Articles

Health of UK servicemen who served in Persian Gulf War

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Summary

Background Various symptoms in military personnel in the Persian Gulf War 1990–91 have caused international speculation and concern. We investigated UK servicemen.

Methods We did a cross-sectional postal survey on a random sample of Gulf War veterans (Gulf War cohort, n=4248) and, stratified for age and rank, servicemen deployed to the Bosnia conflict (Bosnia cohort, n=4250) and those serving during the Gulf War but not deployed there (Era cohort, n=4246). We asked about deployment, exposures, symptoms, and illnesses. We analysed men only. Our outcome measures were physical health, functional capacity (SF-36), the general health questionnaire, the Centers for Disease Control and Prevention (CDC) multisymptom criteria for Gulf War illness, and post-traumatic stress reactions.

Findings There were 8195 (65·1%) valid responses. The Gulf War cohort reported symptoms and disorders significantly more frequently than those in the Bosnia and Era cohorts, which were similar. Perception of physical health and ability were significantly worse in the Gulf War cohort than in the other cohorts, even after adjustment for confounders. Gulf War veterans were more likely than the Bosnia cohort to have substantial fatigue (odds ratio 2·2 [95% CI 1·9–2·6]), symptoms of post-traumatic stress (2·6 [1·9–3·4]), and psychological distress (1·6 [1·4–1·8]), and were nearly twice as likely to reach the CDC case definition (2·5 [2·2–2·8]). In the Gulf War, Bosnia, and Era cohorts, respectively, 61·9%, 36·8%, and 36·4% met the CDC criteria, which fell to 25·3%, 11·8%, and 12·2% for severe symptoms. Potentially harmful exposures were reported most frequently by the Gulf War cohort. All exposures showed associations with all of the outcome measures in the three cohorts. Exposures specific to the Gulf were associated with all outcomes. Vaccination against biological warfare and multiple routine vaccinations were associated with the CDC multisymptom syndrome in the Gulf War cohort.

Interpretation Service in the Gulf War was associated with various health problems over and above those associated with deployment to an unfamiliar hostile environment. Since associations of ill health with adverse events and exposures were found in all cohorts, however, they may not be unique and causally implicated in Gulf-War-related illness. A specific mechanism may link vaccination against biological warfare agents and later ill health, but the risks of illness must be considered against the necessity of protection of servicemen.

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Introduction

From late 1990, the UK deployed 53 462 military personnel to the Persian Gulf War. In the months after the end of the war, anecdotal reports emerged in the USA of various disorders affecting Gulf War veterans. In the UK, similar observations surfaced in 1993, after a television broadcast in June. Some UK Gulf War veterans have experienced health problems since their return. Such anecdotal reports cannot, however, establish whether these complaints have any particular pattern, nor whether they are related to Gulf War service.

Previous studies of the health of Gulf War veterans have had limitations. Comparisons with non-military populations may be misleading, since military recruitment involves medical screening. Clinical assessment programmes for non-randomly selected veterans with symptoms cannot provide epidemiological information or answer questions about links to active service.[1] Some of these limitations have been addressed. A large-scale study of US veterans found no substantial differences in admissions between Gulf War veterans and military controls.[2] However, only admissions to military hospitals were included, without contact with outpatients, primary-care physicians, or civilian hospitals, which may have led to bias towards sicker veterans.[3] One cohort study used complete outcome data from an unselected military population, but looked only at mortality.[4] The Centers for Disease Control and Prevention (CDC) study[5] was restricted to serving air-force personnel. Sicker veterans are more likely to have left the services because of ill health. To date, only one study has used a random sample of veterans and tried to follow up still serving and discharged personnel.[6]

We investigated, among UK male Gulf War veterans from army, navy, and air force, whether there was a relation between ill health and the Gulf War.

Methods

We carried out a cross-sectional epidemiological survey to compare the health profiles of three randomly selected UK military cohorts.

Participants

The target population was male and female Gulf War veterans (n=53 462) who served in the Gulf region between Sept 1, 1990, and June 30, 1991. We excluded special forces for security

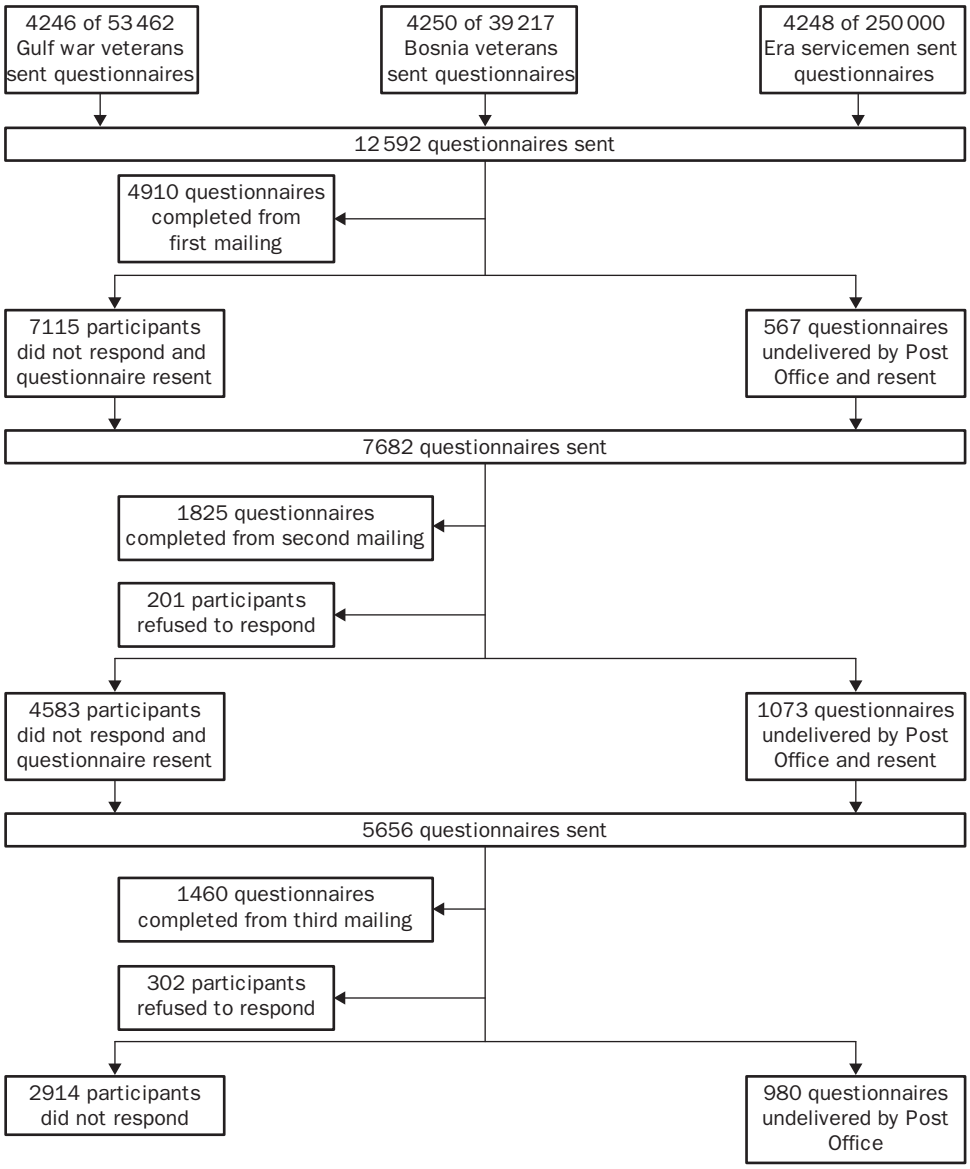

Figure 1: **Profile of mailing and response rates**

reasons. We recruited a random stratified sample of 4250 personnel into the Gulf War cohort, which would give sufficient power to detect an expected increased relative risk of chronic fatigue syndrome (CFS) of between 1·2 and 1·3. The key variables for stratification were service (Royal Navy, Army, Royal Air Force), sex, age, service status (regular or reservist), rank (officer or other), and fitness (army and air force only). By stratified selection we aimed to represent the population who served in the Gulf War. We deliberately over-sampled women.

As comparison cohorts, we randomly selected, from 39 217 personnel who had served in Bosnia, 4250 servicemen deployed between April 1, 1992, and Feb 6, 1997 (Bosnia cohort), and, from the 250 000 personnel serving in the armed forces on Jan 1, 1991, who were not deployed to the Gulf War, we selected 4246 (Era cohort) according to the stratification variables used for the Gulf War cohort. For the Era cohort, we used all the stratification variables; for the Bosnia cohort we used only age, sex, and rank because only the army served in Bosnia; reservist status and fitness data were not available. For any serviceman who died during follow-up, we excluded their data and recruited another.

We restricted our analyses to men. Although 1235 women served in the UK armed forces during the Gulf War, their roles and background health complaints were not the same as those for men and results will be reported elsewhere.

Methods

After an initial pilot phase, we sent questionnaires to all particpants in August and September, 1997. Two further mailings of non-responders were done between November, 1997, and June, 1998 (figure 1). Follow-up ended on Nov 11, 1998.

We obtained addresses from the Ministry of Defence. For personnel still in service we obtained current addresses and for those who had left the forces (discharged) we obtained the last known addresses in the UK or overseas. We used multiple tracing mechanisms for non-responders. For personnel who had left the services we used the National Health Service central registry to obtain health authority ciphers and current addresses. We used the electoral register to check current addresses. For those still in service, various service bodies provided regularly revised addresses, including discharge and pension address sources. Several media appeals were made by the research teams, with additional support from the Ministry of Defence, and we posted a study website on the internet.

In the third mailing, for serving participants, we sent questionnaires in batches to unit commanding officers with a letter asking them to facilitate the delivery of the questionnaires to servicemen. After 1 month, we again approached the commanding officers with the highest non-response rates.

Characteristic	Sample (%)
Sex	
Men	3905 (92·0)
Women	341 (8·0)
Age at 1 Jan, 1991 (years)	
<20	497 (11·7)
20–24	1503 (35·4)
25–29	1036 (24·4)
30–34	623 (14·7)
35–39	342 (8·1)
⩾40	244 (5·7)
Rank	
Officer	537 (12·7)
Other	3708 (87·3)
Status	
Regular	3644 (96·3)
Reservist	141 (3·7)
Fitness*	
Highest	3516 (92·9)
Mid	33 (0·9)
Lowest	5 (0·1)
Unknown	231 (6·1)
Service	
Army	2992 (70·5)
Navy	460 (10·8)
Royal Air Force	794 (18·7)

*Not available for navy.

Table 1: **Sample characteristics for Gulf War cohort**

To assess potential response bias, we tried after two mailings to trace a randomly selected sample of 100 participants in the Gulf War cohort, 50 in the Bosnia cohort, and 50 in the Era cohort who were non-responders and separated equally into still serving and discharged. We sent questionnaires by registered post, contacted family physicians if we could trace them, as well as the Driving and Vehicle Licensing Agency, and did interviews by telephone with a shortened version of the questionnaire.

The questionnaire was constructed from existing measures, questionnaires used in similar studies in the USA, and from our interviews with UK servicemen. We tested the questions on several military samples, including Gulf War veterans, and refined them to ensure that the questionnaire was understandable and acceptable to the intended recipients. We dropped items that were irrelevant to UK experiences or because of length.

The questionnaire that we used in the study asked about demographic details (age, sex, education, military history), alcohol intake and cigarette smoking, exposure history (29 items), medical symptoms (50 items), and medical disorders (39 items). We included several symptoms of post-traumatic stress disorder taken from the Mississippi scale,[7] physical health and functional capacity from SF-36,[8] the 12-item general health questionnaire,[9] a shortened measure of symptoms of possible chemical sensitivity,[10] and a chronic fatigue scale.[11]

We asked participants in the Gulf War and Bosnia cohorts to give details of vaccinations received 2 months before and during each conflict. If copies of vaccination records were available, we asked participants to refer to them when completing the questionnaire. We asked about vaccination side-effects and ingestion of pyridostigmine bromide tablets.

In the absence of a valid or agreed definition of ill health arising after Gulf War service, we used the subjective health perception and the physical functioning subscales of the SF-36 as the principal outcome measures. These were supplemented by a-priori syndromes created from the items and scales used in the questionnaire. We used the conventional cut-off for the fatigue questionnaire (3/4) and general health questionnaire (2/3) to define whether or not respondents were "cases". We created a

Characteristic	Region			p Gulf *vs* Bosnia‡	p Gulf *vs* Era‡
	Gulf (n=2735)	Bosnia (n=2393)	Era (n=2422) %		
Sex					
Male/female	2527 (92·4%)/208 (7·6%)	2184 (91·3%)/209 (8·7%)	2245 (92·7%)/177 (7·3%)	0·16	0·68
Current age					
>25	0	502 (21·0%)	266 (1·1%)		
25–29	692 (25·3%)	866 (36·2%)	518 (21·4%)	<0·001	<0·001
30–34	826 (30·2%)	517 (21·6%)	751 (31·0%)		
35–39	569 (20·8%)	299 (12·5%)	540 (22·3%)		
⩾40	648 (23·7%)	211 (8·8%)	586 (24·2%)		
Marital status					
Married or living with partner	2070 (75·7%)	1453 (60·7%)	1846 (76·2%)		
Never married	432 (15·8%)	744 (31·1%)	339 (14·0%)	<0·001	0·07
Separated, divorced, widowed	232 (8·5%)	196 (8·2%)	240 (9·9%)		
Education					
Lower than 'O' levels	517 (18·9%)	388 (16·2%)	448 (18·5%)		
'O' levels	1592 (58·2%)	1517 (63·4%)	1335 (55·1%)	<0·001	0·01
'A' levels and higher	626 (22·9%)	488 (20·4%)	639 (26·4%)		
Currently in employment	2581 (94·4)	2333 (97·5%)	2269 (93·7%)	<0·001	0·30
Alcohol intake (units per week)					
None	257 (9·4%)	158 (6·6%)	223 (9·2%)		
1–3	629 (26·5%)	479 (20·0%)	610 (25·2%)		
4–10	829 (30·3%)	689 (28·8%)	765 (31·6%)	<0·001	0·43
11–20	585 (21·4%)	589 (24·6%)	552 (22·8%)		
⩾21	336 (12·3%)	479 (20·0%)	274 (11·3%)		
Smoking history					
Currently smoke	968 (35·4%)	912 (38·1%)	761 (31·4%)		
Ex-smoker	662 (24·2%)	498 (20·8%)	620 (25·6%)	<0·001	<0·001
Never smoked	1102 (40·3%)	984 (41·1%)	1041 (43·0%)		
Still in service/discharged	1469 (53·7%)/ 266 (46·3%)	2120 (88·6%)/272 (11·4%)	1402 (57·9%)/1020 (42·1%)	<0·001	<0·001
Rank					
Officer	366 (13·4%)	306 (12·8%)	310 (12·8%)		
Other	2368 (86·6%)	2087 (87·2%)	2076 (85·7%)	0·54	0·32
Serving status†					
Regular	2702 (98·8%)	2393 (100·0%)	2405 (99·3%)	. .	0·08
Medically discharged†	41 (1·5%)	Not known	51 (2·1%)	. .	0·10

*Denominators for three groups differ slightly because of non-response on some items.
†Statistic not calculated for Gulf *vs* Bosnia because of empty cells. ‡χ^2 or heterogeneity.

Table 2: **Characteristics of responders**

Characteristic	Intensively followed up (n=139)	Responders (n=7375)*	p
Age			
<25	3·6%	7·0%	
25–29	18·7%	27·8%	
30–34	14·4%	27·6%	<0·001
35–39	31·7%	18·5%	
⩾40	31·7%	19·1%	
Marital status			
Married or living with partner	77·8%	72·5%	
Never married	10·4%	18·9%	0·03
Separated, divorced, widowed	11·9%	8·6%	
Education			
Lower than 'O' levels	29·7%	18·7%	
'O' levels	57·8%	59·9%	<0·001
'A' levels and higher	12·5%	21·4%	
Currently in employment	93·4%	95·6%	0·21
Medically discharged	0·7%	1·3%	0·56
Still in service/discharged	47·8/52·2%	67·1%/32·9%	<0·001
Mean (SD) health outcomes			
Health perception	66·3 (25·5)	71·3 (23·6)	0·01
Physical functioning	90·3 (17·3)	92·5 (15·8)	0·11

*Denominators differ slightly because of non-response on some items.

Table 3: **Characteristics of intensively followed up *vs* main study responders**

variable for post-traumatic stress reaction: the experience of one symptom in each of four classifications—intrusive thoughts, avoidance, arousal and irritability—and at least two further symptoms of unrefreshing sleep, fatigue, alcohol intolerance, forgetfulness, poor concentration, loss of sexual interest, and decrease in appetite.

Although not in the original protocol, we added a further outcome measure based on the multisymptom empiric syndrome identified by the CDC study,[5] which we have labelled the CDC multisymptom syndrome. Mapped on to our questions, this outcome required one or more symptoms in at least two classifications of: fatigue, mood/cognition (depression, poor concentration or memory, moodiness, anxiety, word-finding difficulties, sleep difficulties), and musculoskeletal (joint pain, joint stiffness, muscle pain).

For all outcomes we used only current symptoms, defined as occurring in the past month because evidence suggests that questionnaire data alone are reliable only for that length of time.[12]

Statistical analysis

We analysed data with SPSS (version 7.5) and STATA (version 5.0). Data for SF-36 were entered on to SPSS twice. The proportions of symptoms, disorders, and exposures were compared between the Gulf cohort and the two comparison cohorts by calculation of odds ratios and 95% CIs. We controlled for potential confounders (sociodemographic factors: age, marital status, rank, education, employment, still serving or discharged; lifestyle factors: smoking, alcohol consumption) by logistic-regression analysis. We assessed relations between a-priori outcomes (fatigue, general health questionnaire score, SF-36, traumatic stress) and reported exposures, stratified by deployment.

In the Bosnia cohort, 800 of 4250 servicemen had also been deployed to the Gulf conflict, but we took them to be part of the Gulf War cohort. The Bosnia cohort consisted of servicemen who had served only in the Bosnia conflict.

Results

Responses

We received 8195 (65·1%) questionnaire replies (2961 [70·4%] Gulf War cohort, 2620 [61·9%] Bosnia cohort, 2614 [62·9%] Era cohort). Addresses were not available for 152 participants. 503 (4·0%) servicemen refused to respond. 980 (7·9%) questionnaires were returned undelivered to the research team by the Post Office at the end of the three mailings (figure 1). If the undelivered questionnaires are taken into account, the minimum effective response rate was 70·6%. The characteristics of the Gulf War cohort at the start of the study are shown in table 1.

Responders did not differ from non-responders by sex, but were older (mean age: responders 34·7 years, non-responders 29·3, p<0·001) and more likely to be still in service (66·4 *vs* 61·1%, p<0·001, table 2). The number of medical discharges among responders and non-responders did not differ across the entire sample (1·8 *vs* 2·0%, p=0·44) or by deployment (Gulf War cohort 1·5 *vs* 1·3%, p=0·59; Bosnia cohort, not known; Era 2·1 *vs* 2·6%, p=0·28). Some veterans had attended the medical assessment programme established by the Ministry of Defence for Gulf War veterans with symptoms, but because of confidentiality, we did not know which veterans. The Ministry of Defence, however, did an anonymous record linkage on our behalf. In our Gulf War cohort, 158 (4·0%) veterans had attended the programme. Of these veterans, 79% responded to the survey, compared with 67·3% of the two control groups (p<0·01).

The Bosnia responders were more likely to be still in service, were younger, and more servicemen were unmarried, as expected from the chronology of the conflicts. They also drank more alcohol. The Era cohort was similar to the Gulf sample, but contained more non-smokers.

We also assessed non-response by differences in the health of responders to the third mailing, since they would have been non-responders without a third mailing. The responders from the first, second, and third mailings did not differ significantly for a-priori key outcome measures. Mean SF-36 ratings of health perception were 71·3, 71·1, and 71·5, respectively (p=0·91). Ratings of physical function were 92·5, 92·5, and 92·1 (p=0·64). The mean total symptom score declined by mailing (8·1, 7·3, 7·0, p<0·001), which shows that servicemen with the most symptoms replied first. There was no significant interaction between deployment, late response, and health outcome (p=0·42), since Gulf War late responders did not differ from the Bosnia or Era late responders.

200 serviceman who had not responded after two mailings were randomly chosen for intensive follow-up (table 3). 139 (69·5%) returned the questionnaire or completed a telephone survey, 22 (11·0%) refused to participate, 11 (5·5%) questionnaires were returned undelivered, and 28 (14·0%) did not respond. The intensive follow-up group contained more discharged

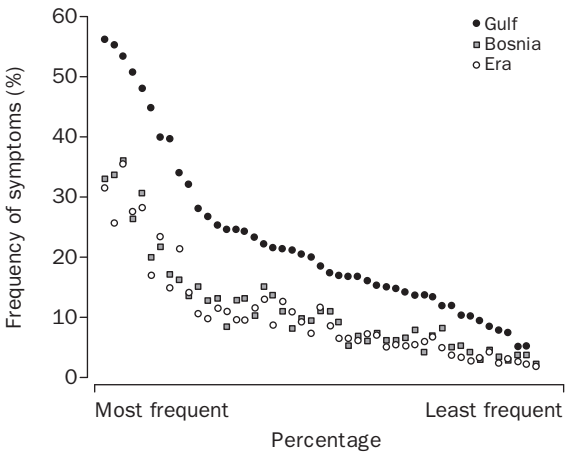

Figure 2: **Symptoms by deployment**

Symptoms	Frequency (%)			Gulf *vs* Bosnia			Gulf *vs* Era		
	Gulf (n=3284)	Bosnia (n=1815)	Era (n=2408)	Univariate odds ratio	Odds ratio model 1*	Odds ratio model 2†	Univariate odds ratio	Odds ratio model 1*	Odds ratio model 2†
Feeling unrefreshed after sleep	56·1	33·0	31·6	2·6 (2·3–2·9)	2·4 (2·1–2·8)	2·3 (1·9–2·7)	2·8 (2·5–3·1)	2·7 (2·4–3·1)	2·3 (2·0–2·6)
Irritability or outbursts of anger	55·2	33·6	25·8	2·4 (2·2–2·7)	2·3 (2·0–2·6)	2·1 (1·8–2·4)	3·5 (3·2–4·0)	3·7 (3·3–4·2)	3·2 (2·8–3·7)
Headaches	53·5	36·0	35·6	2·0 (1·8–2·3)	1·9 (1·7–2·3)	1·8 (1·6–2·1)	2·1 (1·9–2·3)	2·1 (1·9–2·3)	1·8 (1·6–2·0)
Fatigue	50·7	26·3	27·7	2·9 (2·5–3·3)	2·5 (2·2–2·9)	2·4 (2·0–2·8)	2·7 (2·4–3·0)	2·7 (2·4–3·1)	2·2 (2·0–2·6)
Sleeping difficulties	48·0	30·7	28·4	2·1 (1·8–2·4)	1·9 (1·6–2·2)	1·7 (1·5–2·0)	2·3 (2·1–2·6)	2·4 (2·1–2·7)	1·9 (1·7–2·2)
Forgetfulness	44·9	19·9	17·1	3·3 (2·8–3·7)	2·8 (2·4–3·2)	2·8 (2·3–3·3)	3·9 (3·5–4·5)	4·2 (3·6–4·8)	3·7 (3·2–4·4)
Joint stiffness	40·0	21·8	23·5	2·4 (2·1–2·7)	2·7 (2·3–3·3)	2·6 (2·1–3·1)	2·2 (1·9–2·4)	2·8 (2·4–3·3)	2·4 (2·0–2·8)
Loss of concentration	39·7	17·2	15·1	3·2 (2·8–3·7)	2·8 (2·4–3·3)	2·9 (2·4–3·5)	3·7 (3·2–4·2)	4·0 (3·4–4·6)	3·6 (3·0–4·2)
Flatulence or burping	34·1	16·4	21·5	2·6 (2·3–3·0)	2·1 (1·8–2·5)	2·0 (1·7–2·4)	1·9 (1·7–2·1)	2·0 (1·8–2·3)	1·8 (1·5–2·0)
Pain without swelling or redness in several joints	32·2	13·8	14·4	3·0 (2·5–3·5)	2·1 (1·8–2·4)	1·9 (1·6–2·2)	2·8 (2·5–3·2)	2·2 (2·0–2·6)	1·9 (1·7–2·2)
Feeling distant or cut off from others	28·1	15·2	11·0	2·2 (1·9–2·5)	2·0 (1·7–2·4)	1·8 (1·5–2·3)	3·2 (2·7–3·7)	3·4 (2·9–4·0)	2·8 (2·3–3·3)
Avoiding doing things or situations	26·8	13·0	10·3	2·4 (2·1–2·9)	2·0 (1·7–2·4)	1·8 (1·5–2·3)	3·2 (2·7–3·7)	3·5 (2·9–4·1)	2·8 (2·3–3·4)
Chest pain	25·3	13·2	11·8	2·2 (1·9–2·6)	2·0 (1·7–2·4)	1·9 (1·6–2·3)	2·5 (2·2–2·9)	2·6 (2·2–3·0)	2·1 (1·8–2·5)
Tingling in fingers and arms	24·7	8·7	11·1	3·4 (2·8–4·1)	2·7 (2·2–3·3)	2·5 (2·0–3·1)	2·6 (2·3–3·1)	2·7 (2·3–3·2)	2·3 (2·0–2·7)
Night sweats	24·6	12·8	9·9	2·2 (1·9–2·6)	2·0 (1·7–2·4)	1·9 (1·5–2·2)	3·0 (2·5–3·5)	2·9 (2·5–3·5)	2·5 (2·1–2·9)

*Controlled for age (continuous variable [years]), smoking, alcohol consumption, marital status, educational attainment, officer or other ranks, employment status, and civilian or military status on follow-up.
†As for model 1, but adds general health questionnaire score (0–12). Odds ratio (95% CI).

Table 4: **15 most frequent self-reported symptoms by deployment**

personnel than the main study (p<0·001), were more likely to be married (p=0·03), and more likely to have lower educational achievement (p=0·001). They were older (p<0·001, table 3) and did not differ significantly by medical discharges, employment status, alcohol consumption, and smoking (data available on Lancet website, www.thelancet.com).

For the three cohorts combined, individuals who underwent intensive follow-up reported slightly worse health perception (SF-36) than the main study responders (66·3 *vs* 71·3). Physical function scales did not, however, differ significantly (table 3).

Symptoms

The Gulf War cohort reported all symptoms and disorders on the questionnaires more frequently than the comparison cohorts (figure 2). In addition to the 15 most frequent outcomes included in the tables, there were differences for other outcomes of interest, such as self-reported chronic fatigue syndrome.

We present logistic regression results for only the 15 most frequently reported symptoms and complaints (tables 4 and 5), since only one symptom (vomiting) became non-significantly associated with Gulf War service after adjustment for all confounders. Gulf War service was, however, associated with increased psychological distress, measured by the full general health questionnaire, and we entered this variable into a second model that also controlled for demographic and lifestyle factors. There was a slight general decrease in the association between symptoms and Gulf War service (table 4). Only unintended weight loss of more than 10 lbs became non-significant.

Adjustment for possible confounders and psychological disorders lessened the associations for symptoms in the Gulf War cohort, but most remained significant (tables 4 and 5). The strongest association was for self-reported chronic fatigue syndrome, although it was infrequently reported in all three cohorts.

For SF-36 variables, by linear regression differences in physical functioning between the three cohorts were non-significant, but that all other outcomes were significantly associated with Gulf War service (tables 6 and 7).

Complaints	Frequency (%)			Gulf *vs* Bosnia			Gulf *vs* Era		
	Gulf (n=3284)	Bosnia (n=1815)	Era (n=2408)	Unadjusted odds ratio	Odds ratio model 1*	Odds ratio model 2†	Unadjusted odds ratio	Odds ratio model 1*	Odds ratio model 2†
Back disorders	35·7	23·9	27·6	1·8 (1·5–2·0)	1·5 (1·3–1·7)	1·4 (1·2–1·6)	1·5 (1·3–1·6)	1·5 (1·3–1·7)	1·3 (1·1–1·5)
Hayfever	21·6	18·7	15·8	1·2 (1·0–1·4)	1·2 (1·0–1·5)	1·2 (1·0–1·4)	1·5 (1·3–1·7)	1·5 (1·3–1·8)	1·4 (1·2–1·6)
Dermatitis	21·3	13·7	12·3	1·7 (1·5–2·0)	1·8 (1·5–2·1)	1·6 (1·3–2·0)	1·9 (1·7–2·2)	1·9 (1·6–2·2)	1·6 (1·4–1·9)
Sinus disorders	19·6	11·7	12·0	1·8 (1·5–2·2)	1·6 (1·3–1·9)	1·4 (1·2–1·8)	1·8 (1·5–2·1)	1·7 (1·5–2·0)	1·5 (1·3–1·8)
Migraines	18·1	10·2	9·2	1·9 (1·6–2·3)	1·7 (1·4–2·1)	1·6 (1·3–1·9)	2·2 (1·8–2·6)	2·1 (1·8–2·5)	1·7 (1·4–2·1)
Disease of hair or scalp	16·5	7·6	8·6	2·4 (2·0–2·9)	2·4 (1·9–3·0)	2·2 (1·8–2·8)	2·1 (1·8–2·5)	2·0 (1·7–2·4)	1·8 (1·5–2·1)
Ear infection	12·3	7·2	8·8	1·8 (1·5–2·2)	1·5 (1·2–1·9)	1·4 (1·1–1·8)	1·5 (1·2–1·7)	1·4 (1·2–1·7)	1·2 (1·0–1·5)
Loss of hearing	11·8	5·9	9·4	2·1 (1·7–2·7)	1·5 (1·1–1·9)	1·4 (1·0–1·8)	1·3 (1·1–1·5)	1·4 (1·1–1·6)	1·1 (0·9–1·4)
Arthritis or rheumatism	9·7	4·1	7·9	2·5 (1·9–3·3)	1·5 (1·1–2·0)	1·3 (0·9–1·7)	1·2 (1·0–1·5)	1·4 (1·1–1·7)	1·1 (0·9–1·4)
Sexual problems	9·0	3·0	3·1	3·2 (2·4–4·3)	2·2 (1·5–3·1)	1·9 (1·3–2·7)	3·0 (2·3–3·9)	3·2 (2·4–4·2)	2·2 (1·7–3·0)
High blood pressure	8·8	4·3	6·6	2·2 (1·7–2·8)	1·4 (1·0–1·9)	1·3 (1·0–1·8)	1·5 (1·1–1·7)	1·5 (1·2–1·9)	1·2 (1·0–1·6)
Eczema or psoriasis	7·8	5·8	6·7	1·4 (1·1–1·8)	1·3 (1·1–1·7)	1·3 (1·0–1·6)	1·2 (1·0–1·5)	1·2 (1·0–1·5)	1·2 (0·9–1·5)
Asthma	6·5	4·5	3·7	1·5 (1·1–1·9)	1·2 (0·9–1·6)	1·2 (0·8–1·6)	1·8 (1·4–2·3)	1·8 (1·4–2·4)	1·6 (1·2–2·1)
Bronchitis	4·4	2·2	2·5	2·0 (1·4–2·9)	1·7 (1·1–2·5)	1·5 (1·0–2·3)	1·8 (1·3–2·5)	1·7 (1·2–2·3)	1·4 (1·0–1·9)
Disease of genital organs	3·8	3·3	2·2	1·1 (0·8–1·6)	1·6 (1·1–2·4)	1·5 (1·0–2·3)	1·7 (1·2–2·4)	1·5 (1·1–2·2)	1·3 (0·9–1·8)
Chronic fatigue syndrome or myalgic encephalitis	3·3	0·8	0·8	4·2 (2·4–7·4)	2·5 (1·3–4·8)	2·1 (1·1–4·0)	4·4 (2·7–7·3)	4·2 (2·5–7·2)	2·7 (1·6–4·6)
Multiple chemical sensitivity	0·8	0·4	0·3	1·9 (0·8–4·4)	1·1 (0·4–3·1)	1·0 (0·4–2·8)	2·2 (1·0–4·9)	2·2 (0·9–5·3)	1·7 (0·7–4·0)

*Controlled for sociodemographic and lifestyle variables (as for table 4).
†Controlled for sociodemographic variables plus general health questionnaire.

Table 5: **15 most frequently self-reported medical disorders, plus chronic fatigue syndrome and multiple chemical sensitivity, by deployment**

	Outcome (mean [SD])			Gulf *vs* Bosnia			Gulf *vs* Era		
	Gulf (n=3284)	Bosnia (n=1815)	Era (n=2408)	Unadjusted mean difference	Model 1 adjusted mean difference*	Model 2 adjusted mean difference†	Unadjusted mean difference	Model 1 adjusted mean difference	Model 2 adjusted mean difference†
SF-36 health perception‡	65·5 (25·1)	76·3 (20·8)	75·3 (22·0)	10·8 (9·4–12·1)	8·3 (6·8–9·7)	6·0 (4·7–7·4)	9·8 (8·5–11·0)	9·6 (8·4–10·8)	5·6 (4·5–6·7)
SF-36 physical functioning‡	91·2 (16·4)	95·0 (12·6)	92·3 (17·0)	3·8 (2·9–4·7)	1·4 (0·4–2·3)	0·5 (0·4–1·4)	1·1 (0·2–1·9)	1·2 (0·3–2·0)	−0·6 (1·4–0·3)

*Controlled for sociodemographic and lifestyle factors.
†Controlled for model 1 variables plus general health questionnaire score. ‡Higher scores show better health. Odds ratio (95% CI)

Table 6: **SF36 and other health outcomes in three groups**

	Frequency (%)			Gulf *vs* Bosnia (95% CI)			Gulf *vs* Era (95% CI)		
	Gulf (n=3284)	Bosnia (n=1815)	Era (n=2408)	Unadjusted odds ratio	Model 1 adjusted odds ratio	Model 2 adjusted odds ratio	Unadjusted odds ratio	Model 1 adjusted odds ratio	Model 2 adjusted odds ratio
General health questionnaire	39·2	26·3	24·0	1·8 (1·6–2·0)	1·6 (1·4–1·8)	· ·	2·0 (1·8–2·3)	2·1 (1·9–2·4)	· ·
Post-traumatic stress reaction	13·2	4·7	4·1	3·1 (2·4–3·9)	2·6 (1·9–3·4)	2·3 (1·7–3·2)	3·6 (2·8–4·4)	3·8 (2·8–4·9)	<2·7 (2·1–3·6)
Fatigue case	46·9	25·8	20·5	2·5 (2·2–2·9)	2·2 (1·9–2·6)	2·2 (1·9–2·7)	3·4 (3·0–3·8)	3·6 (3·2–4·2)	<3·5 (2·9–4·1)
CDC Gulf	61·9	36·8	36·4	2·8 (2·5–3·1)	2·5 (2·2–2·8)	2·4 (2·0–2·8)	2·8 (2·5–3·2)	2·9 (2·6–3·3)	<2·4 (2·1–2·8)

*Controlled for sociodemographic and lifestyle factors.
†Controlled for model 1 variables plus general health questionnaire score.

Table 7: **Odds ratios for health outcomes in three groups**

When we tested the CDC multisymptom syndrome,[5] for severe symptoms only, the outcome frequencies fell to 25·3% for the Gulf cohort, 11·8% for the Bosnia cohort, and 12·2% for the Era cohort, but the pattern of symptom reporting did not change. The addition of a time criterion (only symptoms since the Gulf deployment) made little difference (24·6% in the Gulf War cohort). Our severe criteria were not directly comparable with those of the CDC because not every symptom in our questionnaire included a severity dimension.

Exposures

For exposures (table 8), we checked reports of unusual exposures in the particular deployments, and all responses were true with no data-entry errors. We report associations with exposures only for self-reported physical health, the CDC syndrome, and post-traumatic stress reactions (table 9). There was no difference in the pattern of results for the other three main outcome measures (self-reported health perception, general health questionnaire, and fatigue cases). There was no difference in the pattern of responses to ingestion of pyridostigmine bromide tablets and all outcomes.

We found an association with the belief of exposure to a chemical attack. This exposure was associated with the lowest health perception (Gulf War cohort, odds ratio 2·4 [95% CI 1·8–31·2]) and had the strongest association with the CDC syndrome (2·6 [1·9–3·5]), followed by the general health questionnaire case criteria (2·0 [1·5–2·5]) and fatigue case criteria (2·2 [1·7–2·9]).

Vaccinations

31·8% of the Gulf War cohort reported that they had vaccination records. Few were forwarded, but checks suggested that most individuals used their records when completing the questionnaire. Of a random sample of 100 respondents who retained their records, 29 included the details of the vaccine batch number, the exact date of vaccination, or both. We recontacted a further 20 servicemen who reported that they possessed their records but whose responses did not indicate that they used them when completing the questionnaire. 16 (80%) said they had copied the vaccination records directly. Finally, although pertussis was always administered with anthrax vaccine, only 2·8% of veterans without records remembered receiving pertussis vaccine, compared with 36·2% of those with records (table 10), which is strong evidence that records were used. The outcome measure did not differ between those with and without records.

Vaccines were divided into biological warfare vaccines (plague and anthrax plus adjuvant pertussis) and routine vaccinations, which include IgG for hepatitis A (table 10). There was a relation between reporting biological warfare vaccination and outcome, irrespective of the use of records (table 11). The pattern for routine vaccines was less clear. Servicemen who had served in the Gulf War showed a weak relation between receiving individual non-biological warfare vaccines and the outcome, but this relation was not seen in the Bosnia cohort. The relation for routine, as opposed to biological warfare vaccines, was, however, seen only in Gulf War veterans who did not use their records.

Because there has been much speculation that veterans who received multiple vaccinations were at risk of illness, we added the total number of vaccinations received. This was broken down into quintiles (40% of veterans reported receiving no vaccines and form the first two quintiles). Overall, there was a significant effect that was specific to

Exposures	Gulf† (%)	Bosnia (%)	Era (%)
Diesel or petrochemical fumes	84·0	75·9	68·5
NBC suits	81·7	3·1	3·3
Pyridostigmine bromide	81·6	1·9	5·2
Exhaust from heaters or generators	78·2	79·3	61·5
Smoke from oil-well fires	72·4	3·9	3·1
Sound of chemical alarms	70·7	2·7	6·6
Personal pesticides	69·2	48·9	38·2
Local food‡	69·1	65·9	· ·
Burning rubbish or faeces	66·7	58·7	33·1
Diesel or petrochemical fuel on skin	66·6	60·7	53·3
Dismembered bodies	66·3	39·7	25·1
Other paints or solvents	63·9	54·9	54·0
Dead animals	56·6	57·1	23·0
Handled prisoners of war	53·6	28·7	10·0
Maimed soldiers	48·0	32·0	25·2
Pesticides on clothing or bedding	38·4	25·5	18·3

*All exposures except dead animals and exhaust from heaters or generators were more frequent in Gulf cohort than Bosnia and Era.
†Ordered by frequency in Gulf cohort.
‡Not asked in Era group.

Table 8: **15 most frequently self-reported exposures* by deployment**

	Gulf War	Bosnia	Era
SF-36 physical functioning			
Diesel or petrochemical fumes	1·4 (1·2–1·7)	1·4 (1·0–1·8)	1·8 (1·5–2·2)
NBC suits	1·5 (1·3–1·8)	1·5 (0·8–2·7)	1·4 (0·9–2·3)
Pyridostigmine bromide	1·3 (1·1–1·5)	1·7 (0·8–3·5)	1·1 (0·8–1·7)
Exhaust from heaters of generators	1·4 (1·2–1·7)	1·4 (1·1–1·9)	1·7 (1·4–2·0)
Smoke from oil-well fires	1·2 (0·99–1·3)	0·7 (0·4–1·3)	1·2 (0·7–2·0)
Hear chemical alarms sounding	1·5 (1·3–1·8)	1·5 (0·7–2·8)	1·5 (1·0–2·0)
Personal pesticides	1·5 (1·3–1·8)	1·4 (1·1–1·8)	1·5 (1·2–1·8)
Local food*	1·0 (0·9–1·2)	1·3 (1·0–1·7)	. .
Burning rubbish or faeces	1·2 (1·0–1·4)	1·0 (0·8–1·2)	1·3 (1·1–1·6)
Diesel or petrochemical fuel on skin	1·4 (1·2–1·6)	1·2 (0·9–1·5)	1·5 (1·3–1·8)
Dismembered bodies	1·3 (1·2–1·5)	1·3 (1·0–1·6)	1·3 (1·0–1·5)
Other paints or solvents	1·4 (1·2–1·6)	1·3 (1·0–1·7)	1·6 (1·3–1·9)
Dead animals	1·2 (1·1–1·4)	1·2 (0·9–1·5)	1·2 (0·9–1·4)
Handled prisoners of war	1·1 (0·9–1·3)	1·3 (1·0–1·6)	1·0 (0·7–1·3)
Maimed soldiers	1·2 (1·0–1·4)	1·3 (1·0–1·6)	1·3 (1·1–1·6)
Pesticides on clothing or bedding	1·4 (1·2–1·6)	1·5 (1·4–1·9)	1·6 (1·2–1·9)
Other exposures of interest			
Chemical or nerve gas attack	2·2 (1·7–2·9)	9·5 (1·9–47·1)	1·5 (0·8–2·9)
Mustard gas	1·8 (1·2–2·9)	1·2 (0·3–4·4)	1·7 (0·6–4·5)
Combat-related injury	1·8 (1·4–2·4)	1·6 (1·1–2·4)	2·1 (1·5–2·9)
Witness anyone dying	1·4 (1·2–1·7)	1·5 (1·2–2·0)	1·3 (1·0–1·5)
SCUD missile explosion within 1 mile	1·5 (1·3–1·8)	3·1 (1·0–9·7)	1·3 (0·5–3·6)
Come under small-arms fire	1·1 (0·9–1·3)	1·8 (0·9–1·5)	1·3 (1·1–1·6)
Artillery close by	1·4 (1·2–1·6)	1·2 (0·9–1·5)	1·2 (0·9–1·5)
CDC syndrome			
Diesel or petrochemical fumes	2·1 (1·7–2·5)	1·8 (1·4–2·3)	2·4 (1·9–2·9)
NBC suits	2·7 (2·3–3·3)	2·7 (1·6–4·8)	2·3 (1·5–3·7)
Pyridostigmine bromide	2·6 (2·2–3·1)	3·4 (1·7–6·8)	1·9 (1·4–2·8)
Exhaust from heaters or generators	1·9 (1·6–2·2)	2·8 (2·1–3·7)	2·4 (1·9–2·8)
Smoke from oil-well fires	1·8 (1·5–2·1)	1·4 (0·8–2·3)	1·8 (1·1–2·9)
Hear chemical alarms sounding	2·2 (1·9–2·6)	2·5 (1·4–4·5)	2·3 (1·7–3·2)
Personal pesticides	2·2 (1·9–2·6)	1·8 (1·5–2·2)	1·8 (1·5–2·2)
Local food*	1·1 (0·9–1·3)	1·8 (1·5–2·3)	. .
Burning rubbish or faeces	1·9 (1·6–2·2)	1·9 (1·6–2·3)	1·8 (1·5–2·1)
Diesel or petrochemical fuel on skin	1·8 (1·5–2·1)	1·8 (1·5–2·2)	2·0 (1·7–2·4)
Dismembered bodies	2·0 (1·7–2·3)	2·0 (1·6–2·4)	1·9 (1·5–2·3)
Other paints or solvents	1·7 (1·5–2·0)	1·9 (1·5–2·3)	1·9 (1·6–2·3)
Dead animals	1·8 (1·5–2·0)	2·4 (1·9–2·9)	2·3 (1·9–2·8)
Handled prisoners of war	1·7 (1·5–1·9)	2·2 (1·8–2·7)	1·9 (1·5–2·5)
Maimed soldiers	1·7 (1·5–2·0)	2·0 (1·6–2·5)	1·8 (1·5–2·2)
Pesticides on clothing or bedding	1·9 (1·6–2·2)	1·7 (1·4–2·2)	1·9 (1·5–2·3)
Other exposures of interest			
Chemical or nerve gas attack	2·6 (1·9–3·5)	6·0 (1·2–29·0)	2·2 (1·2–4·2)
Mustard gas	1·9 (1·2–3·3)	7·7 (1·6–35·9)	3·2 (1·2–8·7)
Combat-related injury	2·9 (2·1–4·2)	2·4 (1·7–3·6)	3·1 (2·2–4·2)
Witness anyone dying	1·6 (1·4–1·9)	2·0 (1·6–2·6)	1·8 (1·4–2·1)
SCUD missile explosion within 1 mile	1·6 (1·4–1·9)	2·4 (0·8–7·5)	2·2 (0·8–6·0)
Come under small-arms fire	1·5 (1·3–1·7)	1·7 (1·4–2·1)	1·6 (1·4–1·9)
Artillery close by	1·9 (1·6–2·2)	1·8 (1·4–2·2)	1·6 (1·3–2·0)
Post-traumatic stress reaction			
Diesel or petrochemical fumes	2·5 (1·7–3·6)	3·2 (1·5–6·7)	1·9 (1·1–3·1)
NBC suits	3·0 (2·1–4·4)	2·0 (0·8–5·3)	3·3 (1·6–6·7)
Pyridostigmine bromide	3·1 (2·1–4·4)	1·9 (0·6–6·4)	2·1 (1·1–4·2)
Exhaust from heaters or generators	2·3 (1·7–3·1)	4·4 (1·8–11·0)	2·6 (1·6–4·2)
Smoke from oil-well fires	2·3 (1·7–2·9)	3·2 (1·6–6·8)	3·0 (1·4–6·5)
Hear chemical alarms sounding	2·1 (1·6–2·8)	1·4 (0·4–4·5)	1·8 (0·9–3·5)
Personal pesticides	2·3 (1·7–2·9)	1·8 (1·1–2·8)	1·8 (1·2–2·8)
Local food*	0·8 (0·6–0·9)	2·1 (1·2–3·7)	. .
Burning rubbish or faeces	2·0 (1·5–2·5)	3·5 (1·9–6·1)	2·8 (1·8–4·2)
Diesel or petrochemical fuel on skin	2·0 (1·6–2·6)	2·1 (1·2–3·4)	2·0 (1·3–3·0)
Dismembered bodies	2·7 (2·1–3·5)	3·9 (2·4–6·3)	3·7 (2·5–5·5)
Other paints or solvents	1·4 (1·1–1·7)	2·2 (1·3–3·5)	3·3 (2·0–5·4)
Dead animals	1·6 (1·3–1·9)	3·9 (1·9–5·9)	2·9 (1·9–4·3)
Handled prisoners of war	2·3 (1·8–2·8)	4·0 (2·6–6·3)	1·5 (0·9–2·7)
Maimed soldiers	2·8 (2·3–3·5)	3·8 (2·4–6·0)	3·7 (2·5–5·5)
Pesticides on clothing or bedding	2·4 (1·9–2·9)	1·9 (1·2–3·0)	2·9 (1·9–4·5)
Other exposures of interest			
Chemical or nerve gas attack	3·1 (2·3–4·1)	2·4 (0·3–19·7)	1·2 (0·3–4·9)
Mustard gas†	2·1 (1·2–3·6)	· ·	1·4 (0·2–11·0)
Combat-related injury	2·4 (1·8–3·3)	2·4 (1·3–4·6)	5·0 (3·1–8·2)
Witness anyone dying	2·2 (1·8–2·7)	2·5 (1·6–3·9)	2·8 (1·9–4·2)
SCUD missile explosion within 1 mile	1·7 (1·4–2·1)	3·3 (0·7–14·9)	3·9 (0·9–18·3)
Come under small-arms fire	2·0 (1·6–2·5)	2·9 (1·8–4·8)	3·9 (2·6–5·9)
Artillery close by	2·4 (1·9–2·9)	2·3 (1·5–3·6)	3·8 (2·5–5·7)

*Not asked in Era group. †Statistic for Bosnia not calculated due to empty cell. Odds ratio (95% CI).

Table 9: **Association of 15 most frequent exposures and exposures of interest with principal health outcomes**

	Gulf (%)			Bosnia (%)		
	All	Record (n=940)	No record (n=2242)	All	Record (n=1127)	No record (n=1718)
Biological warfare vaccine						
Anthrax	57·2	69·3	55·1	2·6	2·9	2·5
Plague	25·7	34·1	23·3	0·2	0·4	0
Pertussis	12·2	36·2	2·8	0·1	0·3	0
Any biological	58·4	69·7	56·4	2·9	3·5	2·5
Routine vaccines						
Hepatitis A	6·3	7·8	6·1	23·8	37·2	14·2
Hepatitis B	7·2	10·6	6·1	12·3	17·8	8·6
Yellow fever	14·0	15·8	13·9	13·4	19·3	9·5
Typhoid	12·5	25·4	7·6	15·9	27·7	7·4
Poliomyelitis	13·7	15·9	12·8	14·7	20·0	11·2
Cholera	13·7	31·5	6·2	2·1	2·7	1·6
Tetanus	33·8	34·3	32·3	29·3	39·5	22·2
Any routine vaccination	48·1	62·4	42·0	45·6	61·8	33·3

Table 10: **Frequency of reported vaccines by theatre of war and vaccine records**

the Gulf cohort, with a significant interaction term (table 11). The effect persisted after control for receipt of biological warfare vaccines (table 12). Stratification by use of records to control for recall bias did not affect the association (table 13). The same analyses were repeated for the other five main outcomes. For each of these outcomes, multiple vaccinations were associated with poorer health after control for deployment. The interaction term between deployment and multiple vaccinations was significant for only two of these outcomes—health perception and physical health. There was no interaction between pyridostigmine bromide ingestion and multiple vaccinations (p=0·7).

We repeated the analyses to find out whether side-effects experienced at the time of vaccinations were associated with the outcome. Veterans who recalled experiencing side-effects were more likely to have current symptoms (Gulf War cohort 2·8 [2·4–3·3]; Bosnia cohort 2·2 [1·6–3·1]). Analyses including reporting side-effects in the model, for the variables shown in table 11, showed only one significant association between tetanus vaccination and ill health in the Gulf War cohort (1·2 [1·0–1·4]). After control for reported side-effects the association between all vaccinations and illness was weakened, but remained significant (table 13). The relation between multiple vaccinations and outcome was almost unchanged in servicemen who had vaccination records.

Discussion

UK veterans of the Gulf War report higher rates of many symptoms and disorders and have a decreased perception of well being than servicemen who were not deployed to the Gulf War, despite no evidence of increased frequencies and no excess of objective outcomes, such as birth defects, cancers, or death.[1,2,4] By contrast, we report that servicemen in the Gulf were about three times more likely to fulfil criteria for chronic fatigue, post-traumatic stress reaction, or the CDC multisymptom syndrome criteria than those in the control cohorts, even after adjustment for confounders. These participants were at least twice as likely to experience similar outcomes as those deployed to Bosnia. Despite these findings, disability was not severe, and there is no evidence of an increased rate of adverse outcomes such as unemployment or marital breakdown. Nevertheless, we believe that our data constitute firm evidence that service in the Gulf War has affected the health of servicemen.

	Gulf			Bosnia		
	Odds ratio for all	With records odds ratio	Without records odds ratio	Odds ratio for all	With records odds ratio	Without records odds ratio
Biological warfare vaccine						
Anthrax	1·5 (1·3–1·7)	1·4 (1·0–1·8)	1·4 (1·2–1·7)	1·5 (0·7–2·9)	2·6 (0·9–7·4)	0·9 (0·4–2·3)
Plague*	1·3 (1·1–1·6)	1·1 (0·9–1·5)	1·4 (1·1–1·7)	· ·	· ·	· ·
Pertussis*	1·1 (0·9–1·4)	1·3 (1·0–1·7)	0·9 (0·5–1·6)	· ·	· ·	· ·
Any biological	1·5 (1·3–1·7)	1·4 (1·1–1·9)	1·5 (1·2–1·8)	1·5 (0·8–2·8)	2·5 (0·9–6·6)	0·9 (0·4–2·3)
Routine vaccines						
Hepatitis A	1·1 (0·8–1·5)	1·1 (0·7–1·9)	1·0 (0·7–1·5)	1·1 (0·8–1·4)	1·1 (0·7–1·5)	1·1 (0·7–1·6)
Hepatitis B	1·0 (0·8–1·3)	1·0 (0·7–1·6)	0·9 (0·6–1·3)	1·2 (0·9–1·7)	1·2 (0·8–1·9)	1·2 (0·7–2·1)
Yellow fever	1·3 (1·1–1·7)	1·4 (0·9–2·0)	1·3 (0·9–1·6)	1·0 (0·7–1·4)	0·8 (0·5–1·2)	1·2 (0·7–1·9)
Typhoid	1·0 (0·8–1·3)	1·0 (0·7–1·4)	1·1 (0·8–1·5)	1·1 (0·8–1·5)	1·1 (0·7–1·6)	1·1 (0·7–1·9)
Poliomyelitis	1·2 (0·96–1·5)	0·9 (0·8–1·4)	1·3 (1·0–1·8)	1·2 (0·9–1·7)	0·9 (0·6–1·4)	1·6 (1·1–2·5)
Cholera	1·1 (0·9–1·4)	1·1 (0·8–1·4)	1·3 (0·9–1·9)	0·8 (0·3–2·1)	0·5 (0·1–2·3)	1·1 (0·3–4·0)
Tetanus	1·3 (1·1–1·5)	1·1 (0·8–1·4)	1·3 (1·1–1·6)	1·0 (0·8–1·3)	1·0 (0·7–1·3)	1·1 (0·8–1·5)
Any routine	1·2 (1·1–1·4)	1·0 (0·7–1·3)	1·3 (1·1–1·5)	1·1 (0·9–1·3)	1·0 (0·7–1·3)	1·2 (0·9–1·6)

*Odds ratios not calculated for Bosnia because of empty cells.

Table 11: **Associations between reported vaccinations and CDC syndrome, stratified by theatre of war and whether respondent had vaccination record**

Study limitations

As in similar studies, the most important factor for participation in the survey was our ability to find accurate addresses.[5,6,13,14] The second factor influencing response was demography. Young men generally change addresses frequently and are not inclined to respond to lengthy questionnaire surveys,[15] which has been experienced in previous studies of Gulf War veterans.

A key question is whether or not participation was biased towards those with health complaints. Responders were more likely to still be in service, but did not differ from non-responders on various relevant health outcomes, including the proportion of those given medical discharges. There was no suggestion that veterans with worse health outcomes were more or less likely to respond at the earliest opportunity, although those with more symptoms responded earlier and proportionally more responders attended the medical assessment programme. An identical pattern of response was reported in the US study most comparable with our own.[14] By contrast, servicemen traced by intensive follow-up, who were assumed to represent non-responders to the main study, had worse health perception than responders. The difference was not significant, did not differ by cohort, and was not accompanied by a similar decline in self-reported physical functioning. We conclude that the pattern that those who had more symptoms responded earlier was in keeping with other large surveys. A few veterans probably had worse health and were also non-responders, which has been shown in individuals who attribute poor health to living close to hazardous waste sites.[16] We suspect that few of the persistently non-responding veterans may feel distrust for and alienation from "authority", a phenomenon reported previously in soldiers returning from war.[17,18] The most important conclusion is that differential non-response between the three cohorts does not explain the observed results.

Total vaccinations	All (Gulf and Bosnia)	Gulf		Bosnia	
		All records	With records	All records	With records
0*	· ·	· ·	· ·	· ·	· ·
1–2	0·9 (0·8–1·1)	0·9 (0·7–1·2)	1·2 (0·7–2·0)	1·0 (0·8–1·3)	1·0 (0·7–1·4)
3–6	1·4 (1·2–1·6)	1·2 (1·0–1·4)	1·1 (0·8–1·6)	1·1 (0·8–1·4)	0·8 (0·6–1·2)
⩾7	2·6 (2·2–3·1)	1·8 (1·5–2·2)	1·9 (1·3–2·8)	1·1 (0·4–3·4)	1·2 (0·3–5·5)
p	<0·0001	<0·0001	0·001	0·6	0·5

Interaction term vaccinations by theatre of war χ^2 4·6 (p=0·03).
*Reference.

Table 12: **Associations between multiple vaccination and CDC syndrome**

Total vaccinations	Control for biological warfare vaccines		Control for experience of side-effects after vaccination	
	All	Records only	All	Records only
0*	· ·	· ·	· ·	· ·
1–2	0·8 (0·6–1·0)	0·9 (0·6–1·5)	0·8 (0·6–1·1)	1·3 (0·7–2·2)
3–6	1·0 (0·6–1·0)	1·1 (0·8–1·5)	1·0 (0·8–1·2)	1·1 (0·8–1·6)
⩾7	1·5 (1·2–1·9)	1·7 (1·2–2·4)	1·3 (1·0–1·6)	1·7 (1·1–2·5)
p	0·0005	0·008	0·05	0·01

*Reference.

Table 13: **Associations between multiple vaccination and CDC syndrome, controlled for experience of side-effects and biological warfare vaccine, Gulf only**

There has been dispute about the choice of controls in Gulf War studies. Some argue that deployed veterans may be healthier than servicemen who are not deployed, which would lead to a "healthy warrior" bias,[3] and which could have obscured an increase in adverse outcomes in those deployed. The issue is unresolved,[19] but cannot account for our findings. The associations between the Gulf War and Era cohorts were only slightly more robust than those between the Gulf War and Bosnia cohorts, which suggests that the "healthy warrior" effect was not strong. We controlled for predeployment fitness, a proxy for general health. Given the robust increases in ill health reported by Gulf War veterans, any "healthy warrior" effect would add to the strength of our findings.

All the chosen outcomes are questionnaire-based and relied on self-report. We have not reported the frequency of disorders such as asthma, neuropathy, major depression, chronic fatigue syndrome, or post-traumatic stress disorder, which require a clinical interview and examination for diagnosis. Instead our chosen outcomes should be interpreted as indicating that the responder was more likely to have a disorder but not as being diagnostic. The differential patterns between the three cohorts therefore show more than the absolute numbers for each classification.

We did not do physical examinations. Previous studies of selected and randomly chosen Gulf War veterans have shown an absence of unexpected abnormal findings.[1,5,20,21] Routine surveillance of Gulf War veterans for infectious disease has generally been negative.[5] In addition, Gulf War veterans seem to have no increased rates of defined physical disorders that might explain increased symptom reporting.[4] Likewise, whereas Vietnam veterans complain

of a range of self-reported symptoms and disorders, these were rarely diagnosed on physical examination or investigation.[22] A few veterans may have undetected physical disease, but this possibility would not affect the pattern of our results. We intend to do further studies that include detailed physical, neurophysiological, and neuropsychological examinations of veterans who report symptoms and of controls.

Implications

The finding that active military service has led to long-term adverse health effects is not new and has been reported in US and Australian Vietnam veterans,[22,23] and inferred after earlier conflicts.[24] Furthermore, the US study of Gulf veterans most comparable to ours reported a similar decline in self-reported health status and higher rates of various symptoms and disorders.[6]

The most obvious explanation for this increase in symptoms in the Gulf War veterans is that it relates to different experiences of hazardous exposures. The differences in many self-reported exposures between Gulf veterans and controls was not substantial. For example, although reported use of pesticides was common among UK Gulf veterans (more so than US servicemen[6]), it was also frequently reported in the Bosnia and Era cohorts.

Three types of self-reported exposures did differ substantially between the Gulf War veterans and the comparison cohorts: exposure to the smoke of burning oil wells, vaccinations against biological warfare, and measures to protect against, and possible exposure to, chemical warfare.

All service personnel deployed abroad are routinely vaccinated against several infective agents. Some personnel received booster doses of one or more of these vaccinations before deployment. At the time of the Gulf War, two new vaccination programmes were started to protect troops against plague and anthrax. Pertussis vaccine was administered with the anthrax vaccine as an adjuvant, to speed the immunological response. Servicemen who received vaccinations against biological warfare agents were more likely to report long-term symptoms. Those who received routine vaccinations were generally not at increased risk. Receipt of multiple non-biological warfare vaccinations was, however, associated with an increased risk of illness, but only among Gulf War veterans, even though Bosnia veterans also received multiple vaccinations. This finding was not explained by simultaneous exposure to biological warfare vaccines. A striking relation between retrospective recollection of side-effects of vaccines at the time and later illness seemed to explain the association between individual vaccines and illness, but not multiple vaccines and illness.

The association between receipt of any routine vaccinations and adverse outcomes was significant only in servicemen who had not used their vaccination records, which suggests some recall bias. However, servicemen who had used their records were more likely to report biological warfare vaccination, which suggests that some had forgotten that they had received biological warfare vaccines. Slight positive and negative recall biases were, therefore, present, but our main findings on the long-term outcome of biological vaccines and multiple vaccines in the Gulf War was unlikely to be because of recall bias. The association persisted in servicemen who had their records, which were generally used when completing the questionnaire.

We cannot explain the vaccine findings. Multiple vaccinations in a short period of time have been suggested to produce a shift in the cytokine profile from Th1 to Th2.[25] We hope to be able to test this hypothesis directly. Likewise, there may be an interaction between stress and response to vaccination,[25] as has been suggested for pyridostigmine ingestion in experimental animal models.[26] We found no interactions between exposures such as immunisations and pyridostigmine bromide. Finally, psychological mechanisms should be taken into account that are consistent with our data; for example, symptoms experienced acutely after vaccination could generate health anxiety and prime recipients to detect similar generalised symptoms occurring later. Given the results of our accompanying paper (pages 179–82), multiple or biological warfare vaccination may be a further non-specific trigger for later symptoms.

The third factor specific to the Gulf conflict was the realistic threat of chemical warfare. Nearly 70% of US personnel surveyed just before the active conflict reported that anticipation of attack by chemical weapons, biological weapons, or both was their most common fear.[27] 7 years later we found that nearly all Gulf veterans remember wearing nuclear-biological-chemical suits and hearing chemical alerts, 26% reported a SCUD missile explosion nearby, and 9% believed that they had been exposed to chemical attack.

Gulf and Bosnia veterans differed in their experience of needing to protect themselves against chemical attack, their perception that such attack might be imminent, and the belief that such an attack had taken place. Whether or not such attack occurred is uncertain, although an accidental discharge of chemical agents did take place after the war (the Khamisiyah incident[28]). Irrespective of whether actual exposure took place, the threat of such exposure was real to the servicemen and may be a risk factor for development of the adverse outcomes we report.

Previous attempts to give at least a part explanation of the health difficulties of US veterans have drawn specific analogies with combat stress and subsequent post-traumatic stress disorder. Classic traumatic events, such as seeing dismembered bodies, maimed soldiers, or witnessing death were associated with Gulf War service, but were not unique to that deployment. Combat-related injury, one of the most robust associations of post-traumatic stress,[29] was one of the strongest associations of all the outcomes, but did not differ between the cohorts. Adjustment for psychological distress did not alter the pattern of results. Although clinically diagnosed post-traumatic stress disorder has been associated with increased experience of physical symptoms,[30,31] narrowly defined post-traumatic stress pathways can only partly explain the pattern of results. Likewise, war trauma, although important, is not by itself sufficient explanation for our findings. We prefer to broaden the definition of stress to include environmental as well as direct battle traumas, as noted in the Vietnam War[32] and in civilian life.[33]

Our findings suggest that general mechanisms link adversity and health outcomes. These mechanisms include the general effect of conflict on self-reported health and the general association between all potentially adverse exposures and health.[6] Therefore, although some of the exposures were unique to the Gulf War, the mechanisms linking them to ill health might not be specific. One pathway could involve perceived risk and later ill health.

We suspect that the threat of chemical attack was one such exposure, analogous to previous observations that link self-reported exposure to herbicide ("Agent Orange") and various similar outcomes.[34] Recall bias in which servicemen with more symptoms recall more exposures may be a further general link, as seen in assessment of possible toxic hazards several years after exposure.[35] The increase in symptoms, for whatever reason, leads to lower health perception, and an increased probability of endorsing any specified medical disorder.

Finally, we cannot exclude possible unique biological mechanisms that link Gulf War service and later ill health. We have shown an adverse effect of multiple vaccination specific to the Gulf War and aim to confirm this finding in further studies. We cannot make recommendations about the medical preparation for future military conflicts from our findings.

A fuller understanding of why service in the Persian Gulf War was associated with a definite decline in general well-being will come from assessment of the effects of true and perceived exposure to physical and psychological adversity, and the interaction between the two.

Contributors

Catherine Unwin coordinated the study, and was involved in analysis and the writing of the paper. Nick Blatchley gave statistical support and created the study cohorts. William Coker and Ian Palmer are grant holders, and provided military advice and liaison. Lisa Hull traced veterans and coordinated the study and follow-up. Khalida Ismail did the follow-up study, and was involved in the analysis and the writing of the paper. Susan Ferry was the initial study coordinator. Matthew Hotopf gave epidemiological advice and was involved in the analysis and the writing of the paper. Anthony David and Simon Wessely were the principal investigators and planned, designed, and supervised the study, as well as drafting the paper.

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