case on the GHQ-12 at stage one was associated with a worse outcome. For all outcomes except GHQ-12 score, the belief that one was suffering from Gulf War syndrome was associated with a worse outcome.

DISCUSSION

The aim of this study was to determine predictors of persistent illness. We chose three main outcomes measured on validated questionnaires, however we based our *a priori* hypotheses on the outcome of fatigue, and this should be considered our primary outcome. For this outcome we were able to find some support for four of our hypotheses. There was a modest association between fatigue score and increasing age, but this was of marginal statistical significance. Unsurprisingly, fatigue score at stage one was strongly associated with both fatigue score and fatigue persistence at follow-up. We found a modest association between fatigue and fatigue persistence and psychological distress at stage one. Finally, there was a clear association between the belief that the individual had Gulf War syndrome and fatigue score and persistence at follow-up. The pattern of risk factors was slightly different for the other two outcomes, but we found a general pattern that officers had a better outcome than other ranks; that severity at baseline predicted severity at follow-up; and the belief that one was suffering from Gulf War syndrome was a risk factor for worse physical functioning, higher fatigue score, and fatigue and GHQ-12 persistence. Our analysis of individual deployment-related exposures indicates that no single risk factor was strongly associated with poor outcome.

We achieved a satisfactory follow-up rate of 74% for this study. However, it is still possible that unknown biases may have affected the

Table 4. *Summary of independent predictors in full models using forward stepwise regression* (P *values are shown in parentheses*)

Predictor	Outcome				
	Fatigue score	GHQ score	Physical functioning	Fatigue persistence	GHQ persistence
Male	Better (0·02)				Worse (0·05)
Increasing age	Worse (0·07)		Worse (0·05)		
Officers	Better (0·07)	Better (0·02)			
Royal Navy *v.* Army				Better (0·05)	
Greater severity at stage one	Worse (<0·001)	Worse (<0·001)	Worse (<0·001)	Worse (<0·001)	Worse (<0·001)
GHQ case at stage one	Worse (0·07)		Worse (0·04)	Worse (0·04)	
Belief in Gulf War syndrome	Worse (0·02)		Worse (<0·001)	Worse (0·006)	Worse (0·02)

results we present here. We relied on self-report questionnaires, which may be subject to recall biases. Finally, we tested multiple associations between five outcomes and eleven predictors, so there is scope for type I error. However, we developed *a priori* hypotheses for the principal outcome (fatigue), and followed a predetermined analytic strategy.

Our findings support four of the five hypotheses we tested with regard to fatigue, and indicate an association between higher rank and better fatigue outcomes. How do these findings fit into our understanding of these outcomes in civilian populations? First, they suggest that exposures associated with the onset of illness are not necessarily risk factors for a poor prognosis. Our original study indicated that veterans who report more exposures have more symptoms (Unwin *et al.* 1999). This could be due to recall bias, or to more distinct biomedical explanations between hazards experienced during deployment and subsequent illness. However, these hazards do not appear to be associated with poorer prognosis either individually or when total exposures are considered. This may echo the literature on chronic fatigue occurring after known physical risk factors such as glandular fever – initial severity of the illness (including immune response) may be associated with more severe acute symptoms or onset of symptoms, but illness severity does not seem to be a predictor of subsequent outcome (White *et al.* 2001; Candy *et al.* 2003).

Secondly, we found an association between both fatigue and physical functioning and previous psychological distress on the GHQ-12. This is in accordance with work on chronic fatigue and physical disability: having depressive symptoms seems to predict a poor outcome for other symptoms – possibly due to reporting bias, but also possibly due to changed behaviour (Joyce *et al.* 1997). Depressive symptoms may lead to behavioural change and deconditioning which in turn cause worsening fatigue or physical disability.

Finally, we found that attribution that the individual was suffering from Gulf War syndrome played a role in maintaining all the outcomes we assessed. This association held even after controlling for severity of the initial illness, demographic variables and total exposures. In chronic fatigue syndrome there is extensive evidence that attribution has an important effect on outcome. Attributions which explain the fatigue in a narrow physical light are associated with a poor outcome. Cognitive behaviour therapy (CBT) (at least when provided in specialist centres using experienced therapists) has been shown to be effective in chronic fatigue syndrome (Whiting *et al.* 2001). It is important to note, however, that the 'active ingredient' of such therapy is not changing the original causal attribution, but the sufferer's belief that symptoms relating to physical or mental exertion are a sign that such exertion causes harm (Deale *et al.* 1998).

For veterans of the Gulf War, the concept of Gulf War syndrome is closely linked to images of exposure to toxic hazards, and the typical narrative is of previously fit military personnel

who have been irreparably damaged by their experiences. The group who endorsed the label 'Gulf War syndrome' have a poorer outcome, and it is possible that this is in part explained by their seeing symptoms as indicators of sinister and irreparable underlying pathology. While it is tempting to draw parallels with chronic fatigue syndrome, the conditions have important differences, not least the relatively good physical functioning of Gulf War veterans as a group (Unwin *et al.* 1999). We have insufficient knowledge of the behavioural consequences which might follow from a belief that one has 'Gulf War syndrome'. A recent trial of cognitive behaviour therapy for symptomatic Gulf War veterans showed only a marginal benefit for CBT (Donta *et al.* 2003). We have argued elsewhere that the lack of a treatment effect could have been due to an inadequate model of the cognitive and behavioural perpetuating factors in Gulf War illness (Hotopf, 2003).

The results we present here suggest that further, more detailed exploration of the attributions in Gulf War veterans may be a fruitful path to follow in understanding the continued illnesses of many veterans. Such work should aim to go inside the 'black box' of the label of 'Gulf War syndrome', and describe the constellation of attributions which this label undoubtedly contains. Attributions of the many individuals who do not necessarily believe they have Gulf War syndrome, but have significant symptoms attributed to service in the Gulf should be explored. The behavioural consequences of such attributions also needs further exploration – if a fear avoidance model, which might be amenable to CBT, is to be proposed, what avoidant behaviours are present in Gulf War veterans? Attributions may be strongly influenced by social influences such as the media as well as social networks. These influences also require exploration in future research on psychosocial understandings of Gulf War illness. Finally, our data suggest that detailed qualitative studies to understand the experiences of deployment, and the fears and concerns which may arise out of this extraordinary life event, should be a routine part of military health studies. We are currently planning to follow the veterans of the recent war in Iraq, and such embedded qualitative work is already under way.

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