



Original Contribution

Physical, Psychological, and Functional Comorbidities of Multisymptom Illness in Australian Male Veterans of the 1991 Gulf War

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Multisymptom illness is more prevalent in 1991 Gulf War veterans than in military comparison groups; less is known about comorbidities. The authors compared physical, psychological, and functional comorbidities in Australian male Gulf War I veterans with those in actively (non-Gulf) deployed and nondeployed military personnel by using a questionnaire and medical assessment in 2000–2002. Multisymptom illness was more common in male Gulf War veterans than in the comparison group (odds ratio (OR) = 1.80, 95% confidence interval (CI): 1.48, 2.19). Stratifying by deployment status in the comparison group made little difference in this association. Gulf War veterans with multisymptom illness had increased psychiatric disorders, including major depression (OR = 6.31, 95% CI: 4.19, 9.52) and posttraumatic stress disorder (OR = 9.77, 95% CI: 5.39, 18.59); increased unexplained chronic fatigue (OR = 13.32, 95% CI: 7.70, 23.05); and more reported functional impairment and poorer quality of life, but objective physical and laboratory outcomes were similar to those for veterans without multisymptom illness. Similar patterns were found in the comparison groups; differences across the 3 groups were statistically significant for only hospitalization, obstructive liver disease, and Epstein-Barr virus exposure. Multisymptom illness is more prevalent in Gulf War I veterans, but the pattern of comorbidities is similar for actively deployed and nondeployed military personnel.

comorbidity; fatigue; Gulf War; psychology; quality of life; veterans

Abbreviations: GHQ-12, 12-item version of the General Health Questionnaire; SF-12, 12-item version of the Short-Form Health Survey.

One of the earliest health complaints reported by veterans returning from the 1991 Gulf War (Gulf War I) was multiple symptoms across several body systems (1). Multisymptom illness, based on the case definition of the Centers for Disease Control and Prevention (2), has been found to be more common in Gulf War veterans than in military comparison groups (2–6). Multisymptom illness is likely to be an important factor in the future health burden and health care needs of Gulf War veterans, and, to assist in their management, it is important to identify comorbid physical and psychological conditions (7).

There has been limited research in this area, especially using objective measures of health. Most cross-sectional studies of Gulf War veteran health did not undertake face-

to-face medical or psychological assessments of participants. In developing the Centers for Disease Control and Prevention definition, Fukuda et al. (2) found that multisymptom illness was not associated with abnormal physical or laboratory findings in a limited sample of 158 clinically evaluated Gulf War veterans but that it was associated with diminished functioning and well-being. Blanchard et al. (8) found several physical and psychiatric measures to be comorbid with chronic multisymptom illness complex in US Gulf War veterans, although similar comorbid patterns were found in the military comparison group. This study was limited by low participation rates among the Gulf War veteran (53%) and comparison (39%) groups. To our knowledge, no other published study has attempted to identify

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comorbidities with multisymptom illness by using objective physical and psychological health measures or to investigate the effect of other deployments among the comparison group.

We have previously reported (9), consistent with findings in US (4, 10, 11), United Kingdom (3, 12), Canadian (13), and French (14) Gulf War veterans, that self-reported symptoms are more common in Australian Gulf War veterans than in a military comparison group. Australian Gulf War veterans also demonstrated poorer psychological health (15, 16) and increased risk of fatigue-related outcomes, including medically unexplained chronic fatigue (17). The strength of these associations was reduced when Gulf War veterans were compared with subjects in a non-Gulf active deployment comparison group.

Our aims in this study were to identify important comorbid physical and psychological disorders in Australian male Gulf War I veterans with multisymptom illness. We hypothesized that multisymptom illness was more prevalent in Gulf War veterans than in a military comparison group. We further hypothesized that there would be less comorbidity in comparison group subjects with multisymptom illness who had never deployed compared with those who were previously actively deployed.

MATERIALS AND METHODS

Study population

Details of recruitment and of demographic and service characteristics of study participants have been reported previously (9, 15). In brief, 1,456 (80.5%) eligible Australian Gulf War veterans who had served during the period from August 2, 1990, to September 4, 1991, participated, as did 1,588 (56.8%) eligible comparison group subjects randomly selected from 26,411 Australian Defence Force personnel who were in operational units at the time of the Gulf War but were not deployed to that conflict. They were frequency matched to the Gulf War veteran group by sex, service branch, and 3-year age bands. Participants were recruited via mailed invitation in 2000–2002. Because of the small number of female Gulf War veterans ($n = 38$), analyses were limited to males. The Monash University, Departments of Veterans' Affairs, and Department of Defence Human Research Ethics Committees approved the study.

Data collection

Participants completed a postal questionnaire that included items regarding demographics, military service, tobacco use, current use of medication, hospitalization in the past 12 months, functional impairment in the past 2 weeks (10), the Alcohol Use Disorders Identification Test (18), the 12-item General Health Questionnaire (GHQ-12, a measure of psychological distress) (19), and the 12-item Short-Form Health Survey (SF-12, a measure of health-related quality of life) (20). A 63-item symptom questionnaire asked about the occurrence and severity of symptoms in the past month (9). Information was collected on active non-Gulf War deploy-

ments, defined as war or peacekeeping deployments of 1 month or longer.

At a face-to-face health assessment, height, weight, waist and hip circumferences, and blood pressure were measured. Lung function was tested by using spirometry according to recommended American Thoracic Society procedures (21, 22). Medical physicians conducted a full physical examination (23). Suitably healthy participants performed a fitness test, which involved stepping, at a designated cadence, to a 40-cm platform for 3 minutes, with mean recovery heart rate within 5 seconds of the test and 15 seconds later used to determine aerobic fitness (17, 24). Blood samples were taken.

Participants were evaluated for any history of affective, anxiety, somatic, and substance use disorders according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (25) diagnostic criteria. The interviewer-administered, computer-assisted Composite International Diagnostic Interview (26), administered by psychologists (27), was used.

Multisymptom illness definition

Our multisymptom illness definition was based on the Centers for Disease Control and Prevention operational definition established in the United States (2) and adopted for studies of United Kingdom (3) and US (8) Gulf War veterans. The Centers for Disease Control and Prevention definition required one or more chronic symptoms from at least 2 of 3 categories (fatigue, mood-cognition, and musculoskeletal, where the latter 2 categories comprised the 2 factors identified in factor analysis of symptoms in US veterans (2)). Our definition required one or more symptoms in the past month rated as at least of moderate severity from at least 3 of 4 categories (fatigue, psycho-physiological, cognitive, and arthro-neuromuscular, where the latter 3 categories comprised the 3 factors identified in factor analysis of symptoms in Australian veterans (28)) (Table 1).

Definition of comorbid conditions

Medically evaluated conditions were assessed according to definitions described previously (17, 23). Briefly, medically unexplained chronic fatigue was defined as at least 6 months of fatigue for which no explanatory medical or psychiatric condition was identifiable (17). A neuropathy score was obtained by combining subscores for cranial nerve, muscle weakness, reflex, and sensation abnormalities (23). Blood pressure was categorized according to contemporary guidelines (29). Obesity was defined by using a body mass index of ≥ 25.0 kg/m² (30) and a waist circumference of > 102 cm (31). Maximal forced expiratory measurements were obtained by using flow-sensing QRS Spirocard spirometers (32) with Office Medic software (QRS Diagnostic, Plymouth, Minnesota) according to recommended American Thoracic Society procedures (21, 22). American Thoracic Society criteria for performance of spirometry, including forced expiratory volume in 1 second and forced vital capacity reproducibility, were used to decide which spirometric data to include in the analysis (21, 22).

Table 1. Case Definition of Multisymptom Illness^a

Category	Self-reported Symptoms in the Past Month of At Least Moderate Severity
I. Fatigue	Fatigue
II. Psycho-physiologic distress factor ^b	Vomiting; nausea; stomach cramps; diarrhea; wheezing; indigestion; shortness of breath; dry mouth; feeling feverish; tender or painful swelling of lymph glands in the neck, armpit, or groin; lump in the throat; persistent cough; pain on passing urine; constipation; difficulty speaking; dizziness, fainting, or blackouts; loss of balance or coordination; sore throat; flatulence or burping; loss of control over the bladder or bowels; burning sensation in the sex organs; skin ulcers; loss of or decrease in appetite
III. Cognitive distress factor ^b	Loss of concentration, feeling distant or cut off from others, feeling unrefreshed after sleep, forgetfulness, loss of interest in sex, sleeping difficulties, avoiding things or situations, feeling jumpy/easily startled, problems with sexual functioning, distressing dreams, irritability/outbursts of anger, difficulty finding the right word, feeling disorientated, increased sensitivity to noise, shaking, increased sensitivity to light, increased sensitivity to smells or odors
IV. Arthro-neuromuscular distress factor ^b	Stiffness in several joints, pain without swelling or redness in several joints, general muscle aches or pains, loss of sensation in the hands or feet, low back pain, tingling or burning sensation in the hands or feet

^a Requires one or more recent symptoms of at least moderate severity in 3 or more of the 4 categories.

^b Factor determined by factor analysis of symptoms in Australian Gulf War veterans (28). Case definition of multisymptom illness is based on the Centers for Disease Control and Prevention definition (2).

Individuals were classified as having a current psychiatric disorder according to any Composite International Diagnostic Interview–defined *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, disorder present in the previous 12 months (15). GHQ-12 caseness was determined empirically as a score of ≥ 2 (16) and Alcohol Use Disorders Identification Test caseness as a score of ≥ 10 (15, 33).

Blood samples were analyzed at a single national accredited laboratory to eliminate interlaboratory variability. Outcome definitions were based on the laboratory's reference intervals:

- Anemia (hemoglobin < 13.5 g/dL)
- Inflammation (erythrocyte sedimentation rate > 10 mm/hour or > 15 mm/hour if > 50 years of age), C-reactive protein > 10 mg/L or leukocyte count $> 11.0 \times 10^9/L$)
- Renal impairment (creatinine > 120 $\mu\text{mol/L}$)
- Elevated random plasma glucose (> 11 mmol/L)
- Obstructive liver disease (alkaline phosphatase > 110 U/L and γ -glutamyl-transferase > 60 U/L)
- Inflammatory (hepatic) liver disease (alanine aminotransferase > 55 U/L and aspartate aminotransferase > 45 U/L)
- Prior Epstein-Barr virus exposure (positive antibody test)
- Prior cytomegalovirus exposure (positive antibody test)

Statistical analysis

Statistical analyses were performed by using Stata version 10 software (34). Associations of deployment status or categorical comorbidities with multisymptom illness, adjusting for potential confounding factors, were assessed by using logistic regression (35). If cell sizes were 5 or less (anemia, renal impairment, elevated random plasma glucose, obstructive liver disease, posttraumatic stress disorder), exact logistic regression was performed (36, 37).

Differences in the mean values of recovery heart rate and SF-12 physical and mental summary scores were obtained by using linear regression. Differences in the mean values of lung function indices were obtained by using robust linear regression (38). The ratio of mean counts in the neuropathy score was obtained by negative binomial regression (39, 40). A significance level of 5% was used to compare whether comorbidities in those with and without multisymptom illness differed between the 3 study groups, followed by pairwise comparisons when the overall test was significant. All *P* values are 2 sided.

The possible confounding factors were chosen on the basis of prior analyses and consisted of age, branch of military service, rank, marital status, and highest level of education as well as known risk factors for respiratory disease (weight, height, atopy, smoking), unexplained chronic fatigue (smoking, hazardous alcohol use), and neurologic disease (hazardous alcohol use, diabetes). The values of crude and adjusted estimates were found to be similar; therefore, only adjusted results are reported in this paper.

RESULTS

The study groups for the current analyses consisted of 1,381 male Gulf War I veterans and 1,377 male comparison group members (292 (21.2%) of whom had been on an active non-Gulf War deployment). These groups included all of those with sufficient data for definition of a multisymptom illness, including completion of a medical assessment.

A total of 353 (25.6%) Gulf War veterans and 220 (16.0%) subjects in the total comparison group were defined as having a multisymptom illness (odds ratio = 1.80, 95% confidence interval: 1.48, 2.19). The relation between Gulf War deployment and multisymptom illness was slightly weaker (although still statistically significant) when Gulf War veterans were compared with those actively deployed elsewhere (18.5%; odds ratio = 1.45, 95% confidence interval: 1.03, 2.04) and was similar when Gulf War veterans

were compared with the nondeployed comparison group. (15.3%; odds ratio = 1.91, 95% confidence interval: 1.55, 2.36). The proportion of missing data was very low—<1% for most comorbidities—and was marginally greater for laboratory comorbidities (1.1%–1.7%), unexplained chronic fatigue (1.5%), neuropathy score (2.8%), and SF-12 (2.8%), which were based on several components or a summary score, and for spirometric data (3.0%).

Tables 2–4 show the relation between multisymptom illness and physical, functional, psychological, and laboratory-defined comorbidities in Gulf War veterans and in the actively deployed and nondeployed comparison groups, as well as a test of whether there is any statistical interaction between multisymptom illness and group with regard to comorbidity. In other words, is the association between the presence of multisymptom illness and a given comorbidity constant across the above 3 groups, or is it stronger in a particular group?

Fewer Gulf War veterans with multisymptom illness, compared with Gulf War veterans without multisymptom illness, were assessed as being able to perform the fitness test, and more stopped the test prematurely, although the average recovery heart rate in those who completed the fitness test was similar (Table 2). Multisymptom illness in Gulf War veterans was associated with reported functional and occupational impairment, increased health care utilization, unexplained chronic fatigue, slightly elevated neuropathy score, and increased waist circumference. However, it was not associated with reduced spirometry performance (forced expiratory volume in 1 second, forced vital capacity, both forced expiratory volume in 1 second and forced vital capacity reproducibility; data not shown) according to American Thoracic Society criteria, poorer lung function indices, or elevated blood pressure. The slightly lower forced vital capacity in Gulf War veterans with a multisymptom illness compared with those without a multisymptom illness was not considered clinically important. The association of multisymptom illness with physical and functional comorbidities was similar in the actively deployed and nondeployed groups, exceptions being lack of an association of multisymptom illness with increased waist circumference or neuropathy score in the actively deployed group. The test of statistical significance of interaction involving the relation between multisymptom illness and comorbidities across the 3 groups was statistically significant ($P = 0.04$) in relation to only recent hospitalization in the past 12 months (with pairwise comparison of Gulf War veteran vs. nondeployed $P = 0.01$, data not shown).

Multisymptom illness in Gulf War veterans was associated strongly with psychiatric conditions, psychological distress, and lower (poorer) SF-12 physical- and mental-health-related quality-of-life scores (Table 3). The relation between multisymptom illness and poorer psychological health was similar in the actively deployed and nondeployed comparison groups. The test of interaction indicated no significant differences in psychological comorbidities in those with and without multisymptom illness across the 3 groups. We found no association of multisymptom illness with post-traumatic stress disorder and alcohol-related comorbidities in the actively deployed group. The small number of post-

traumatic stress disorder cases among those with and without multisymptom illness ($n = 3$, $n = 6$ actively deployed; $n = 9$, $n = 5$ nondeployed, respectively) resulted in poor precision around the point estimates.

Table 4 shows a mixed picture regarding associations of multisymptom illness with laboratory-defined comorbidities. Multisymptom illness was associated with inflammation and elevated plasma glucose in Gulf War veterans and with inflammatory liver disease and elevated random plasma glucose in the deployed comparison group. The significantly different associations of multisymptom illness with obstructive liver disease and prior exposure to Epstein-Barr virus in the 3 groups were largely driven by lower odds of obstructive liver disease in the Gulf War veterans and lower odds of exposure to Epstein-Barr virus in the actively deployed group (pairwise comparison of actively deployed vs. nondeployed $P = 0.05$ and vs. Gulf War veterans $P < 0.01$).

DISCUSSION

We found that multisymptom illness was more prevalent in Australian male Gulf War I veterans than in both a military male comparison group that had previously actively deployed to a non-Gulf War or peacekeeping operation and a military male comparison group that had never actively deployed (nondeployed). Multisymptom illness in male Gulf War veterans was strongly associated with psychiatric conditions, medically unexplained chronic fatigue, and poorer health-related quality of life and was more likely to be associated with physical or functional comorbidities when these were based on reported rather than objective measures, such as measures of respiratory, neurologic, or laboratory-based comorbidities. These patterns of association of multisymptom illness with comorbidities were very similar in the actively deployed and nondeployed comparison groups.

One previous study (8) found that multisymptom illness in US Gulf War veterans, compared with Gulf War veterans without multisymptom illness, during a similar period post-Gulf War was associated with more symptom-based or reported conditions, metabolic syndrome but not other non-symptom-based physical conditions, increased hospitalizations, use of medications, and psychiatric disorders; the pattern was similar in a non-Gulf comparison group, although the effect of comparison group deployment status was not investigated. Multisymptom illness in US Gulf War veterans 14 years after deployment was associated with increased hospitalization and poorer health-related quality of life, but the pattern in the comparison group was not reported (6).

Our study also presents findings on a range of comorbidities, some based on additional, such as fitness, or different (GHQ-12, Alcohol Use Disorders Identification Test) instruments or measures. Multisymptom illness was associated with elevated random plasma glucose in Australian but not with diabetes mellitus in US (8), Gulf War veterans, possibly because fasting blood glucose was included in a more restrictive definition in the US study. Multisymptom illness was associated with inflammation in Australian Gulf

Table 2. Physical and Functional Comorbidities Among Male Gulf War I Veterans and Actively Deployed and Nondeployed Comparison Groups With and Without Multisymptom Illness, Australia, 2000–2002

Physical and Functional Comorbidity	Gulf War Veterans (N = 1,381)						Deployed Comparison Group (n = 292): Multisymptom Illness vs. No Multisymptom Illness		Nondeployed Comparison Group (n = 1,085): Multisymptom Illness vs. No Multisymptom Illness		P Value for Test of Interaction Between Multisymptom Illness and Comorbidity Across Each of the 3 Groups	
	Multisymptom Illness (n = 353)		No Multisymptom Illness (n = 1,028)		OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI		
	No.	%	No.	%								
Fit to perform the fitness test	250	71.2	901	87.9	0.36	0.26, 0.49	0.48	0.23, 1.00	0.28	0.19, 0.41	0.37	
Stopped the fitness test prematurely	18	7.4	35	3.9	2.10	1.15, 3.82	2.71	0.40, 18.24	1.53	0.68, 3.43	0.73	
Overweight or obese (BMI ≥ 25 kg/m ²)	271	77.0	811	79.2	0.85	0.63, 1.15	0.85	0.39, 1.87	1.08	0.70, 1.65	0.67	
Waist circumference >102 cm	123	49.8	303	41.7	1.47	1.08, 1.99	1.54	0.65, 3.64	1.78	1.18, 2.69	0.76	
Medically unexplained chronic fatigue	73	21.7	18	1.8	13.32	7.70, 23.05	7.47	1.78, 31.34	17.98	7.49, 43.14	0.71	
Elevated blood pressure (systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg)	80	22.9	216	21.2	1.13	0.84, 1.54	0.83	0.36, 1.90	1.17	0.78, 1.74	0.72	
Functional impairment in the past 2 weeks ^b	153	43.6	131	12.8	4.90	3.67, 6.53	3.02	1.46, 6.24	5.50	3.76, 8.03	0.47	
Not working because of ill health/unemployed	33	9.4	34	3.3	2.72	1.64, 4.51	16.35	1.70, 156.87	3.87	2.11, 7.09	0.24	
Hospitalization in the past 12 months	53	15.1	96	9.4	1.66	1.15, 2.41	2.47	1.17, 5.22	3.47	2.17, 5.54	0.04	
Current use of medication	169	48.7	313	30.7	2.28	1.76, 2.96	2.16	1.10, 4.22	2.94	2.08, 4.16	0.29	
	Mean (SD)		Mean (SD)		Comparison of		Mean		95% CI		OR ^a	95% CI
	Mean (SD)		Mean (SD)		Mean		95% CI		Mean			
Recovery heart rate, beats/minutes ^c	138.2 (17.9)		139.7 (17.5)		-1.29 -3.89, 1.30		0.13 -6.06, 6.31		2.55 -1.40, 6.49		0.22	
Neuropathy score ^d	3.0 (5.6)		1.7 (3.7)		2.39 1.50, 3.79		1.61 0.65, 4.03		1.74 1.25, 2.43		0.71	
FEV ₁ , L ^e	4.02 (0.64)		4.09 (0.64)		-0.04 -0.11, 0.03		-0.08 -0.25, 0.10		-0.03 -0.13, 0.07		0.97	
FVC, L ^e	5.04 (0.77)		5.16 (0.78)		-0.08 -0.17, -0.005		-0.06 -0.27, 0.14		-0.11 -0.22, 0.004		0.74	
FEV ₁ /FVC%	80.3 (5.8)		79.3 (6.1)		-0.88 -0.02, 1.6		0.07 -2.0, 2.1		0.9 -0.2, 2.1		0.95	

Abbreviations: BMI, body mass index; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio; SD, standard deviation.

^a Odds ratios were adjusted for age, military service, rank, education, and marital status; medically unexplained chronic fatigue was also adjusted for hazardous alcohol use and smoking.

^b Positive response to the following question: Thinking back over the past 2 weeks, did you stay in bed or at home all or part of any day because you did not feel well or as a result of illnesses or injury? (10).

^c Difference between means was adjusted for age, military service, rank, education, and marital status.

^d Ratio of mean neuropathy scores was adjusted for age, military service, rank, education, marital status, hazardous alcohol use, and history of diabetes.

^e Difference between means for spirometry results was adjusted for age, height, weight, smoking, atopy, military service, rank, education, and marital status.

War veterans but not with an increased white cell count (a laboratory parameter included in our definition of inflammation) in US Gulf War veterans (8).

Self-reported physician-diagnosed prewar infectious mononucleosis has been associated with chronic multisymptom illness in US Gulf War veterans (8). In our study, multisymptom illness was not associated with laboratory-identified prior exposure to Epstein-Barr virus, the cause of infectious mononucleosis, in Gulf War veterans or the non-

deployed group, but it was associated with lower odds of positive Epstein-Barr serology in the actively deployed group. The only other laboratory-defined condition for which there was a significant difference between groups was obstructive liver disease, the risk for which was lower for Gulf War veterans. Therefore, we found no evidence of a link between multisymptom illness and serologic abnormalities in Gulf War veterans or comparison group members.

Table 3. Psychological Comorbidities Among Male Gulf War I Veterans and Actively Deployed and Nondeployed Comparison Groups With and Without Multisymptom Illness, Australia, 2000–2002

Psychological Comorbidity	Gulf War Veterans (N = 1,381)						Deployed Comparison Group (n = 292): Multisymptom Illness vs. No Multisymptom Illness		Nondeployed Comparison Group (n = 1,085): Multisymptom Illness vs. No Multisymptom Illness		P Value for Test of Interaction Between Multisymptom Illness and Comorbidity Across Each of the 3 Groups	
	Multisymptom Illness (n = 353)		No Multisymptom Illness (n = 1,028)		OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI		
	No.	%	No.	%								
Any current psychiatric disorder	153	43.3	131	12.7	5.04	3.77, 6.74	4.55	2.13, 9.74	4.43	2.96, 6.62	0.81	
Any affective disorder	96	27.2	48	4.7	7.27	4.93, 10.73	7.68	2.57, 22.96	5.47	3.25, 9.22	0.51	
Major depression	81	22.9	43	4.2	6.31	4.19, 9.52	7.68	2.57, 22.96	4.36	2.45, 7.73	0.33	
Any anxiety disorder	108	30.6	69	6.7	5.98	4.24, 8.44	5.04	1.99, 12.75	5.46	3.25, 9.19	0.88	
PTSD	53	15.0	18	1.7	9.77	5.39, 18.59	1.86	0.44, 7.92	8.58	2.41, 33.71	0.15	
Somatoform disorder	18	5.1	10	1.0	6.22	2.74, 14.13	— ^b	— ^b	5.56	1.55, 19.87	— ^b	
Alcohol use/dependence disorder	27	7.6	33	3.2	2.33	1.35, 4.01	3.23	0.81, 12.89	4.26	1.87, 9.73	0.46	
GHQ-12 caseness	253	71.9	297	28.9	6.49	4.92, 8.57	4.44	2.22, 8.88	6.68	4.61, 9.69	0.46	
AUDIT caseness	170	48.4	332	32.3	1.78	1.37, 2.31	1.44	0.76, 2.73	1.62	1.13, 2.32	0.67	
							Difference Between					
	Mean (SD)		Mean (SD)				Mean ^c	95% CI	Mean ^c	95% CI	Mean ^c	95% CI
SF-12 PCS score	41.9 (10.7)		51.7 (7.1)				−9.53	−10.54, −8.51	−8.96	−11.60, −6.33	−9.20	−10.53, −7.88
SF-12 MCS score	38.8 (11.6)		50.3 (9.3)				−11.12	−12.35, −9.89	−9.43	−12.22, −6.64	−10.00	−11.46, −8.55

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; CI, confidence interval; GHQ-12, 12-item version of the General Health Questionnaire; MCS, Mental Component Summary; OR, odds ratio; PCS, Physical Component Summary; PTSD, posttraumatic stress disorder; SF-12, 12-item Short-Form Health Survey; SD, standard deviation.

^a Odds ratios were adjusted for military service, age, rank, education, and marital status. Exact logistic regression was performed for PTSD.

^b No deployed comparison group had a somatoform disorder diagnosis; therefore, the odds ratio and subsequent overall *P* value were not calculable.

^c Differences between means were adjusted for military service, age, rank, education, and marital status.

The magnitude of the association between Gulf War deployment and multisymptom illness in Australian veterans versus the overall comparison group (odds ratio = 1.80) was lower than that in US veterans during a comparable period (odds ratio = 2.16) (8) and 14 years after the Gulf War (odds ratio = 3.05) (6), and it was lower than that in United Kingdom veterans compared with a non-Gulf War group approximately 7 years after the Gulf War (odds ratio = 2.9) (3). Minor alterations in definitions may account for these differences.

Our finding that the strength of the association weakened when Australian Gulf War veterans were compared with an actively deployed comparison group (odds ratio = 1.45) is consistent with the reduction in effect observed when United Kingdom Gulf War veterans were compared with a Bosnia-deployed group (odds ratio = 2.5) (3). Overall, the findings in relation to multisymptom illness in Australian, US, and United Kingdom Gulf War veterans suggest an increased level of multisymptom illness in Gulf War veterans compared with the background level in military personnel, but a manifestation of such multisymptom illness in terms of comorbid physical and psychiatric conditions was similar in Australian and US Gulf War veterans.

Differences between those with and without multisymptom illness were far greater for outcomes based upon self-report measures such as the GHQ-12 and current use of medication, as well as the psychiatric Composite International Diagnostic Interview, than for objective measures such as fitness, body size, spirometry, and blood markers (apart from random plasma glucose levels). The objective test of physical fitness, which should have been influenced by respiratory or cardiovascular impairment, or anemia, was performed as well by those with multisymptom illness who completed the test as by those without multisymptom illness who also completed the test. Although the Composite International Diagnostic Interview is a far more comprehensive instrument than brief tests such as the GHQ-12 and SF-12, diagnoses are still contingent upon the responses of the person being interviewed, there being a dearth of objective measures of psychiatric disorders such as depression and posttraumatic stress disorder in epidemiologic research (41).

Such discrepancies between objective and more subjective measures could point to a response bias, with veterans or others with multisymptom illness, which is itself based upon the report of symptoms across several categories and body systems, reporting the presence of many symptoms.

Table 4. Laboratory-defined Comorbidities Among Male Gulf War I Veterans and Actively Deployed and Nondeployed Comparison Groups With and Without Multisymptom Illness, Australia, 2000–2002

Laboratory-defined Comorbidity	Gulf War Veterans (N = 1,364)						Deployed Comparison Group (n = 292): Multisymptom Illness vs. No Multisymptom Illness		Nondeployed Comparison Group (n = 1,071): Multisymptom Illness vs. No Multisymptom Illness		P Value for Test of Interaction Between Multisymptom Illness and Comorbidity Across Each of the 3 Groups
	Multisymptom Illness (n = 348)		No Multisymptom Illness (n = 1,016)		OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI	
	No.	%	No.	%							
Anemia	3	0.9	26	2.6	0.34	0.07, 1.15	0.59	0.00, 4.48	1.06	0.26, 3.23	>0.99
Inflammation	56	16.1	119	11.7	1.55	1.06, 2.28	1.58	0.59, 4.27	1.60	0.99, 2.58	0.95
Renal impairment	8	2.3	12	1.2	1.82	0.63, 4.99	2.33	0.02, 82.40	1.67	0.03, 21.15	>0.99
Elevated random plasma glucose	7	2.0	4	0.4	6.88	1.54, 41.88	16.24	1.77, ∞	4.35	0.62, 26.41	0.40
Obstructive liver disease	3	0.9	19	1.9	0.43	0.08, 1.51	6.00	0.00, 234.00	7.47	2.01, 30.27	<0.01
Inflammatory liver disease	15	4.3	43	4.2	1.03	0.56, 1.89	6.20	1.61, 23.93	1.33	0.60, 2.97	0.12
Prior exposure to EBV	332	95.4	931	91.7	1.67	0.96, 2.93	0.22	0.07, 0.71	1.05	0.52, 2.12	0.02
Prior exposure to CMV	170	48.8	524	51.6	0.83	0.65, 1.08	1.34	0.70, 2.56	1.25	0.88, 1.77	0.12

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; EBV, Epstein-Barr virus; OR, odds ratio.

^a Odds ratios were adjusted for military service, age, rank, education, and marital status. Exact logistic regression was performed for anemia, renal impairment, elevated random plasma glucose, and obstructive liver disease.

On the other hand, the large difference in a particular objective measure, random plasma glucose levels, between those veterans with and without multisymptom illness could not be explained by such a response bias. However, psychiatric illness has been found to be associated with higher levels of “metabolic syndrome,” the definition of which includes elevated glucose and increased waist circumference, both of which appear to be higher in those with multisymptom illness. Unfortunately, fasting glucose and triglyceride levels were not measured in the present study because of logistic reasons, so this possibility could not be further examined (42, 43).

Our study had several strengths. We achieved high participation rates among Gulf War veterans (80.5%) and the comparison group (56.8%). Most of our assessment of comorbid conditions was based on objective physical or standardized, instrument-defined psychological health data. Our military comparison group was randomly sampled from Australian Defence Force personnel in operational units at the time of the Gulf War, and thus eligible for deployment, but were not deployed to that conflict. Their further categorization as actively deployed or nondeployed was undertaken post hoc based on reported military service history and independently of health status. Our previously reported evaluation suggested that participation bias was unlikely to explain the differences (or lack thereof) found between Gulf War veterans and the comparison group (9, 15).

Our study had some limitations. Some measures such as hospitalization and current use of medication relied on self-report. The numbers of cases of several laboratory-defined outcomes, and posttraumatic stress disorder in the comparison groups, were small, and the relevant results need to be interpreted with caution. The serology tests did not indicate timing of prior Epstein-Barr or cytomegalovirus exposure. We performed numerous statistical tests and it is therefore

possible that some positive associations may have been chance findings. Our study was cross-sectional, and we were unable to determine the longitudinal course of multisymptom illness and the relation with physical and psychological health over time. At follow-up 10 and 14 years after the Gulf War, United Kingdom (44) and US (6) Gulf War veterans, respectively, had poorer subjective and symptomatic ill health compared with the comparison groups, but the health gap had narrowed slightly over time in United Kingdom veterans (44). Little is known about the longer-term health of Gulf War veterans from coalition forces after this period.

Development of excess physical symptom reporting and psychological disorders after stressful life events is also increasingly recognized as an important health outcome in a range of population groups, including emergency services workers (45), accident victims (46), and refugees (47). The total number of physical symptoms has been predictive of psychiatric disorders and functional impairment in veteran, civilian, and primary care populations (7, 48, 49) and is associated with increased predicted mortality (50).

Multiple symptom reporting manifested across several body systems has implications for the management of Gulf War veterans and for military personnel more generally. Symptoms in their own right require attention. However, clinicians also need to be aware of the possibility of multisymptom illnesses as defined and of comorbid psychiatric conditions, medically unexplained chronic fatigue, and poorer health-related quality of life, which we found to have the strongest associations.

In conclusion, multisymptom illness is increased in Australian Gulf War I veterans compared with an actively deployed and nondeployed comparison group. The pattern of association between having a multisymptom illness and comorbid physical, functional, and psychological conditions (especially those based on self-report) was similar in the 3

groups, suggesting that, although Gulf War I veterans with multisymptom illness may have increased comorbidities, Gulf War deployment is not associated with a characteristic form of multisymptom illness. To date, there has been little research on the longer-term impacts of multisymptom illness and its relation to later physical and psychological health, an important area for further study.

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