Health and exposures of United Kingdom Gulf war veterans. Part II: The relation of health to exposure

N Cherry, F Creed, A Silman, G Dunn, D Baxter, J Smedley, S Taylor, G J Macfarlane

Abstract

***Objectives*—To investigate whether, in personnel who served with the United Kingdom forces in the Gulf war, self reported exposures were related to symptoms in a way that was consistent, specific, and credible.**

***Methods*—Responses to symptom and exposure questionnaires, completed 7 or more years after the war, were collected from 7971 subjects deployed in the Gulf, from two exposed cohorts, in a study with an overall response rate of 85.5%. Exposures were considered in three groups, those outside the control of the subjects, the use of prophylaxis, and indicators of susceptibility. Health indices derived from symptom questionnaires were related to reports of 14 exposures in these three groups in a series of multiple regression analyses to allow for confounding. The relation of exposure to complaints of widespread pain and to symptoms suggesting peripheral neuropathy were examined by logistic regression.**

***Results*—Consistent but weak correlations between exposures and with health effects were found in independent analyses of the two (main and validation) cohorts. Three exposures outside the control of the subject, the number of inoculations, the number of days handling pesticides, and the days exposed to smoke from oil fires, were consistently and independently related to severity. The number of inoculations was also associated with higher scores on a factor weighted on symptoms associated with skin and musculoskeletal complaints. The number of days handling pesticides related particularly to scores on a neurological factor and to symptoms consistent with toxic neuropathy.**

***Conclusion*—The relations between exposures and ill health were generally weak. Consistent, specific, and credible relations, warranting further investigation, were found between health indices and two exposures, the reported number of inoculations and days handling pesticides.**

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Centre for Occupational and Environmental Health, University of Manchester, UK
N Cherry
D Baxter
J Smedley

School of Psychiatry and Behavioural Science
F Creed

Arthritis Research Campaign Epidemiology Unit
A Silman
S Taylor

Biostatistics Unit
G Dunn

Unit of Chronic Disease Epidemiology
G J Macfarlane

Correspondence to:
Dr N Cherry, Department of Public Health Sciences, University of Alberta, 13–103 Clinical Sciences Building, Edmonton, Alberta, Canada T6G 2G3
ncherry@ualberta.ca

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Men and women who were deployed to the Gulf war reported more symptoms than comparable service personnel who did not serve in the Gulf,[1–6] but the cause of such symptoms has not been clearly established.

In particular, there remain questions about whether such ill health can be ascribed, in whole or in part, to specific chemical, physical, infectious, or prophylactic exposures while in the Gulf. This uncertainty stems from the absence of adequate records of exposure; record keeping during the Gulf war was less than optimal even for exposures susceptible to objective measurement—such as the number of inoculations received or the use of pesticides. Other exposures—such as pyridostigmine bromide (nerve agent prophylaxis or NAPs) tablets or use of insecticides on the skin—could not easily be recorded objectively as the choice of taking the tablet or using the product was within the control of each person. Although in the past some attempts have been made to investigate ill health by classifying troops on likely exposures derived from official records,[7] such a procedure is time consuming, of limited coverage, and may bear little relation to the experiences of individual service men or women. Self reported exposures may better reflect real events but are susceptible to bias in perception, recall, or reporting and may be influenced by personal characteristics of the individual person; those who tend to complain may report many symptoms and many exposures whereas the more stoical report neither. Perhaps because of these uncertainties about self reported exposures, few studies have reported comprehensive analyses of the relation between exposures in the Gulf and ill health and this incomplete information makes it difficult to judge whether findings between studies are consistent.

Unwin *et al*[3] reported the relation between symptoms and exposures common both to the Gulf and to other deployments. They concluded that although the reporting of exposures was associated with increased reporting of symptoms this was not confined (except for reports of inoculations) to those who went to the Gulf and seemed to be non-specific; those with symptoms were more likely to report a wide variety of exposures. A similar lack of specificity was noted in some, but not all, studies of United States veterans.[1 8–10]

Some relations that might be biologically plausible have been reported. Among United States troops deployed from Germany at the end of the Gulf war, distance from an oil well fire was related to subsequent cough and shortness of breath soon after return from the Gulf.[11] In a previous report of United Kingdom

service personnel who went to the Gulf, the likelihood of a poor health outcome increased with the number of inoculations.[3] In Canadian veterans non-routine immunisations were related to some health outcomes (including chronic fatigue and cognitive dysfunction) but not others (anxiety, fibromyalgia).[2] In a study of sick and well veterans. Haley and Kurt[12] found associations between symptoms suggestive of neurological dysfunction and self reports of chemical exposures. Proctor *et al* predicted several relations between exposures and ill health, and among these, found one between exposure to pesticides and neurological and musculoskeletal symptoms in 252 United States veterans.[13] In a study of Danish Gulf war veterans[14] long term gastrointestinal symptoms occurred more often in those reporting that they had been exposed to burning of waste or manure or had used insecticides against cockroaches. In each of these studies, however, the possibility of bias in reporting exposures by those now unwell, or enhanced awareness of symptoms in those who had received exposures, could not be excluded.

Several studies have attempted to assess the extent to which bias may have occurred in the reporting of either exposures or ill health by Gulf war veterans. It was found that self referrals to United States programmes for the medical assessment of veterans increased immediately after episodes of intense media interest.[15] A further study, with limited data, was unable to show any effect of such media interest on the type of exposure reported.[16] This study, of 939 Gulf war veterans from the north west United States, found evidence of overreporting of some exposures, but importantly, no difference in the reliability of reporting exposures between those with and without symptoms.[16] A small study, of 59 reservists who served in the Gulf, found greater recall of traumatic events at 2 years than at 1 month after return; this was found particularly in those who, at 2 years, reported more symptoms of post-traumatic stress disorder.[17] There is further evidence that the reporting of symptoms may not be stable over time,[10 16] but in so far as information could be collected, self reported contact with medical services seemed to be equally valid in Gulf and non-Gulf veterans in the United States.[5]

The present study was designed to investigate whether self reported exposures were related to symptoms, and if so, whether such relations were specific, consistent, and credible.

Table 1 Exposure information collected from subjects

Exposures largely outside the control of the subject:
1 Duration in the Gulf between September 1990 and June 1991 (months)
2 Number of inoculations received
3 Days handling pesticides
4 Days living in quarters sprayed with insecticides
5 Days respraying vehicles
6 Days exposured to smoke from oil well fires
7 In combat (yes/no)
8 Lived at any point in tented accommodation (yes/no)
Prophylatic measures under the subject's control:
9 Days taking NAPs tablets
10 Days taking antimalarial tablets
11 Days applying insecticide to skin
Factors reflecting individual susceptibilities:
12 Felt that life was in danger (yes/no)
13 Sought medical attention while in the Gulf (yes/no)
14 Experienced side effects from NAPs tablets (yes/no)

Methods

Two cohorts of service personnel deployed to the Gulf (a main Gulf (n=4755) and a validation Gulf (n=4750) cohort) were identified and contacted with methods described in Part I of this report, which also gives details of information collected on the health of the veterans. Two parts of the health questionnaire used are relevant to the present paper, the symptom questionnaire in which subjects were asked to mark, on a visual analogue scale, the extent to which they had been troubled by each of 95 symptoms during the previous month, and two manikins on which subjects were asked to shade areas to indicate either pain or numbness and tingling.

A second questionnaire was also completed by those sent to the Gulf, giving details of the dates they had been sent to each location and of the exposures that they had experienced while in that area. Specific questions were included on the number and type of inoculations that had been given in preparation for or during deployment, and whether or not the respondent had, in his possession, a record of the inoculations he had received. Further questions considered the number of days during which antimalarial or NAPs tablets were taken, insect repellent was used on the skin, pesticides were handled, accommodation treated with pesticides was slept in, vehicles were resprayed, and smoke from burning oil wells was breathed. In addition questions were asked, for each location, about sleeping in tented accommodation, involvement in combat, feeling that their life was in danger, and side effects from NAPs. A final question asked about the respondent's belief that there had been exposure to poison gas or other chemicals likely to have caused harm. The self reported exposure information used in the present analysis is shown in table 1.

STATISTICAL METHODS

The methods used to derive scores reflecting overall symptom severity and specific patterns of complaint have been described in detail in part I. Briefly, responses on each 10 cm visual analogue scale were allocated, as a symptom score, to 1 of 21 equally spaced segments and a mean symptom score (severity) was calculated for each respondent. As the mean scores were skewed, with most respondents reporting little trouble, the square root of the mean score, which approximated normality, has been used in regression analysis and to test differences between groups.

Factor scores were derived by principal component analysis (with varimax rotation) of the 95 symptoms. Seven orthogonal factors were extracted which, from the weightings given to individual symptoms (see part I), were interpreted (and labelled) as reflecting specific aspects of ill health. In the present paper, multiple regression was used to determine the relation between exposures and the overall severity score and also to the seven specific factors, after

allowing for confounding. The relation between exposures, confounders, and symptoms consistent with toxic neuropathy and widespread pain were examined by logistic regression.

In each analysis exposures were entered either as ranked or binary variables as indicated in table 1. To allow for missing data (see below) and to reduce possible distortions from extreme values, exposures reflecting duration were recoded into five levels (from not at all to more than 2 months) and similarly the number of inoculations were grouped into five levels from none to 10 or more. These recoded values were entered as continuous variables in the regression analysis.

To test for consistency, analyses were carried out separately for the main and validation cohorts, and results are reported where they reached a significance level of 0.001 in the whole cohort and of 0.01 in each of the main and validation cohorts. As confounding by service was likely (respondents from the army recording greater symptom severity even in those not sent to the Gulf) the service was entered as a confounder or the analysis was repeated with restriction to the army alone.

The analysis was conducted in four stages. Correlations among exposure factors were first examined and univariate correlations between each exposure and each health index (severity or specific factor score) were then determined. The crux of the analysis was the multiple regression of each health index on all exposures and other potential confounders. Finally an analysis was carried out to explore whether exposures relating to widespread pain (possibly of somatic origin) differed from those associated with symptoms suggestive of toxic peripheral neuropathy.

MISSING VALUES

On the symptom questionnaire, where five or fewer questions had not been answered (n= 681, 8.5%) the mean score for the completed symptoms was used. For the manikins, a missing response was coded as no pain or no numbness and tingling. On the exposure questionnaire missing data were treated as unknown, with several listed exceptions.

Where a subject reported that he had been exposed but did not give full details, the following rules applied to minimise the number of subjects excluded. For inoculations, those who reported that they had received some, but the number was unknown (n=153), were assigned to the category 4–6, the most frequent category overall. Subjects who completed an exposure questionnaire but did not give their dates in the Gulf (n=168) were assumed to have been there for 3 months, the most common period in those responding completely. For the six factors reflecting days of exposure but where the precise number of days had not been recorded, the following rules were used. Subjects reporting some exposure but giving no information on the number of days (with greatest numbers for antimalarial tablets, n=489, and least for handling pesticides n=27) were assigned to the category most often reported by exposed subjects overall. Those who reported being exposed for at least 14 days (the highest category) but with unknown number were assigned to the category most often used by those who reported at least 14 days of exposure. For exposures where information was collected only for each location, with no overall assessment, a binary factor was created with a positive response at any location constituting a positive response overall; in this way questions on the specific exposure that were missing in all locations would be treated as no exposure.

Those in the navy were not asked about living in tented or sprayed accommodation, handling pesticides, or respraying vehicles. Where these factors have been included in analysis of all three services together, those in the navy were treated as not exposed.

Table 2 Frequency (%) of exposure by service

	Army	*Navy*	*Air force*	*Overall*
Duration >3 months	45.2	61.6	38.7	53.0
Inoculations >6	33.8	18.8	24.3	30.5
Ever (in the Gulf):				
In combat	36.8	42.4	9.4	32.1
In tented accommodation	74.4	—	24.2	57.2
Handled pesticides	8.8	—	4.0	7.0
In sprayed quarters	24.5	—	14.5	20.1
Resprayed vehicles	50.5	—	8.3	37.3
Exposure to oil fire smoke	69.7	54.8	33.8	61.4
Use of prophylaxis >14 days:				
Antimalarial treatment	18.7	45.4	23.2	22.3
NAPs	66.6	57.9	37.1	60.1
Insect repellent	41.5	12.9	20.5	34.6
Ever (in the Gulf):				
Life in danger	77.6	71.0	65.5	74.6
Medical attention	24.8	8.2	21.4	22.4
Side effect from NAPs	32.0	33.7	32.4	32.2
n	5636	809	1526	7971

Results

Response to the study has been described elsewhere. In the main Gulf cohort 4755 were eligible to respond and of these 4076 (85.7%) did so. In the validation cohort 4750 could have responded and 4134 (87.0%) did so. Of those in the Gulf cohorts 76 reported that they had not been in the Gulf (and are excluded from this report), and a further 51 from a comparison cohort of non-deployed service personnel replied that they had served (and are included). The analysis reported in this paper is restricted to those 7971 subjects, from all cohorts, who reported that they had been in the Gulf, completed a questionnaire about their exposures, responded to at least 90 of the 95 symptom questions, and been contacted by any means other than the MOD medical assistance programme (seven subjects). Of these 7971 subjects, 189 (2.4%) were women, 3813 (47.8%) aged <25 years, and 1027 (12.9%) were officers. The largest numbers were from the army 5636 (70.7%) with 1526 (19.1%) from the Royal Air Force, and 809 (10.1%) from the Royal Navy.

EXPOSURES

The frequency of exposures, reduced to binary contrasts for ease of presentation, is shown for each service in table 2. Few veterans thought that they had been exposed to nerve gas (93 subjects) or depleted uranium (52) and these

Table 3 Intercorrelations between exposure factors (exposures with Pearson correlation coefficients >0.20 in whole population)

Exposure	*Correlated with*				
Duration	NAPs	Combat†			
Inoculation	NAPs	Life in danger			
Handling pesticides*	Living in sprayed quarters				
Living in sprayed quarters*	Handling pesticides				
Respraying vehicles*	Using insect repellent	Living in tented accommodation			
Smoke from oil wells	Combat				
Combat	Duration†	NAPs	Smoke from oil wells	Life in danger	
Tented accommodation*	NAPs	Respraying vehicles	Life in danger†		
Days of NAPs	Duration	Inoculations	Combat	Life in danger	NAPs side effects
Using insect repellent	Respraying vehicles				
Life in danger	Inoculation	NAPs	Combat	Tented accommodation†	NAPs side effects†
NAPs side effects	NAPs	Life in danger†			

*Correlation calculated for army and air force only.
†Correlation >0.2 overall and in only one cohort (main or validation) only.

exposures have not been considered further in this report. It is evident from table 2, that the experiences in the three services were very different in some respects but similar in others. Two thirds of respondents in each service thought that their life had been in danger, and one third reported side effects from NAPs tablets. Those in the army were most likely to have lived in tented accommodation, to have been exposed to smoke from oil well fires, and to have spent time respraying vehicles. Those in the navy spent longer times in the Gulf, were more likely to use antimalarial tablets and to be engaged in combat, whereas members of the air force were the least likely to report extended use of NAPs, exposure to smoke from oil well fires, or to report that they had been in combat.

Reports of exposures were significantly correlated, with 78 of the possible 91 independent bivariate Pearson correlations being calculated to have $p<0.01$. Factors with one or more correlation coefficients greater than 0.20 in the whole population are shown in table 3. Correlations found were, on the whole, ones that are readily explainable; those with longer time in the Gulf were more likely to have taken NAPs tablets for longer periods, those handling pesticides more likely to have lived in sprayed quarters, and those in combat more likely to think that their life had been in danger. Other correlations were determined by the series of events during the war; smoke from the oil well fires occurred immediately after the period of combat, and a correlation between the two would be expected. The size and direction of correlations was stable between the main and validation cohorts (only three of the 14 independent correlations >0.20 in the population had a correlation of <0.20 in one of the two cohorts) suggesting that the pattern of exposures was consistently reported.

EXPOSURES AND HEALTH INDICES

Univariate correlations were calculated between exposures and each of the health indices. None of the correlation coefficients was large, but those with the severity score were always higher than with any individual factor. Use of antimalarial tablets was not related to any of these health indices and time spent in the Gulf was only related, weakly, to severity. The strongest correlations with severity were the number of days using insect repellent, days using NAPs tablets, and the number of inoculations reported. For each of the seven individual factors, at least one correlation with exposure was found consistently across cohorts. Three exposures, the use of insect repellent, feeling that life was in danger, and side effects from NAPs, were related to five of the seven specific health outcomes (data not shown).

Such a spread of correlations between outcome and exposure would be expected, given the correlations between exposures. To adjust for this, multiple regression including all exposures simultaneously was carried out for each of the indices of ill health. These regressions also allowed for the potential confounders of officer status (officers generally reported fewer symptoms), service (those in the army reported more symptoms, even those who did not go to the Gulf), and current serving status (those who had left the service generally reported more symptoms). Age (as a binary factor with those <25 years contrasted with older subjects) sex, marital status (living alone or living as married) and possession (yes or no) of the record of inoculations were also entered into each of the equations but were not related to health indices and are not shown in table 4 which summarises the results of these regression analyses. In this table, coefficients are shown only if they were present ($p<0.01$) in both the main and validation cohorts; as service was included in the equation (army contrasted with navy and air force), the subanalysis for the army alone was not taken into account.

Severity scores were lower in officers and in those still serving, even after allowing for reported exposures. From the first group of exposures (those largely outside the control of the subject, table 1) number of inoculations, days handling pesticides, and days exposed to smoke from burning oil wells were related to severity score after adjusting for potential confounders. Relations with severity were also seen for exposures from "prophylactic measures under the subject's control" and "factors reflecting individual susceptibilities" in table 1, with reported days of use of NAPs tablets and insect repellent, feelings that life was in danger, need for medical attention while in the Gulf, and side effects from NAPs tablets all associated with a tendency to be more troubled by symptoms.

The seven individual health factors were found to be related to fewer exposures and the effects of other potential confounders were

Table 4 β Coefficients for whole sample from regression of health indices on exposures and potential confounders (n=7971)

		Factor						
Exposure	*Severity*	*Psychological*	*Peripheral*	*Neurological*	*Respiratory*	*Gastrointestinal*	*Concentration*	*Appetite*
Officer	−0.14	−0.08	−0.05					
Army								
Serving	−0.13	−0.17	−0.07	−0.08				
Duration								
Inoculation	0.09		0.05					
Pesticide handling	0.06		0.05	0.08				
Sprayed quarters								
Respraying vehicles								
Smoke from oil fires	0.07							
Combat								
Tented accommodation								
Days of NAPs	0.07							
Antimalarial								
Insect repellent	0.12		0.06		0.06			0.07
Danger	0.07	0.06						
Medical attention	0.09					0.06		
Side effects from NAPs	0.10		0.05			0.06		

Coefficient shown if p<0.001 in the whole sample and p<0.01 in both main and validation cohorts.

weaker than in the analysis of severity. Only two exposures outside the subject's control (table 1) were related to individual factors: the number of inoculations and days handling pesticides both related to the peripheral factor and pesticides alone to the neurological one. Reported days of use of insect repellent were related to scores on the peripheral, respiratory, and appetite factors. Scores on the psychological factor were higher in those who had thought their life had been in danger. Those who had higher scores on the gastrointestinal factor were those who had experienced side effects from NAPs tablets and those who had sought medical attention while in the Gulf.

Mean scores on health indices identified in these analyses were calculated by level of exposure to illustrate the slope of the dose-response gradient for exposures graded by degree (number of days or number of inoculations). Those who reported that they held a record of their inoculations tended to report more inoculations than those who did not have a record, but increasing patterns of scores on severity and the peripheral factor were found with increase in numbers of inoculations in those with and without such a record (table 5). There was no evidence that the place at which the inoculations were received (before leaving for the Gulf or after arrival) had any effect on these health indices (data not shown). Table 6 gives the mean scores on health indices for four exposures, expressed in days, for which consistent effects were found. For use of NAPs and insect repellents there was a marked tendency to increased scores with a greater number of days of use. Such a tendency was less in evidence for exposure to smoke from oil well fires and, particularly, for the handling of pesticides but some trend was still present. The regression coefficients in table 4 are small, but marked increases in severity and factor scores are found with increasing exposures.

Table 5 Mean scores, in whole population, on health indices identified in the regression by number of inoculations for those with and without inoculation records in their possession

	Inoculations (n)					
	0	*1–3*	*4–6*	*7–9*	*⩾10*	*Overall*
Record held (n):						
Yes	22	312	1082	514	243	2173
No	204	1011	2847	1090	553	5705
Overall	226	1323	3929	1604	796	7878
Severity (mean) record held:						
Yes	1.5	2.3	3.2	3.9	4.2	3.3
No	2.0	3.0	3.6	4.4	4.7	3.7
Overall	2.0	2.8	3.5	4.2	4.5	3.6
Peripheral (mean) record held:						
Yes	−18.2	−7.3	5.8	24.2	25.1	10.2
No	−27.2	−1.3	9.1	23.3	38.5	11.5
Overall	−26.4	−2.7	8.2	23.6	34.4	11.1

Table 6 Mean scores on health indices, identified in the regression, by days of exposure

	Days exposed					
	0	*⩽14*	*15–31*	*32–62*	*⩾63*	*Overall*
Handling pesticides (n)	7414	338	51	36	132	7971
Severity (mean)	3.5	5.2	5.1	5.2	5.7	3.6
Peripheral (mean)	8.1	44.4	46.1	41.1	63.8	10.9
Neurological (mean)	−2.8	42.4	18.3	78.2	55.2	0.6
Smoke from oil fires (n)	3080	3502	1002	223	162	7969
Severity (mean)	3.0	3.8	4.1	4.2	4.3	3.6
Using NAPs (n)	1453	1726	2810	1243	726	7958
Severity (mean)	2.7	3.2	3.8	4.0	4.8	3.6
Using insect repellent (n)	3718	1495	539	534	1683	7959
Severity (mean)	3.0	3.7	3.8	4.2	4.6	3.6
Peripheral (mean)	−3.1	16.1	16.1	25.1	31.0	10.9
Respiratory (mean)	−4.1	2.3	9.6	18.1	23.2	5.3
Weight (mean)	−9.6	−5.9	−3.0	2.4	12.4	−3.0

PERIPHERAL NEUROPATHY AND WIDESPREAD PAIN

Areas of numbness or tingling and of pain indicated on two manikins were used as indicators of possible peripheral neuropathy and of widespread pain. Although there may be overlap between the two conditions, the implications of the diagnosis are different, with peripheral neuropathy having objectively measurable physiological signs and some known toxic mechanisms, whereas chronic widespread pain is thought to be largely functional. In those who went to the Gulf, 797 (10.0%) had symptoms consistent with peripheral neuropathy, 605 (7.6%) symptoms of widespread pain, and an additional 368 (4.6%) had symptoms meeting both definitions.

The relation between each set of symptoms and exposure is shown in table 7, which gives those exposures and confounders that were highly significant in the sample as a whole (p<0.001) after adjustment for all other exposures and confounders, and also consistent in that they appeared (p<0.01) in the parallel regressions for the main and validation cohorts

Table 7 Odds ratio from logistic regression of symptoms consistent with peripheral neuropathy and widespread pain (from manikins) on exposures and potential confounders

	Peripheral neuropathy	*Widespread pain*
Officer	0.56	
Army		
Serving	0.68	0.58
Duration		
Inoculations		
Pesticide handling	1.26	
Sprayed quarters		
Respraying vehicles		
Smoke from oil fires		
Combat		
Tented accommodation		
Days of NAPs		
Antimalarial		
Insect repellent		1.15
Danger		
Medical attention		1.57
Side effects from NAPs	1.38	1.54

Odds ratios shown if $p<0.001$ in the whole sample and $p<0.01$ in both main and validation samples.

separately. Officers were less likely to complain of peripheral neuropathy than other ranks and both these symptoms, and those of widespread pain, occurred less often in those still serving. Among the exposures in the Gulf, only handling of pesticides and side effects from NAPs were consistently related to peripheral neuropathy, whereas the use of insect repellent, needing medical attention while in the Gulf, and again, side effects from NAPs, were related to widespread pain. The odds ratio associated with handling pesticides and the use of insecticide are per unit increase were entered as continuous (five level) variables. The differences reflected are substantial. More than a third of those who reported handling pesticides for more than a month complained of symptoms consistent with peripheral neuropathy (34.6%); only 13.6% of those who went to the Gulf but did not handle pesticides complained of these symptoms.

Discussion

This paper aimed to describe the relation between reported exposures and symptoms and to assess whether the pattern that emerged gave credence to hypothesised effects of chemicals or prophylactic exposures rather than simply the traumas of war. In doing so three types of exposures were considered: those outside the control of the subjects themselves, prophylactic measures under their control, and reactions to conditions in the Gulf. Interpretation of the effects of exposures in the second and third groups is complex. It is possible that NAPs tablets and use of insecticides on the skin are indeed a cause of later ill health, but the extended use of such substances in the absence of great risk may also suggest an unusual preoccupation with preventing disease. In so far as this is associated with a tendency to report health complaints, cause and effect may be difficult to untangle. Such interpretation may be even more difficult for the third group of factors—feelings that life was in danger, seeking medical attention, and reporting side effects from NAPs. All these reports may reflect experiences in the Gulf that are themselves risk factors for subsequent illness; alternatively, they may result from pre-existing susceptibilities to later ill health. This discussion considers particularly exposures outside the control of the subjects themselves, which were considered to be less susceptible to bias or confounding.

The analysis first considered exposures associated with severity. In the multivariate analysis only three exposures outside the control of the subjects themselves, the number of inoculations, the handling of pesticides, and exposure to smoke from oil well fires, were consistently related to severity. The analysis then went on to consider the specific health outcomes derived by component analysis of the 95 individual symptoms, and here only inoculations and handling pesticides seemed, from this group of exposures, to have a specific relation to individual health outcomes. The number of inoculations was highly and consistently related to scores of the peripheral factor on which the largest weightings were for symptoms associated with the skin, muscles, and the peripheral nervous system. Handling of pesticides was also associated with this factor and with the neurological factor. Exposure to smoke from oil well fires was not related to scores on the respiratory factor after allowing for other exposures.

The final part of the analysis considered responses to the request to shade on two manikins, areas of the body in which pain, or numbness, or tingling had been experienced persistently during the past month. Examination of the two syndromes had the potential to differentiate between exposure factors associated with somatic distress (as exemplified by widespread pain) and those associated with peripheral neuropathy (which might be due to toxic exposure). If prolonged use of insecticides were a marker of a preoccupation with health that may be associated with later development of somatic symptoms, then it might be expected to be a predictor of widespread pain. Similarly, if exposure to pesticides were indeed responsible for toxic damage, it would be expected to be more closely related to peripheral neuropathy. This distinctive pattern of exposures was found, providing some support for the hypothesis that the symptoms of peripheral neuropathy were not simply somatic. However, it must be noted that the method of assessing numbness and tingling by manikin and the definition of possible neuropathy from such responses were devised specifically for the present study and await validation.

A case has been made for relatively specific, consistent, and credible relations between ill health and the number of inoculations received and the handling of pesticides. It may be appropriate to consider more formally, as others have done,[14 18] whether they meet the criteria for causality postulated by Hill,[19] and whether bias or confounding provide a more plausible explanation of the relations found. The criteria for causality include strength, consistency, dose-response, specificity, and biological plausibility. Importantly, the exposure must precede the effect, a criterion not testable

in the present study as baseline data on symptoms were not available.

The increasing rate of severity and scores on the peripheral factor with number of inoculations is strong, shows a dose-response in the present study, and is consistent between the main and validation cohorts. It also receives external support from a previously published study of United Kingdom Gulf veterans[3] which found a very similar pattern of increasing symptoms with the number of inoculations. Arguments have been made for its biological plausibility,[20] and certainly that it might be thought that such large numbers of inoculations over a short period might have effects not seen under the more gradual programme found outside conditions of sudden deployment. Although a causal hypothesis is supported, bias must also be considered. At the time of the study immunisation had become a focus of concern among groups of veterans. Those who knew that they had had many inoculations may, as a result, have become more preoccupied with their health and reported more severe symptoms, but the specificity of the relation to the peripheral factor (with heaviest weight on skin problems) does not suggest response bias across the full range of common health concerns. The very similar pattern obtained by those with and without the official record of their inoculations suggests that bias in reporting exposure is unlikely to be a factor but there is no evidence in this study whether or not the subject had correctly transcribed the record or indeed had used it at all in completing the questionnaire. Limited investigation of this question by the authors of the previously published United Kingdom study[3] suggests that subjects holding immunisation records had used them accurately.

The evidence for the ill effects of handling pesticides is at once both more and less convincing. Again there is strong, consistent evidence from within the study which is supported by findings elsewhere.[12 13] The dose-response relation is less consistent than that with the number of inoculations. It is biologically plausible that exposure to pesticides should affect the peripheral nervous system; organophosphate pesticides purchased locally may have been of a type that has such an effect, although usually only within days of acute exposure. There is no consensus on whether long term exposure to low levels can cause such damage in the absence of acute poisoning.[21] There has been much speculation that exposure in the Gulf to many substances affecting chlolinesterase may have led to ill health,[22] in particular among those with a genetic susceptibility through a less effective form of an enzyme that metabolises organophosphates.[23–25] It has been shown in the present analyses that the relation with reported use of pesticide is relatively specific to the nervous system and again the evidence would formally support a causal hypothesis. Within the pesticide handlers, however, the potential for both bias and confounding is real. In so far as pesticide handlers are technicians trained to do this work they may have had exposure to other chemicals, before and since the Gulf, that were themselves neurotoxic; no measure of symptoms or exposures before the Gulf is available. Secondly, in the course of such training there would have been discussions of health and safety aspects of the work, including the types of symptoms that might be associated with poisoning. With the knowledge both of exposure and of plausible effects, and with exposure to pesticide a recognised concern among the Gulf War veterans, the pesticide handlers may have developed an increased awareness of every day sensations and discomforts that would not have been reported by others without this knowledge. The lack of a strong dose-respose pattern within handlers might seem to support an explanation of bias or confounding; however, such a pattern could also arise if there were important differences in susceptibility or in the amounts of more toxic pesticides used.

Finally, it may be asked why these effects associated with inoculations and pesticides have been reported in few of the previous studies. It may be that the exposures of United Kingdom forces were sufficiently different from those in other countries to explain this, but equally, this may result from features of design or analysis. Many previously reported studies have simply described exposure as present or absent or have not examined the relation between degree of exposure and extent of response. Some restricted their collection (or analysis) of exposure data or outcomes to psychological traumas of war and did not consider the full range of possible causes of ill health or effects of exposures. Few made (or reported) an attempt to adjust for intercorrelations between exposures or with other confounders; a simple univariate analysis would give the impression that a wide range of exposures was associated non-specifically with a wide range of symptoms. Testing for consistency was an important part of the design of our study and reduced the likelihood of chance, biologically implausible, relations. Thus although this study cannot, in itself, finally determine whether the observed relations were indeed causal, it may be argued that, if any true relation were present, this study would be more strongly placed then previous ones to bring it to light.

When objective assessment is not possible, it may be legitimate to leave to debate the question of cause and effect. In this instance, however, objective measures are feasible and exposure groups sufficiently well defined to answer the questions that arise from this study of self reported symptoms and exposures. It would be a disservice to these men and women who went to the Gulf and who collaborated with this research if the two central questions that arise from it were left unanswered. Do those who received many inoculations have objective markers of ill health that are different from those who did not? Do those who handled pesticides have peripheral nerve damage? Without such answers, preventable effects of future wars may go unrecognised.

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1 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomed journals. *JAMA* 1993;**269**:2282-6.
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