

Medically evaluated psychological and physical health of Australian Gulf War veterans with chronic fatigue

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Abstract

Objective: The aim of this study was to evaluate fatigue in Australian Gulf War veterans and a military comparison group according to the 1994 chronic fatigue syndrome (CFS) definition and investigate the relation with exposures. **Methods:** Comprehensive medical, psychological and reported exposure assessments of 1456 veterans and 1588 comparison group in a cross-sectional study. **Results:** More Gulf War veterans had fatigue at all levels than did the military comparison group. The findings may be at least partly explained as an “active-deployment effect.” The odds

ratios increased with increasing clinical evaluation of the nature of the fatigue, even after adjustment for current psychiatric disorders in addition to other possible confounding factors. **Conclusion:** Medically unexplained chronic fatigue was more common, but not more disabling, in veterans than in the comparison group, but veterans with unexplained chronic fatigue had poorer health than veterans without. Within both populations, CFS is uncommon and at a similar level to the general community.

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Introduction

Fatigue is one of the most common and troublesome symptoms reported by veterans of the 1991 Gulf War (veterans). It has been reported by up to 50% of UK and US veterans in postal and telephone surveys and more commonly than by non-Gulf military comparison groups [1–4]. In Australian veterans, 66% reported fatigue in the past month, compared with 56% of a military comparison group, and more veterans reported fatigue that was moderate or severe in nature [5]. Australian veterans have also been shown to have an increased risk of psychiatric

disorders first present in the post-Gulf War period [6] and higher levels of current psychological ill-health and lower-mental-health status than the military comparison group [6,7]. Somatic features of postdeployment syndromes have been documented at least since the Boer War [8]. The relationship between fatigue and psychological symptoms is well documented in nonmilitary populations in the literature on somatization [9], indicating the need to consider the relationship between medically unexplained fatigue and psychiatric disorders in this veteran population. A comprehensive evaluation of fatigue according to a recognized definition, such as the 1994 chronic fatigue syndrome (CFS) case definition [10], has not been possible in most epidemiological studies of veterans, as a medical and psychological evaluation of subjects has not been undertaken.

Australia deployed 1871 Australian Defence Force (ADF) personnel to the 1991 Gulf War. In a cross-sectional

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study, we combined a comprehensive medical assessment with other health and exposure data collected through a postal questionnaire to investigate whether, at the time of the study, Australian Gulf War veterans have a higher prevalence of levels of fatigue including chronic fatigue, medically unexplained chronic fatigue (denoted unexplained chronic fatigue) and CFS than the comparison group, according to the 1994 CFS definition. We explored whether any excess risk of fatigue outcomes could be explained as an “active-deployment effect.” We further investigated whether veterans and comparison group subjects with unexplained chronic fatigue differ in their demographic, physical and psychological characteristics and whether veterans with unexplained chronic fatigue differ in their physical and mental health status and level of functioning from veterans without unexplained chronic fatigue. We also examined the relationship between unexplained chronic fatigue in veterans and exposures or experiences that may have occurred in the Gulf War deployment.

Methods

Study population

Our study population was the entire group of 1871 Australian veterans who served in the Gulf region during the period August 2, 1990, through September 4, 1991. A comparison group of 2924 subjects was randomly selected from 26,411 ADF personnel who were in operational units at the time of the Gulf War but who were not deployed to that conflict. The comparison group was frequency matched to the veteran group by sex, service branch and 3-year age bands. The study was conducted from August 2000 to April 2002. Overall, 1456 (80.5%) of 1808 eligible veterans (not deceased or living overseas for the duration of the study) and 1588 (56.8%) of 2796 eligible comparison group subjects participated.

Due to the small number of female Gulf War veterans, analyses were limited to males. The study groups consisted of 1424 male veterans who completed a postal questionnaire, of whom 1384 subjects undertook a medical assessment, and 1548 male comparison group subjects who completed a postal questionnaire, of whom 1379 subjects undertook a medical assessment. Participating veterans were slightly younger, more likely to have served in the Navy, less highly ranked and less likely to have tertiary education than comparison group subjects. Further details of recruitment, demographic characteristics, psychiatric disorders, general health symptoms and medical conditions have previously been reported [5–7].

The Human Research Ethics Committees of Monash University, Department of Veterans’ Affairs and the Department of Defence approved the study.

Data collection

Definition and evaluation of fatigue

Fatigue is a complex entity, and in recognition of the need for a comprehensive and systematic approach to the definition and study of CFS, a collaborative International Chronic Fatigue Syndrome Study Group published an approach to defining cases of CFS and other fatiguing illnesses in 1994 [10], which remains the international standard for classification of research subjects in regard to CFS [11]. The 1994 definition defines *fatigue* by varying durations and *CFS* by the presence of severe, disabling fatigue and a combination of at least four of eight designated symptoms (Fig. 1). There is no diagnostic test for CFS, but any medical or psychiatric condition that could explain the chronic fatigue needs to be excluded [10].

We based our methodological approach to the assessment of fatigue in participants on this 1994 definition [10]. All steps in this process, summarized in Fig. 1, were undertaken without knowing the participants’ Gulf War status. Participants completed a self-administered postal questionnaire. A comprehensive medical assessment was carried out at one of 10 medical clinics located around Australia. In a structured clinical interview, doctors assessed *extreme tiredness or fatigue following normal activities in the past 12 months* and its duration as *prolonged* (≥ 1 month) and *chronic* (persistent, relapsing or recurring for ≥ 6 months) *fatigue*. The doctor asked about the onset of fatigue; the percentage of normal activities the participant was able to do during periods of fatigue; and any preceding illness, injury, or event.

The doctor also conducted a physical examination, and suitably healthy participants performed a fitness test, which involved stepping at a designated cadence up and back from a 40-cm platform for 3 min [12]. Heart rate in recovery was used to determine aerobic fitness [13]. Height, weight, waist and hip circumferences and blood pressure were measured, and urinalysis was performed. A respiratory health questionnaire was administered. Lung function was tested using spirometry according to American Thoracic Society (ATS) procedures [14].

In a face-to-face interview with psychologists, participants were evaluated for any history of affective, anxiety, somatic and substance use disorders according to diagnostic criteria described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* [15], using the interviewer-administered and computer-assisted version of the Composite International Diagnostic Interview (CIDI) [16]: the CIDI-Auto 2.1 [17], as previously described [6].

Laboratory investigations, conducted at a single national laboratory, included complete blood examination, erythrocyte sedimentation rate (ESR), urea, creatinine, electrolytes, serum calcium and phosphate, liver function tests, random plasma glucose, C-reactive protein (CRP) and serology tests

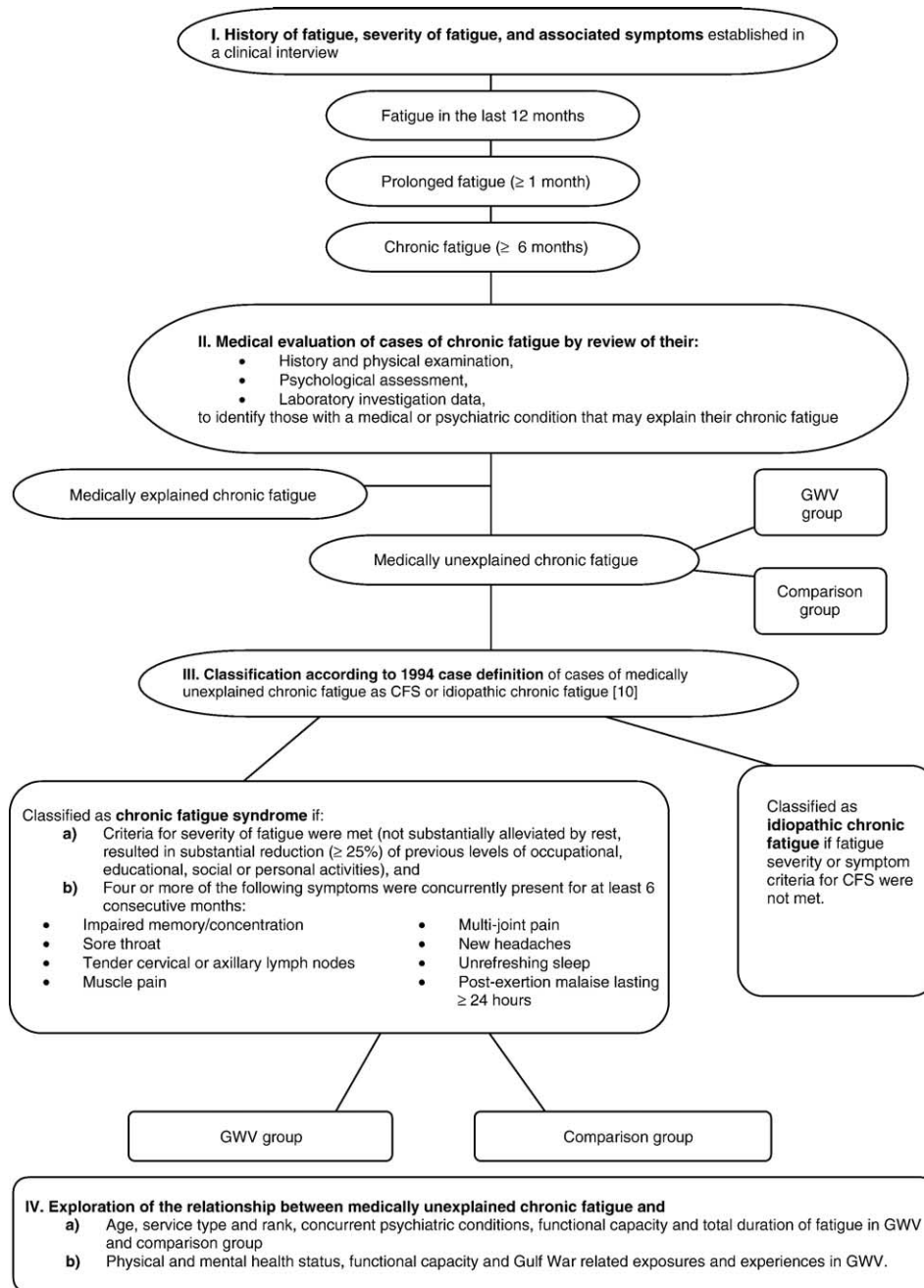


Fig. 1. Process for defining cases of unexplained chronic fatigue and CFS and their further evaluation in Gulf War veterans (GWV) and comparison group.

[Epstein-Barr virus (EBV) IgG, Cytomegalovirus (CMV) IgG and hepatitis C core antibody].

The postal questionnaire included questions about demographic and military service details; active deployments other than the Gulf War; tobacco use; current symptoms; doctor-diagnosed or doctor-treated medical conditions and whether these had been treated by a doctor in the past year; current medications; psychological stressors during the Gulf War using the Military Service Experience (MSE) questionnaire [6]; the Alcohol Use Disorders Identification Test (AUDIT) [18]; 12-item General Health Questionnaire (GHQ-12) [19]; 12-item Short-Form Health

Survey (SF-12) [20] and chemical exposures including solvents, pesticides, insect repellents and self-report of being in an area where chemical warfare agents had probably been used. Veterans were asked about the duration and quantity of pyridostigmine bromide (PB) (a reversible acetylcholinesterase inhibitor given as nerve agent prophylaxis), antimalarial or antibiological warfare tablets taken and for details about immunizations received.

Subsequent to data collection, a medical doctor (HK) reviewed and evaluated the files of those participants with chronic fatigue and identified those with an exclusionary medical or psychiatric condition [10]. *Unexplained chronic*

fatigue was defined as chronic fatigue for which a medical or psychiatric condition that could have explained their fatigue was not identifiable and further classified as CFS or *idiopathic chronic fatigue* on the basis of analysis of severity of fatigue and presence of associated symptoms.

Further definition of exposures and risk factors

Active deployments were defined as war or peacekeeping deployments of 1 month or longer and specifically excluded training exercises or “goodwill” visits. Using standard diagnostic output from the CIDI, individuals were classified as having a current psychiatric disorder according to any CIDI-defined *DSM-IV* disorder present in the previous 12 months [6]. GHQ-12 caseness was determined empirically as a score ≥ 2 [7]. A cluster of immunizations was defined as greater than five immunizations within 1 week or less. Reported exposure to smoke and oil from burning oil wells (SMOIL) was further categorized as “high” (exposed for ≥ 5 h/day outside for ≥ 10 days) or “low” (exposed for fewer hours per day and/or for fewer days). Possible exposure to depleted uranium was defined on the basis of whether the veteran was in Camp Doha, Kuwait when the tank compound caught fire or was involved in the subsequent cleanup operations, or if they reported either using depleted uranium munitions or entering or inspecting destroyed enemy equipment and had been in Kuwait or the battle zone areas. Body mass index (BMI) ≥ 25.0 kg/m² was used as an indicator of obesity [21] and waist-to-hip ratio (WHR) > 0.9 as an indicator of increased risk of cardiovascular disease and all-cause mortality [22].

Statistical analysis

Statistical analyses were performed using Stata version 8.0 [23]. Associations between Gulf War deployment and fatigue-related outcomes, adjusting for potential confounding factors, were assessed using logistic regression [24] and reported as adjusted prevalence odds ratios (OR) with 95% confidence intervals (CI). Exact logistic regression [25] implemented in LogXact 7 [26] was carried out when the cell sizes were five or less. Likelihood ratio tests [24] were performed to investigate homogeneity of the effects of study group across categories of age, rank and service branch, using interaction terms added to the logistic regression model. Differences in the mean values of lung function indices between study groups were obtained using multiple linear regression. Predicted values of lung function were calculated using multiple regression equations for peak expiratory flow rate [27] and other lung function indices [28]. Values of the crude and adjusted odds ratios and difference between means were found to be similar, and so only the adjusted results are reported.

The possible confounding factors were chosen a priori and consisted of a core set of age (<20, 20–<25, 25–<35, ≥ 35 years), service branch (Navy, Army, Air Force), rank (officer, other ranks — supervisory, other ranks —

nonsupervisory), marital status, education, smoking (current, former and never) and hazardous alcohol use (AUDIT score < 8 and ≥ 8).

Exposure response trends were computed using number of immunizations and the MSE score as linear variables with trends reported per unit increase, as well as the number of PB tablets taken and SMOIL exposure as categorical variables with trends reported per category increase. Other exposures were considered as binary covariates in the regressions.

To investigate the possible effects of participation bias on our results, a prediction model [5,6] was used to compute an age-, rank- and service-adjusted odds ratio for self-reported fatigue in the past month in veterans versus comparison group members, as if the study had achieved full participation.

Results

Fatigue outcomes

One percent of veteran and comparison group subjects self-reported that they had been diagnosed with CFS since the Gulf War, and these were endorsed as a possible or probable diagnosis by the doctor during the medical assessment (OR=1.2, 95% CI=0.5–2.9).

Table 1 shows that veterans had all of the fatigue-related health outcomes more commonly than the comparison group, and the odds increased with increasing refinement and clinical evaluation of the nature of the fatigue. From 167 participants with chronic fatigue, 35 were identified as having a medical or psychiatric condition that could have explained their fatigue, including Bipolar I disorder, manic ($n=7$), alcohol abuse (4), active medical conditions across several body systems including cancer (12), sleep apnoea or narcolepsy (8) and physical exertion/lifestyle changes (4).

The odds of veterans having unexplained chronic fatigue were more than twice that of the comparison group. The odds of veterans having CFS according to the study criteria were five times that of the comparison group, but the numbers were small and need to be interpreted with caution.

Of the 1377 comparison group members, 1086 (79%) subjects had never been on an active deployment. Therefore, it was possible that the excess risk of fatigue outcomes in Gulf War veterans could be explained as a general active-deployment effect rather than an effect more specific to the Gulf War [6]. To investigate this, we repeated the analyses for the major fatigue outcomes in Table 1, including only those in the comparison group who reported at least one active deployment. The resulting adjusted odds ratios were marginally higher in the case of fatigue in the last 12 months (OR=1.8, 95% CI=1.2–2.8) but lower for prolonged fatigue (OR=1.5, 95% CI=0.9–2.7), chronic fatigue (OR=1.5, 95% CI=0.8–2.7) and in particular,

Table 1
Prevalence and OR of levels of fatigue in Gulf War veterans and comparison group

Fatigue outcome	Gulf War veterans (n=1382)		Comparison group (n=1377)		Adjusted OR (95% CI) ^b
	No. ^a	%	No. ^a	%	
Fatigue in the last 12 months	262	19.0	159	11.5	1.7 (1.4–2.2)
Prolonged fatigue (≥1 month)	132	9.6	74	5.4	1.8 (1.3–2.5)
Chronic fatigue (≥6 months)	109	7.9	58	4.2	1.9 (1.4–2.7)
Unexplained chronic fatigue ^c	91	6.6	40	2.9	2.3 (1.6–3.4)
Idiopathic chronic fatigue	78	5.7	38	2.8	2.1 (1.4–3.2)
Chronic fatigue syndrome	11	0.8	2	0.1	5.1 (1.1–48.5) ^d

^a There were minor variations in the numbers of participants with each fatigue-related outcome because small numbers of missing variables meant that the outcome could not be computed or data for computation of adjusted odds ratios were not available.

^b ORs are adjusted for age (<20, 20–<25, 25–<35, ≥35 years), service branch, rank, education, marital status, smoking and alcohol use.

^c Two Gulf War veterans with unexplained chronic fatigue could not be classified further because they were missing on one variable, either fatigue severity or associated symptom criteria, that was used to define chronic fatigue syndrome cases.

^d OR was obtained by exact logistic regression adjusting for age (<25, >25 years), service branch (Navy, Army/Air Force) and rank (officer, other ranks — supervisory/nonsupervisory).

unexplained chronic fatigue (OR=1.6, 95% CI=0.8–3.2) than when all comparison group subjects were included. The confidence intervals were all wider, as a result of decreased sample sizes when restricting the comparison group to those who had been on active deployments, and only the 95% confidence interval for fatigue in the last 12 months does not include a value of 1, indicating statistical significance at the .05 level. Neither of the two comparison group subjects with CFS had been on an active deployment, hence no odds ratio was calculated.

Due to the small number of CFS cases, we undertook further investigation of the larger group of subjects identified as having unexplained chronic fatigue.

Adjustment for current psychiatric disorders and assessment of risk across age, service branch and rank

As previously reported, findings indicated that Australian veterans have a higher risk of psychiatric disorders than comparison group subjects [6]; we also adjusted for current

Table 2
Current level of physical and mental health of Gulf War veterans with and without unexplained chronic fatigue

Functional and physical health status	Unexplained chronic fatigue		Adjusted OR or difference between means (95% CI) ^c
	Yes (n=91)	No ^a (n=1318)	
Fit to perform the fitness test	No. (%) ^b	No. (%) ^b	
Fit to perform the fitness test	55 (60.4)	1,085 (85.7)	0.3 (0.2–0.5)
Stopped the fitness test prematurely	6 (11.5)	45 (4.2)	3.2 (1.2–8.3)
Recovery heart rate after fitness test: mean±S.D., beats/min	138.8±16.0	139.5±17.7	–0.3 (–5.5–4.9) ^d
Functional impairment in past 2 weeks ^e	51 (56.0)	221 (17.5)	5.3 (3.4–8.4)
Hospitalizations in past 12 months	13 (14.3)	132 (10.4)	1.2 (0.6–2.4)
Current use of medication	52 (57.8)	415 (33.0)	2.9 (1.9–4.6)
Overweight or obese (BMI≥25kg/m ²)	62 (68.1)	1,005 (79.5)	0.5 (0.3–0.9)
WHR >0.9	51 (56.0)	684 (53.9)	1.0 (0.6–1.6)
Spirometry completed to ATS criteria			
Overall	64 (82.1)	983 (91.7)	0.4 (0.2–0.8) ^f
FEV ₁ reproducibility	74 (94.9)	1,047 (97.7)	0.5 (0.2–1.6) ^f
FVC reproducibility	68 (87.2)	1,008 (94.0)	0.4 (0.2–0.8) ^f
SF-12 Physical Component Summary, mean±S.D.	41.1±11.6	50.0±8.5	–8.3 (–10.2–6.3) ^d
SF-12 Mental Component Summary, mean±S.D.	35.2±11.7	48.5±10.4	–11.8 (–14.0–9.6) ^d
Current psychiatric disorder ^g	51 (56.0)	219 (17.3)	5.1 (3.1–8.1)

^a Seventeen veterans with a medical explanation for their chronic fatigue were removed from the “No unexplained chronic fatigue” group.

^b Value of the denominator from which the percentage is derived varies for each disorder.

^c Adjusted for service branch (Navy, Army/Air Force), age, rank, education, marital status, smoking and hazardous alcohol use by logistic regression and linear regression, respectively.

^d Differences between means.

^e Stayed in bed or at home all or part of any day because they did not feel well or as a result of illnesses or injury in past 2 weeks.

^f ORs for performance of spirometry to ATS criteria and difference between means for lung function indices (in text), are adjusted for age (linear term), height (linear term), weight (linear term), smoking (0, <10, 10–20, >20 pack years), atopy, service branch (Navy, Army/Air Force), rank, education, marital status and hazardous alcohol use by logistic and linear regression, respectively.

^g Current DSM-IV psychiatric disorders that would not exclude a person from being defined as having unexplained chronic fatigue, symptoms of which were present in the past 12 months.

psychiatric disorders in relation to the fatigue outcomes listed in Table 1 in addition to the other possible confounding factors outlined earlier. The resulting adjusted odds ratios were only slightly lower when any current psychiatric disorder was adjusted for, in relation to fatigue in the last 12 months (OR=1.6, 95% CI=1.2–2.0), prolonged fatigue (OR=1.5, 95% CI=1.3–2.5), chronic fatigue (OR=1.6, 95% CI=1.1–2.3) and unexplained chronic fatigue (OR=2.0, 95% CI=1.3–3.0) and followed a very similar pattern when any current affective, anxiety, posttraumatic stress disorder and GHQ-12 caseness (GHQ-12 \geq 2) were adjusted for in place of any current psychiatric disorder. When these analyses were repeated using only those in the comparison group who reported at least one active deployment, the resulting adjusted odds were slightly lower, in a pattern consistent with that described above (data not shown).

Unexplained chronic fatigue was significantly more common in younger veterans (<25 years) and in veterans of lower (nonofficer) ranks than in comparison group subjects of the same age and rank categories, but there was no convincing effect across age or rank groups and no difference in effect across service branch (data not shown, all interaction *P* values >.12).

Characteristics of unexplained chronic fatigue in veterans and comparison group

In veterans and comparison group subjects with unexplained chronic fatigue, there was no difference in mean duration of fatigue (52.0 vs. 52.1 months) or pattern of percentage of normal activities they were able to do during periods of fatigue. Psychiatric morbidity was similar in the veterans and comparison group with unexplained chronic fatigue (data not shown) except for increased odds of posttraumatic stress disorder (OR=3.6, 95% CI=1.0–16.4), which was of borderline statistical significance. More veterans reported a rapid onset of fatigue over hours or days in 21.1% of veterans vs. 7.5% in the comparison group. A preceding illness, injury or event in the days or weeks before the onset of extreme tiredness or fatigue was reported by 48.9% veterans and 60.0% of the comparison group. The association between the rapidity of onset and a preceding illness, injury or event failed to reach statistical significance (*P*=.09).

Physical and mental health of veterans with and without unexplained chronic fatigue

Table 2 shows that a lower proportion of veterans with unexplained chronic fatigue were assessed as being able to perform the fitness test, and a greater proportion stopped the test prematurely, compared with veterans without unexplained chronic fatigue. Of veterans who did complete the fitness test, the average recovery heart rate was similar. A greater proportion of veterans with unexplained chronic

fatigue reported functional impairment and current use of medication, but not hospitalizations in the past 12 months. Veterans with unexplained chronic fatigue had a significantly lower physical and mental health status as measured by the SF-12 than veterans without unexplained chronic fatigue, and the difference was most marked for mental

Table 3
Relationship between unexplained chronic fatigue in Gulf War veterans and Gulf War-related exposures and military service experiences

Gulf War exposure	Veterans with unexplained chronic fatigue ^a			Adjusted OR (95% CI) ^b
	N	No.	%	
MSE score				
0–4	300	8	2.7	1.0
5–8	399	16	4.0	1.6 (0.7–3.9)
9–12	310	20	6.5	2.3 (1.0–5.5)
>12	348	47	13.5	5.1 (2.3–11.2)
Trend ^c	–	–	–	1.12 (1.08–1.17)
Immunizations ^d				
None	115	7	6.1	1.0
Any	918	54	5.9	0.9 (0.4–2.0)
1–4	257	11	4.3	0.6 (0.2–1.8)
5–9	537	33	6.1	0.9 (0.4–2.2)
10 or more	124	10	8.1	1.2 (0.4–3.5)
Trend in those \geq 1 ^c	–	–	–	1.07 (0.99–1.17)
Pyridostigmine bromide ^d				
None	345	11	3.2	1.0
Any	700	58	8.3	2.8 (1.3–6.1)
1–80 tablets taken	150	8	5.3	2.5 (0.9–6.9)
81–180 tablets taken	144	16	11.1	4.1 (1.6–10.4)
>180 tablets taken	146	18	12.3	4.5 (1.8–11.3)
Trend ^c	–	–	–	1.56 (1.16–2.08)
SMOIL				
None	617	25	4.1	1.0
Any	721	64	8.9	2.0 (1.2–3.4)
Pesticides				
No	993	50	5.0	1.0
Yes	348	41	11.8	2.4 (1.5–3.8)
Chemical weapons area				
No	1202	62	5.2	1.0
Yes	143	27	18.9	4.6 (2.7–7.8)
Deployment completed before air war on 17th January 1991				
Yes	322	10	3.1	1.0
No	1037	81	7.8	2.3 (1.1–4.5)

^a Seventeen veterans with a medical explanation for their chronic fatigue were removed from the reference group of veterans with no unexplained chronic fatigue.

^b Odds ratios are adjusted for age (<25, 25–<35, \geq 35 years), service branch (Navy, Army/Air Force), rank, education, marital status, smoking and hazardous alcohol use.

^c Trend is the expected proportionate increase in the odds ratio per unit increase in the MSE questionnaire score, per unit increase in the number of immunizations amongst those who reported “any” immunizations or per category increase in the number of pyridostigmine bromide tablets taken.

^d Some veterans reported that they did not know the number of immunizations they received (*n*=324), and whether they taken pyridostigmine bromide (*n*=311), antimalarial (*n*=520) or antibiological warfare (*n*=762) tablets.

health status. The prevalence of current psychiatric disorders which, by definition [10], did not exclude them from having unexplained chronic fatigue, was increased in veterans with unexplained chronic fatigue, compared with veterans without unexplained chronic fatigue (Table 2). The mean age of veterans with and without unexplained chronic fatigue was similar (26.7 vs. 27.4 years).

Table 2 also shows that a lower proportion of veterans with unexplained chronic fatigue were able to perform spirometry to ATS criteria than veterans without unexplained chronic fatigue. For those able to perform spirometry to ATS criteria, the lung function indices were similar — forced expiratory volume in one second (FEV₁) (mean 4.09 vs. 4.07 L), forced vital capacity (FVC) (mean 5.09 vs. 5.13 L) and the ratio of FEV₁/FVC% (mean 80.4% vs. 79.5%). The results of the laboratory investigations were similar in veterans with and without unexplained chronic fatigue. Similar proportions had markers of inflammation greater than the laboratory reference intervals (ESR >10 mm/h 3.4% vs. 5.2%, CRP >10 mg/L 4.4% vs. 3.8%); and had serological markers detected (EBV IgG 96.7% vs. 92.2%, CMV IgG 47.8% vs. 51.2%, hepatitis C core antibody 0.0% vs. 0.8%).

Association between Gulf War-related exposures and unexplained chronic fatigue in veterans

Table 3 shows that, in veterans, having unexplained chronic fatigue was associated with reported exposure to increasing numbers of Gulf War related psychological stressors in a strong dose-response relationship (indicating an expected increase of 12% in the risk of having unexplained chronic fatigue per additional Gulf War stressor experienced). Having unexplained chronic fatigue was also associated with increasing numbers of PB tablets taken and increasing exposure to SMOIL in dose-response relationships, exposure to pesticides, belief in being in an area where chemical weapons had probably been used and being in the Gulf at or after the start of the air war on January 17, 1991. Having unexplained chronic fatigue was not associated with increasing numbers of immunizations or receiving a cluster of immunizations or with taking prophylactic medications such as antimalarial or antibiologic warfare tablets, using insect repellents, solvent exposure, or possible exposure to depleted uranium. There was no difference between subgroups with low and high exposure to SMOIL (data not shown).

Investigation of possible effects of participation bias

The predicted full-participation adjusted odds ratio for self-reported fatigue in the past month in the postal questionnaire was 1.36, which was only marginally lower than the observed odds ratio of 1.42 found among participants [5].

Discussion

We have found that Australian Gulf War veterans had more fatigue at all levels of fatigue considered in this study, than did a randomly sampled military comparison group who were operational at the time of the Gulf War but were not deployed. The odds increased with increasing refinement and clinical evaluation of the nature of the fatigue, according to established 1994 CFS case definition criteria [10]. The excess risk of fatigue outcomes, apart from fatigue in the last 12 months, in Gulf War veterans was reduced when Gulf War veterans were compared with only those comparison group subjects who had been on active deployments and was no longer statistically significant. This suggests that the “Gulf War effect” on the differences between the two groups could at least be partly explained as a general active-deployment effect whereby deployment to any major active deployment environment may result in fatigue-related outcomes, a finding that is consistent with previously reported findings in relation to poorer psychological health in Australian Gulf War veterans [6,7]. Full investigation of an active-deployment effect is limited, however, by the relatively small number of comparison group subjects reporting active deployments and by the varied destinations and nature of these deployments [6].

Adjustment for current psychiatric disorders, in addition to other possible confounding factors, made little difference to the resulting adjusted odds ratios of fatigue outcomes in Gulf War veterans compared with the comparison group, and the increase in unexplained chronic fatigue in veterans compared with the comparison group does not appear to be explained by current psychiatric disorders. A similar active-deployment effect was observed when the comparison group included only those comparison group subjects who had been on active deployments. That younger veterans and those of more junior ranks may be at increased risk of unexplained chronic fatigue is consistent with our previously reported findings in relation to total number of health symptoms [5] and psychological ill health [7] but not with those relating to CIDI-defined psychiatric disorders [6]. Similar laboratory markers of inflammation and serology markers of viruses that can cause chronic fatigue and lack of an association between rapid onset of fatigue and a preceding illness, injury or event do not support an infectious etiology.

Veterans with unexplained chronic fatigue differ in both self-reported and objective parameters of physical and mental health status from their counterparts without unexplained chronic fatigue. The similar aerobic fitness in veterans with and without unexplained chronic fatigue who were able to perform the test is consistent with similar exercise capacity found in US veterans with and without CFS, according to the 1994 definition [29].

Veterans and comparison group with unexplained chronic fatigue reported fatigue that was of a similar total duration and equally disabling in its impact on their ability

to perform normal activities, suggesting that they were not experiencing a different type of fatigue. Heterogeneity within our study groups is still possible; there may be a subgroup of veterans who have a more severe or debilitating form of unexplained chronic fatigue. However, factor analysis of symptoms reported by US veterans with fatiguing illness and by veterans and non-Gulf subjects without fatiguing illness has not supported this, revealing a similar factor structure in both cases [30].

Comparison with community, primary care and overseas Gulf War veteran studies

The proportions of both study groups reporting chronic fatigue (7.9% vs. 4.2%) are at the lower end of the estimates for chronic fatigue in primary care settings of 5.7% [31] to 27.2% [32]. The prevalence of CFS in our veteran (0.8%) and comparison group (0.1%) subjects is similar to community prevalences of CFS in 0.2% to 2.6% of US and UK populations [33–36] and in 0.3% of the Australian population [37].

Studies of US veterans who undertook partial medical evaluation of subjects with chronic fatigue based on the 1994 CFS definition (and qualified their descriptive outcomes) estimated the prevalence of presumptive CFS to be 2.0% and not significantly different from a Germany-deployed comparison group [38] and of CFS-like illness to be 5.6% with almost five times the risk compared with a nondeployed group [3]. The risk estimate in the latter study is similar to ours. Other studies incorporating a clinical evaluation estimated the CFS prevalence in veterans to be 2.2% [39] and 1.6% (OR=40.6, 95% CI=10.2–161) [40], although the numbers of CFS cases in the latter study were very small and the odds ratio needs to be interpreted with caution. The use of different study populations, terminology and CFS definitions made comparisons between studies and further interpretation difficult.

Association with Gulf War related exposures

In Australian veterans, several Gulf War-related exposures were associated with having unexplained chronic fatigue, including stressful military service experiences and taking pyridostigmine bromide tablets. Belief in being in an area where chemical weapons had probably been used was associated with having unexplained chronic fatigue in veterans. However, other controversially reported exposures such as possible exposure to depleted uranium and increasing number of immunizations did not show such an association. Our finding of an association between having unexplained chronic fatigue and stressful military service experiences is broadly consistent with the finding in UK Gulf War veterans that being a CFS case was associated with reported military exposures including combat-related injury; exposure to the explosion of Scud missiles, nearby artillery and chemical alarms and witnessing a person's

death [41]. US Gulf War veterans diagnosed with chronic fatigue reported significantly more combat and environmental exposures than healthy Gulf War veterans [42].

Strengths and limitations

Our study had several strengths in the assessment of chronic fatigue in a veteran population. The 1994 CFS case definition was equally applied to veterans and a military comparison group in a blinded manner. The comprehensive medical assessment allowed us to evaluate chronic fatigue and its impact on physical and mental health in both study groups in a more objective way than has been done previously. The CIDI allowed determination of the onset and recency, and thus the currency, of psychiatric disorders that, by definition, may have excluded a subject from having unexplained chronic fatigue or CFS or been considered as a concurrent psychiatric condition in those with unexplained chronic fatigue.

We have evaluated the possible effect of participation bias on self-reported fatigue in the past month [5] and CIDI-defined psychological health outcomes [6] in the Australian veterans and the comparison group, and this suggested that participation bias was unlikely to fully explain the differences (or lack thereof) found between our study groups [5,6].

More recently, ambiguities in the 1994 definition that may contribute to inconsistent case ascertainment have been identified [11], with recommendations about interpretation and application in research studies and instruments to measure fatigue, disability and symptoms in subjects with CFS [11]. On reflection, we consider our interpretation to be consistent with these more recent clarifications. Whether concurrent psychiatric disorders are a cause, effect or covariate of CFS is debatable [43], but our findings do reinforce the importance of psychological assessment of patients presenting with fatigue, chronic fatigue or CFS and that concurrent psychiatric disorders need to be considered in their assessment and treatment.

Our study has some potential limitations. Exposure assessment was based on self-report, although we used an algorithm to increase the accuracy in relation to depleted uranium and asked veterans to refer to their immunization booklets. Veterans' uncertainty in relation to their medical exposures, possibly due to the time elapsed since the Gulf War and poor record keeping at the time of the Gulf War, could have influenced our results. This highlights the importance of defence forces' medical record keeping. Recall bias may also have occurred and may explain the association of unexplained chronic fatigue with exposures, as those who currently experience fatigue or a psychiatric disorder or perceive their health as worsening [44] may be more likely to report exposures [45]. Attempts by veterans with unexplained chronic fatigue to make sense of their symptoms in the light of their experiences may, in turn, influence recall and attribution [46]. Adverse perception of health has been linked with fatigue: UK veterans who

believed they had Gulf War syndrome were more fatigued, more distressed and more likely to fulfil the criteria for a multisymptom illness [47].

Fatigue and CFS remain both fascinating and controversial [48]. Fifteen years after the end of the 1991 Gulf War, the nature and possible causes of veterans' ill health are also controversial. A second major conflict in the Gulf region, with thousands of US, UK and other allied military personnel deployed in Iraq, is causing concerns about possible health parallels [49,50].

In summary, Australian Gulf War veterans have significantly more fatigue-related outcomes, including unexplained chronic fatigue and CFS, than a military comparison group. CFS within both populations is uncommon and at a similar level to the general community. Unexplained chronic fatigue is not more disabling in veterans than it is in the comparison group, but veterans with unexplained chronic fatigue have poorer psychological health and poorer physical health on some measures including objective measures such as performance and completion of spirometry and the fitness step test and report more functional impairment than veterans without unexplained chronic fatigue. Our findings highlight the importance of a medical and psychological assessment of people reporting fatigue, although we were unable to identify an explanation for their fatigue for the majority of subjects with chronic fatigue.

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