Chronic Multisymptom Illness Affecting Air Force Veterans of the Gulf War

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Context.—Gulf War (GW) veterans report nonspecific symptoms significantly more often than their nondeployed peers. However, no specific disorder has been identified, and the etiologic basis and clinical significance of their symptoms remain unclear.

Objectives.—To organize symptoms reported by US Air Force GW veterans into a case definition, to characterize clinical features, and to evaluate risk factors.

Design.—Cross-sectional population survey of individual characteristics and symptoms and clinical evaluation (including a structured interview, the Medical Outcomes Study Short Form 36, psychiatric screening, physical examination, clinical laboratory tests, and serologic assays for antibodies against viruses, rickettsia, parasites, and bacteria) conducted in 1995.

Participants and Setting.—The cross-sectional questionnaire survey included 3723 currently active volunteers, irrespective of health status or GW participation, from 4 air force populations.The cross-sectional clinical evaluation included 158 GW veterans from one unit, irrespective of health status.

Main Outcome Measures.—Symptom-based case definition; case prevalence rate for GW veterans and nondeployed personnel; clinical and laboratory findings among veterans who met the case definition.

Results.—We defined a case as having 1 or more chronic symptoms from at least 2 of 3 categories (fatigue, mood-cognition, and musculoskeletal). The prevalence of mild-to-moderate and severe cases was 39% and 6%, respectively, among 1155 GW veterans compared with 14% and 0.7% among 2520 nondeployed personnel. Illness was not associated with time or place of deployment or with duties during the war. Fifty-nine clinically evaluated GW veterans (37%) were noncases, 86 (54%) mild-to-moderate cases, and 13 (8%) severe cases. Although no physical examination, laboratory, or serologic findings identified cases, veterans who met the case definition had significantly diminished functioning and well-being.

Conclusions.—Among currently active members of 4 Air Force populations, a chronic multisymptom condition was significantly associated with deployment to the GW. The condition was not associated with specific GW exposures and also affected nondeployed personnel.

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SOON AFTER cessation of Gulf War (GW) hostilities, anecdotal reports of illness and speculation over environmental, biological, and chemical hazards led to concerns about a "Gulf War syndrome."[1-3] Subsequent studies have shown that GW veterans report numerous chronic nonspecific symptoms, such as fatigue, neurocognitive problems, and musculoskeletal pain, significantly more often than their nondeployed peers.[4,5] No widespread disorder has been linked to that conflict, and the etiologic basis and clinical significance of veterans' symptomatology remain unclear.[6]

The evidence for unique health problems among GW veterans is mixed. Although acute gastroenteritis was frequently reported among troops,[7,8] the overall occurrence of infectious diseases was much lower than expected.[9] No specific illness is evident among the 18 598 GW veterans, according to the Department of Defense Comprehensive Clinical Evaluation Program.[6] Other investigators have found no unusual increases in birth defects,[10] unexplained illness,[11] excess hospitalizations,[12] or excess mortality[13] among GW veterans. However, one study reported excess mortality due to unintentional injuries rather than from disease.[14] Evidence of an Iraqi chemical and biological weapons program has been documented,[15] and although use of such weapons during the GW has not been confirmed,[16] troops may have been exposed to chemical or biological warfare agents during the destruction of storage bunkers. The long-term effects of such chemical exposures are uncertain, although some investigators have suggested that wartime exposures may have contributed to chronic neurotoxic syndromes.[17,18]

For editorial comment see p 1010.

In December 1994, the US Secretary of Defense and the Secretary of Veterans Affairs, and the Commonwealth of Pennsylvania asked the Centers for Disease Control and Prevention (CDC), Atlanta, Ga, to investigate a "mystery illness" reported among GW veterans from an Air National Guard (ANG) unit in Lebanon, Pa.[19] In the first phase of the investigation, we interviewed and examined ill GW veterans and found that their major health problems consisted of persistent fatigue and other chronic symptoms that began during deployment or soon after returning from the GW, but we did not find associated physical signs or clinical laboratory abnormalities.[4] Patients' illnesses resembled those reported previously, and the classification and etiology remain unclear.[2]

This article reports the second phase of our survey of the index ANG unit and 3 comparison air force populations. Our primary objectives were to determine

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Table 1.—Factor Analysis Loadings (× 100) Exploratory Sample and Confirmatory Sample*

	Loading Values				
		Factor		Factor	
Symptoms	PC 1	1	PC 2	2	PC 3
Depression	76	71	−3	−17	−1
Anxiety	73	73	−5	−20	1
Moodiness	71	62	2	0	−10
Memory problems	59	61	6	6	0
Fatigue	50	50	19	19	3
Difficulty with words	48	61	−15	−9	4
Difficulty sleeping	45	42	30	14	−2
Joint stiffness	2	−5	85	76	4
Joint pain	3	−13	84	85	−1
Muscle pain	0	12	63	47	1
Wheezing	−14	19	0	8	75
Shortness of breath	10	35	3	21	73
Cough	−8	29	2	13	59
Chest pain	11	33	0	17	53

*The exploratory sample represents the first 3 principal components of 35 symptoms submitted to a promax oblique rotation (n = 1631). The confirmation factor analysis represents symptoms from the first 3 principal analysis components that were submitted to an unweighted, least squares factor analysis with a Procrustes oblique rotation (n = 1624). Intercorrelations for factors 1 and 2 were 42% and 69%, respectively, for exploratory and confirmatory samples. PC indicates principal components.

whether the prevalence of symptoms was increased among currently active members of the index unit and among GW veterans from other air force populations in comparison with nondeployed personnel and to develop a case definition that would allow further studies of etiology. We also report the third phase, which was intended to characterize clinical and laboratory findings among GW veterans who met our case definition.

METHODS

Cross-sectional Questionnaire Survey

Study Population and Survey Procedures.—We used study protocols that were approved by the Human Subjects Committee of the CDC and followed the human experimentation guidelines issued by the US Department of Health and Human Services in this study. All study participants provided informed consent.

We surveyed the index and 3 comparison air force units between January and March 1995. Unit A, another ANG unit in Pennsylvania, had similar demographic features as the index unit but had a different primary mission. Unit B (US Air Force Reserve) and unit C (active-duty air force) had similar primary missions as the index unit's mission but were located in Florida. Any unit member who was on base was eligible for the study. The index unit and units A and B were each surveyed during 3 consecutive unit training weekends (held monthly) to maximize participation rates. Unit C was surveyed during a 10-day period.

On each base, one of us (K.F., L.R., R.W., or D.N.) met with small groups, explained the study, and distributed questionnaires to subject volunteers whose identities remained anonymous. The questionnaire took 15 to 45 minutes to complete and queried health status, demographic and military characteristics, and potential risk factors for illness. We asked about the 35 symptoms that had been identified during the earlier exploratory study[4] including their severity (mild, moderate, or severe) and duration (<6 months or ≥6 months).

Case Definition

We used 2 conceptually different approaches to develop exploratory case definitions from the symptom data. The first exploratory case definition was derived from clinical and epidemiological reasoning; the second used statistical methods.

Clinical Approach.—We reasoned that if an illness existed among GW veterans, case-defining symptoms would be chronic, prominent among GW veterans, and more common among GW veterans than nondeployed personnel. Thus, we decided that symptoms for the clinical case definition had to be reported for 6 months or longer, by at least 25% of GW veterans and by GW veterans at least 2.5 times more often than by nondeployed personnel. The clinical case definition was identified as fatigue, difficulty remembering or concentrating, moodiness, difficulty sleeping, joint pain, and joint stiffness.

Statistical Approach.—In the statistical approach, we randomly divided the 3255 participants into 2 subsamples of 1631 and 1624 subjects (446 were excluded from analysis because of incomplete symptom data). We conducted an exploratory principal components analysis on the first subsample and a confirmatory factor analysis on the second.

Exploratory Principal Components Analysis.—All 35 symptoms were submitted to a principal components analysis, an exploratory method that can help determine the probable number and nature of common components (or factors).[20] We used a promax rotation because it is a well-formulated procedure to extract correlated factors[21] and provides interfactor correlations. The Kaiser-Guttman rule (an eigenvalue >1) was used to determine the number of factors to retain for rotation. In addition, we examined the scree plot and verified that the slope connecting the eigenvalues approached zero after retaining the number of selected factors. After rotation, the factor pattern was examined to determine whether an oblique rotation yielded high loadings in only one factor. Symptoms with factor loadings of greater than 0.40 were kept for the confirmatory factor analysis.[22] The exploratory analysis yielded 10 components with an eigenvalue greater than 1. The first (feeling depressed, feeling anxious, feeling moody, difficulty remembering or concentrating, trouble finding words, difficulty sleeping, and fatigue) accounted for 16.8% of the total common variance. The second (joint stiffness, joint pain, and muscle pain) accounted for 11.9% of the variance. The third (wheezing, shortness of breath, coughing, and chest pain) accounted for 10.4%. The remaining components each contributed less than 10% of the total variance.

Confirmatory Factor Analysis.—Only symptoms from the first 3 principal analysis components were used in the confirmatory factor analysis.[23] These symptoms were submitted to an unweighted least squares factor analysis with a Procrustes oblique rotation.[24] Confirmatory factor analysis identified 2 factors (mood-cognition-fatigue and musculoskeletal) (Table 1).

Preliminary Working Case Definitions.—The 10 symptoms from factor analysis included all 6 symptoms identified by the clinical approach. We used these 10 symptoms to derive 2 possible working case definitions. First, we derived a case definition on the basis of factor scores. The confirmatory phase factor analysis model was fit to the participants' symptom data and a total factor score was calculated for each participant by adding the scores of the factors. A case was defined as having a combined factor score in the top 25th percentile.

Second, we developed an alternative working case definition based on symptom categories. This grouped the symptoms into 3 categories: fatigue, mood-cognition, and musculoskeletal. We separated chronic fatigue even though it did not load as a separate factor because of the central role of chronic fatigue in virtually all previous studies of GW veterans. We defined a case as having 1 or more symptoms from 2 or more symptom categories.

Comparison of the Preliminary Working Case Definitions.—We compared the case definitions by determining the prevalence of each type of case among GW veterans and nondeployed personnel and calculated their overall agreement by a κ statistic.[25] Forty-seven percent of GW veterans and 15% of nondeployed were classified as factor score cases. Of these, 25% had symptoms that included fatigue, mood-cognition, and musculoskeletal pain; 39.2% fatigue and

mood-cognition; 15.6% fatigue and musculoskeletal pain; 6.6% mood-cognition and musculoskeletal pain. An additional 9.9% reported only mood-cognition symptoms, and 8.1% reported only musculoskeletal pain. Forty-five percent of GW veterans and 15% of nondeployed were classified as symptom-category cases. Of these, 41.8% reported symptoms of fatigue, mood-cognition, and musculoskeletal pain; 26.7% reported fatigue and mood-cognition; 8.4% reported fatigue and musculoskeletal pain; and 23.1% reported mood-cognition and musculoskeletal pain. The κ statistic was 0.79, which indicated substantial overall agreement between the working case definitions.

Chronic Multisymptom Illness.— Since both case definitions were comparable, we chose the symptom-category approach because it was easier to apply in a clinical setting. We defined a case as having 1 or more chronic symptoms (present for $\geq$6 months) from at least 2 of the following categories: fatigue; mood and cognition (symptoms of feeling depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, trouble finding words, or difficulty sleeping); and musculoskeletal (symptoms of joint pain, joint stiffness, or muscle pain). We subclassified a case as severe if each case-defining symptom was rated as severe; otherwise, we considered the case to be mild-to-moderate.

Cross-sectional Clinical Evaluation

Study Population and Enrollment Procedures.— We conducted a third-phase, cross-sectional clinical study during April and May 1995. Subjects were GW veterans currently in the index unit. During the preceding cross-sectional survey, we informed the 667 participants from the index unit of our intent to conduct a follow-up clinical study and asked for volunteers. We also recruited participants by posting notices throughout the base. Our solicitations stressed the need for both symptomatic and nonsymptomatic GW veterans.

Clinical Evaluation.— Each volunteer was mailed an informed consent form, a clinical questionnaire, and the Medical Outcomes Study Short Form 36 (MOS SF-36)[26,27] to complete at home. The clinical questionnaire asked about the presence, duration, and intensity of 35 symptoms and included questions about fatigue, activity levels, and diarrhea.

Each subject was individually evaluated by a CDC field team at the Veterans Affairs (VA) Medical Center in Lebanon, Pa. Subjects completed the Mississippi Post Traumatic Stress Disorder Scale (modified for use among GW veterans).[28] The 1994 revised chronic fatigue syndrome (CFS) working case definition was used to classify cases of CFS.[29] A trained interviewer privately administered selected modules on somatization disorder, major depression, and panic disorder from the Diagnostic Interview Schedule version of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, (*DSM-IV*)[30] The Diagnostic Interview Schedule was modified, so the onset of disorders could be referenced to periods before, during, and after deployment to the GW. Each subject next received a screening physical examination performed by a physician assistant. This examination systematically covered vital signs, height, weight, skin, ears (including gross hearing), eyes (including extraocular eye movements and retina), nasal passages, throat, neck (including thyroid), lungs, heart, abdomen, lymph nodes (cervical, axillary, and inguinal areas), rectal vault (including testing of stool for occult blood), reflexes, and tests of coordination (finger to nose), strength, and sensation (light touch, vibration, and pin prick). The personnel who performed these evaluations were not aware of the subjects' case status.

Case Definition.— We classified participants in the clinical study as cases or noncases based on their responses to the mailed clinical epidemiological questionnaire and the case definition derived in the cross-sectional survey.

Blood and Urine Specimen Tests.— Blood specimen evaluation included a complete blood cell count, erythrocyte sedimentation rate, serum chemistry values (alanine aminotransferase, alkaline phosphatase, total protein, albumin, globulin, calcium, phosphorus, glucose, electrolytes, blood urea nitrogen, and creatinine), and thyroid-stimulating hormone level. Urine specimens underwent routine urinalysis.

Serologic Testing.— To test for arboviruses and rickettsia, serum samples were tested for antibodies to yellow fever, dengue, Sindbis, West Nile, phlebotomus fever viruses (Naples and Sicilian), Toscana, Karimbad, and Isfahan viruses at the Division of Vector-Borne Infectious Diseases, CDC.[31] Serologic testing for antibodies to *Rickettsia typhi*, *Rickettsia rickettsii*, *Coxiella burnetii*, and *Ehrlichia chaffeensis* was performed at the Division of Viral and Rickettsial Diseases, CDC.[32]

To test for parasites, serum samples were tested at the Division of Parasitic Diseases, CDC for reactivity to *Leishmania donovani* and *Leishmania tropica* promastigote antigens,[33] and also were tested for antibodies to *Toxoplasma gondii*, *Schistosoma mansoni*, *Schistosoma haematobium*,[34] and *Strongyloides stercoralis*.

To test for other agents, serum samples were tested for antibodies to *Helicobacter pylori* at the Division of Bacterial and Mycotic Diseases, CDC. To screen for exposure (either by vaccination or in combat) to 2 widely discussed putative biologic warfare agents, we tested serum samples for antibodies to toxin produced by *Clostridium botulinum* and *Bacillus anthracis*. Serum samples were screened at the Division of Bacterial and Mycotic Diseases, CDC, for antibodies to type A botulinum toxin. Serum samples were assayed at the US Army Medical Research Institute of Infectious Diseases, Washington, DC, for antibodies against anthrax protective antigen and lethal factor.

Stool Specimens.— Fresh fecal specimens were examined for red and white blood cells and were cultured for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Escherichia coli* 0157:H7. Fecal specimens were examined at the Division of Parasitic Diseases, CDC, for ova and parasites,[35,36] including but not limited to *Cryptosporidium parvum*, *Cyclospora cayetanensis*, *Isospora belli*, and microsporidia.[37] Fecal specimens also were screened for enteroviruses at Southern General Hospital, Glasgow, Scotland.[36]

Statistical Analyses

We estimated the association between symptoms and deployment to the GW by prevalence ratios. We assessed univariate associations of categorical variables by odds ratios (OR) and 95% confidence intervals (95% CI). We used the χ^2, Fisher exact, and Mantel-Haenszel tests to calculate P values. We used the Student t test and 1-way, between-subjects analysis of variance (ANOVA) to compare means of continuous variables and compared pairs of means by the Scheffé test. We used the PROC FACTOR procedure to perform principal components and factor analyses. In the factor analysis, the proportion of total common variance explained by each factor was determined by the direct contribution method.[23] The PROC CATMOD procedure was used to fit a polytomous logistic regression model and simultaneously assess associations between both mild-to-moderate and severe cases and possible risk factors. All calculations were performed using Statistical Analysis Systems (SAS) software.[39] All statistical tests were 2-tailed.

RESULTS

Cross-sectional Questionnaire Survey

Survey Participation Rates.— Questionnaires were completed by 4036 per-

Table 2.—Demographic, Military, and Health Characteristics of All Subjects

Characteristics	%				
	Index (n = 667)	Unit A (n = 538)	Unit B (n = 838)	Unit C (n = 1680)	Combined (n = 3723)
Age, median, y	39	38	38	31	34
Male	85	85	82	88	86
White	94	93	85	81	86
Married	72	68	73	66	69
Less than college education	36	26	18	35	30
Employed full-time	89	85	84	92	89
Deployed to Persian Gulf	47	22	32	28	31
Current enlisted rank	84	85	85	88	86
Years on active duty					
<1	17	17	10	0.1	8
1-10	78	78	78	59	69
≥11	5	5	11	42	23
Years in guard or reserves					
<1	0.5	0.2	0.4	94	42
1-10	45	48	56	5	30
≥11	54	52	44	1	28
Listed on Veterans Affairs/ Department of Defense registry	15	1	3	1	4
Self-assessed health					
Excellent	27	29	28	22	25
Very good	43	43	43	40	42
Good	25	25	25	33	29
Fair	4	2	4	5	4
Poor	0.4	0.4	0.4	0.5	0.5
Current smoker	20	20	22	25	23
Average No. of alcoholic drinks per week					
None	37	35	42	34	37
1-3	37	39	36	36	36
≥4	26	26	22	30	27

sons. We excluded 313 subjects; 109 were not members of the units, and 204 were younger than 17 years during the GW. Among 3723 remaining participants, 1163 (31.2%) were GW veterans and 2560 (68.8%) had not been deployed. After exclusions, unit participation rates were 62% (667/1083) for the index unit, 35% (538/1520) for unit A, 73% (838/1141) for unit B, and 70% (1680/2407) for unit C.

Demographic, Military, and Health Characteristics.—The median age of participants was 34 years (mean, 35 years; range, 21-60 years); 86% were men; 86% were white; and 89% were employed full-time. Other demographic, military, and general health characteristics were similar in the 4 units (Table 2), except that active-duty subjects (unit C) were younger, less likely to be white, and less likely to describe their current health as "excellent." Demographic characteristics of survey participants were similar to overall unit demographics.

Prevalence of Symptoms.—Overall, 3701 participants (99%) reported at least 1 symptom as a current health problem. Gulf War veterans reported all symptoms, except hay fever and other allergies, significantly more often than nondeployed (Table 3). All symptoms, except headache and difficulty sleeping, were reported more often by GW veterans from the index unit than those from comparison units. Chronic diarrhea was reported substantially more often by GW veterans from the index unit. The prevalence of symptoms among nondeployed personnel was similar among all units (data not shown).

Occurrence of Chronic Multisymptom Illness Cases.—In all, 3675 subjects provided complete data on the 10 case-defining symptoms. Among the 1155 GW veterans, 6% were classified as severe cases and 39% as mild-to-moderate cases compared with 0.7% and 14%, respectively, among the 2520 nondeployed personnel. Deployment to the GW was the most important risk factor for severe and mild-to-moderate illness (Table 4). Multivariate analyses (Table 5) showed that severe cases were associated with GW service, enlisted rank, female sex, and smoking. Mild-to-moderate cases were associated with the same variables, and increasing age and current membership in the index unit. Illness was not associated with the number of deployments, month or season of deployment, duration of deployment, military occupational specialty, direct participation in combat, or self-reported locality in the Gulf region (most were in the Rhiyadh area of Saudi Arabia).

Clinical Evaluation Study

Participation Rate and Classification of Cases.—Among the index unit's 1083 members, 490 (45%) were GW veterans and 173 of those (35%) volunteered to participate in the clinical evaluation study. Fifteen (8.7%) provided incomplete symptom data and were excluded from further analysis. Of the remaining 158 veterans, 13 (8%) were severe cases, 86 (54%) were mild-to-moderate cases, and 59 (37%) were noncases.

General Characteristics and Current Symptoms.—Most participants were men, but 4 of the severe cases (31%) occurred among women. The prevalence of all chronic symptoms (including those not used to define cases) was highest among severe cases, followed by mild-to-moderate cases, and noncases (data not shown). Diarrhea (≥3 loose stools per day) was reported by 3% (n = 2) of noncases, by 26% (n=22) of mild-to-moderate cases (OR, 10; 95% CI, 2.2-44.2), and by 77% (n=10) of severe cases (OR, 95; 95% CI, 14.1-642.3). All but 3 subjects who reported diarrhea indicated it had been present for at least 6 months, and all but 2 dated onset from the period during or immediately following their return from the Gulf region. Only 2 subjects with diarrhea also reported weight loss.

Medical History Prior to Deployment.—Severe cases reported histories of depression before deployment significantly more often (15%) than noncases (0%) (Fisher exact test $P<.05$) and also were associated with self-reported sinusitis prior to first deployment more frequently (38%) than noncases (10%) (OR, 5.8; 95% CI, 1.4-24.5). Otherwise, there were no statistically significant differences referable to the year before deployment to the GW between severe or mild-to-moderate cases and noncases in terms of 11 allergy symptoms; 7 self-reported surgical, dental, or invasive medical procedures (including blood or blood product transfusions and mercury amalgam repair of dental cavities); or self-reported lifetime prevalence, before deployment to the Persian Gulf, of 35 medical and psychiatric conditions (including heart disease, hypertension, diabetes, alcohol or substance abuse, anorexia or bulimia, migraine or severe headaches, anxiety, diarrhea, irritable bowel syndrome, and impotence).

Physical Examination.—Physical examinations were most notable for the general paucity of abnormal findings. Severe cases were associated with slightly higher body mass indices, a measure of weight in kilograms divided by the square of height in meters (BMI, 29.6), than noncases (BMI, 26.5) ($P<.01$). Rash

was present more often among mild-to-moderate (14%) and severe (15%) chronic multisymptom cases than among noncases (3%), but the differences were not statistically significant. Several minor abnormalities were found on lymph node, liver, spleen, or neurologic examination, but none was associated with cases. A summary of physical examination data is available from the authors.

Functional Status and Well-being.— As measured by the MOS SF-36, severe and mild-to-moderate cases were associated with a significant decrease in functioning and well-being. Severe cases were associated with a decrease on all of the 6 subscales (Table 6).

Blood and Urine Testing.—The mean values of a few routine blood tests differed among cases and noncases, but the differences were marginal and clinically unimportant. None of the urinalysis results differed between cases and noncases. A summary of blood and urine data is available from the authors.

Stool Specimen Testing.—No fecal specimen tested positive for occult blood, white blood cells, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, enteropathogenic *Escherichia coli*, microsporidia, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, *Isospora belli*, or *Entamoeba histolytica*. *Blastocystis hominis* was found in stool specimens from 7 noncases (12%) and from 6 mild-to-moderate and chronic (7%) multisymptom cases. *Giardia lamblia* was found in stool specimens from 1 noncase (2%) and 1 mild-to-moderate case (1%). Enteroviruses were found in stool specimens from 6 noncases (10%) and 8 mild-to-moderate cases (9%). A summary of stool specimen data is available from the authors.

Serologic Testing.—There was no association between seropositivity to various infectious agents and chronic multisymptom cases. Troops are routinely vaccinated against yellow fever virus, and 83% of subjects had antibodies against this agent, but there were no differences between cases and noncases. Ten subjects reacted to botulina toxin and 14 to anthrax protective antigen, but there were no differences between cases and noncases. Eight participants (4.9%) seroreacted to leishmanial antigens. However, no severe case was seroreactive; reactivity rates were higher among noncases than mild-to-moderate cases; the difference was not significant; and titers were low (range, 1:16-1:64). Nine subjects were seropositive to phlebotomus fever viruses, but rates were similarly low among noncases (2%), mild-to-moderate cases (9%), and severe cases (8%). Thirty persons (19%) were seroreactive to *Toxoplasma gondii*, and rates were similar between cases and noncases. Sixteen subjects had antibodies to dengue virus and rates were similar in cases and noncases. Similar, low, and equally distributed (among noncase and cases) seroreactivity existed to *Coxiella burnetii* (7 positive), *R rickettsii* (6 positive), *E chaffeensis* (5 positive), and *R typhi* (1 positive). No subject had antibodies to Sindbis, West Nile, Toscana, Karimbad, or Isfahan viruses, *Schistosoma* species, or *S stercoralis*. A summary of serologic data is available from the authors.

Table 3.—Prevalence (percent) of 35 Current and Long-term Symptoms Among Gulf War Veterans (n = 1163) and Nondeployed Military Personnel (n = 2538)

	Current Symptoms		Symptoms Lasting More Than 6 mo	
Symptoms	Veterans	Nondeployed Military Personnel	Veterans	Nondeployed Military Personnel
Sinus congestion	52	39	47	32
Headache	50	41	45	32
Fatigue	43	17	41	13
Joint pain	36	13	33	11
Difficulty remembering or concentrating	34	9	32	8
Joint sitffness	30	11	28	9
Difficulty sleeping	28	13	25	9
Gas, bloating, cramps, or abdominal pain	27	15	25	11
Trouble finding words	26	9	24	8
Moody or irritable	25	9	25	7
Rash or sores	23	7	12	5
Numbness or tingling	21	8	19	5
Muscle pain	20	8	18	6
Hay fever or allergies*	19	19	18	17
Feeling depressed	18	10	16	8
Diarrhea (≥3 loose stool samples per 24 h)	18	4	16	3
Sore throat	17	10	15	6
Cough	17	11	14	6
Feeling anxious	17	7	15	5
Unintended weight gain ≥10 lb	17	8	15	6
Shortness or breath	16	6	14	5
Chest pain	15	7	13	5
Decreased interest in sex	14	6	13	4
Dizziness or trouble maintaining balance	14	4	12	2
Night sweats that soak bed sheets	13	4	12	2
Fatigue lasting 24 h after exertion	13	2	12	2
Nasal sores	11	6	9	4
Swollen lymph nodes	10	4	8	2
Milk intolerance	7	5	7	4
Episodes of disorientation	7	1	5	1
Nausea or vomiting	6	2	6	1
Wheezing	6	3	5	2
Chemical sensitivity	5	2	5	2
Fever	5	2	4	1
Unintended weight loss ≥10 lb	3	1	2	1

*Except hay fever or other allergies, all current and chronic symptoms were reported significantly ($P<.05$) more often by Gulf War veterans than nondeployed military personnel.

Syndromic Disorders

Posttraumatic Stress Disorder.—One subject screened positive for posttraumatic stress disorder also was classified as a severe chronic multisymptom case.

Depression.—Twenty-two subjects met the Diagnostic Interview Schedule of the *DSM IV* criteria for major depression occurring after their last deployment to the GW, and 19 also reported depression within the last year (1994-1995). Overall, major depression was more common among GW veterans after deployment than before deployment. The prevalence of current depression was significantly higher among severe chronic multisymptom cases (54%) and mild-to-moderate cases (13%) than among noncases (2%).

Somatization and Panic Disorders.—Four subjects (all classified as severe chronic multisymptom cases) met *DSM-III-R* criteria for somatization disorder. Three met criteria for panic disorder (2 were mild-to-moderate cases and 1 was a severe case). Panic disorder was uncommon in the periods before and during deployment to the GW. Four of the subjects met criteria for panic disorder during their deployment to the war, including 1 classified a as mild-to-moderate case and 1 classified as a severe case.

Table 4.—Univariate Associations With Mild-to-Moderate and Severe Cases

Variables	Noncase (n = 2786), No.	Mild-to-Moderate Case (n = 803)		Severe Case (n = 86)	
		No.	OR (95% CI)*	No.	OR (95% CI)
Gulf War veteran	638	449	4.3 (3.6-5.0)	68	12.7 (7.5-21.5)
Enlisted rank August 1990-July 1991	1930	663	1.5 (1.2-2.0)	82	15.5 (2.2-111.8)
Current enlisted rank	2350	701	1.3 (1.1-1.7)	85	14.9 (2.1-107.1)
Age, y					
<30	879	153	1.0	17	1.0
30-39	1109	296	1.5 (1.2-1.9)	39	1.8 (1.1-3.2)
40-49	535	254	2.7 (2.2-3.4)	19	1.8 (0.9-3.6)
≥50	191	84	2.5 (1.9-3.4)	9	2.4 (1.1-5.6)
≥30 Combined	1835	634	2.0 (1.6-2.4)	67	1.9 (1.1-3.2)
Current smoker	580	213	1.4 (1.1-1.6)	32	2.2 (1.4-3.5)
Index unit member August 1990-July 1991	272	196	2.6 (2.1-3.2)	19	2.2 (1.3-3.8)
Current index unit member	414	222	2.2 (1.8-2.6)	23	2.1 (1.3-3.4)
Other deployment	567	236	1.6 (1.4-2.0)	27	1.8 (1.1-2.9)
Less than college education	795	270	1.3 (1.1-1.5)	34	1.6 (1.1-2.5)
Female	396	112	1.0 (0.8-1.2)	17	1.5 (0.9-2.5)
White	2339	713	1.5 (1.2-2.0)	69	0.7 (04-1.2)
Married	1870	597	1.4 (1.2-1.7)	60	0.1 (0.7-1.8)

*OR indicates odds ratio; CI, confidence interval.

Table 5.—Multivariate Associations With Mild-to-Moderate and Severe Cases

Variables	Mild-to-Moderate Case	Severe Case
	OR (95% CI)*	OR (95% CI)
Gulf War veteran	4.08 (3.39-4.93)	16.18 (8.99-29.14)
Current enlisted rank	1.71 (1.29-2.26)	17.38 (2.36-127.89)
Female	1.64 (1.27-2.12)	3.13 (1.65-5.94)
Age, y		
<30	1.00	1.00
30-39	1.24 (0.98-1.57)	1.32 (0.72-2.44)
40-49	2.14 (1.65-2.78)	1.47 (0.71-3.04)
≥50	1.59 (1.11-2.27)	1.63 (0.65-4.08)
Current index unit member	1.54 (1.24-1.91)	1.49 (0.86-2.57)
Current smoker	1.27 (1.03-1.55)	1.72 (1.06-2.77)

*OR indicates odds ratio; CI, confidence interval.

Chronic Fatigue Syndrome.—Eight subjects met all criteria for CFS.[29] Of these, 7 (54%) also were classified as severe cases, and 1 (1%) was a mild-to-moderate case.

COMMENT

Our study of currently active members from 4 air force populations showed a substantially higher prevalence of symptoms among GW veterans than nondeployed. This result was similar to findings of an earlier and unrelated epidemiological study of Pennsylvanian and Hawaiian ANG personnel,[40] a population-based study from all branches of service,[5] and is consistent with clinical data from GW veteran registries.[6] Thus, air force GW veterans likely experience an illness similar to that reported from other branches of the service.

The number and diversity of symptoms reported by our study subjects and by GW veterans in other studies make analytic epidemiological study difficult. Therefore, a major objective was to develop a case definition that captured the chronic multisymptomatic nature of illness in GW veterans. We used 2 independent methods to identify case-defining symptoms. An exploratory clinical approach showed that veterans had a condition defined by fatigue, neurocognitive symptoms, and joint pain and stiffness. Factor analysis identified 2 major factors that included and extended symptoms identified by the clinical approach.

Besides extending the number of correlated symptoms, factor analysis used data collected from all participants and did not bias our study toward finding a higher case prevalence among veterans. Factor analysis also uses rigorous empirical statistical methods to identify factors and associated factor scores. Thus, we used information from factor analysis to derive the final case definition. We first derived a factor score case definition that included as cases those subjects whose total factor scores were in the upper 25th percentile of the study population. We derived a second case definition by grouping the symptoms identified by factor analysis into 3 of the following categories: fatigue, mood-cognition, and musculoskeletal pain. We separated chronic fatigue, even though it did not load as a separate factor because of the central role of chronic fatigue in all studies of GW veterans.

The κ statistic measuring agreement between the 2 preliminary case definitions was 0.79, which represents substantial agreement.[41] Disagreement between the 2 definitions occurred because factor score–defined cases could have symptoms from only 1 factor and symptom score–cases could have symptoms from 2 categories but not exceed the 25th percentile of factor scores. We chose the symptom category approach for the final working case definition because it generally identified the same cases as the factor score approach, better captured the multisymptom nature of illness, was clinically more understandable, and allowed us to subclassify cases according to severity. To further evaluate the validity of defining case subjects based on symptom categories rather than factor scores, we examined univariate and multivariate associations (variables from Tables 4 and 5) with cases defined by both methods and found no meaningful differences.

Our case definition represents a unique approach toward organizing symptom data. We intended it to provide a summary measure of illness to test for associations with clinical abnormalities and risk factors and not as a definitive label for a single, distinct illness. The resulting case definition needs to be replicated by other studies of GW veterans. However, in a civilian population, factor analysis methods identified fatigue, mood, and cognition as the most important factors among symptoms similar to the ones in the current study.[42]

The key observation of this study was that air force GW veterans were significantly more likely to meet criteria for severe and mild-to-moderate illness than were nondeployed personnel. There was no association between the chronic multisymptom illness we defined and risk factors specific to combat in the GW (month or season of deployment, duration of deployment, duties in the GW, direct participation in combat, or locality of GW service). Our finding that 15% of nondeployed also met illness criteria was equally important and suggests that the multisymptom illness we observed in this population is not unique to GW service.

To characterize the clinical features of GW veterans with this chronic multisymptom illness, we evaluated veterans from one unit. Neither mild-to-moderate nor severe cases were associated with clinically significant physical examination or routine laboratory test abnormalities. However, GW veterans classified as having mild-to-moderate and severe illness had a significant decrease in functioning and well-being compared with noncases, as measured by the MOS SF-36.

We tested participants for exposure to several infectious agents that are im-

portant health problems in the Gulf region, that may have been used in vaccines, and that might be associated with a chronic illness. Leishmaniasis is endemic to the region, and a syndrome termed *viscerotropic leishmaniasis* has been described in GW veterans.[43,44] Approximately 5% of participants seroreacted to leishmanial antigens, but the titers were low and seroreactivity rates were not significantly different between cases and noncases. No study subject had clinical manifestations of visceral or cutaneous leishmaniasis. However, the manifestations of viscerotropic leishmaniasis can be nonspecific.[43,44] The serologic assay we used is a sensitive diagnostic tool for classic visceral leishmaniasis, but there is, as yet, no reliable screening test for viscerotropic leishmaniasis.[43,44] As a surrogate for exposure to phlebotomine sand flies, which transmit *Leishmania* parasites and sand fly fever viruses, we tested participants for antibodies against Naples and Sicilian phlebotomus fever viruses. Seroprevalence was similar to that noted with the *Leishmania* serologic assay. Clearly, neither seroreactivity to leishmanial antigens nor exposure to the phlebotomine vectors was associated with the illness we defined.

Similarly, we found no association between illness and antibody against the other viruses, rickettsiae, parasites, or bacteria for which we assayed. Chronic diarrhea was reported among 77% of severe cases, but we found no associations with any infectious agents. Although we did not evaluate subjects for noninfectious causes of diarrhea, such as malabsorption syndromes, the descriptive stool sample characteristics and lack of weight loss suggest irritable bowel syndrome as the predominant reason for the reported chronic diarrhea.

Our study has several limitations. Most important, the study involved currently active air force personnel (primarily reservists) and cannot be generalized to other branches of service or to GW veterans who have left the service. The primary objectives were to devise a case definition, evaluate the occurrence of illness, and clinically describe the illness. We did not intend to test specific hypotheses, many of which have arisen subsequent to the study; rather, we intended to establish basic parameters to aid in future studies.

The symptom data were self-reported and, thus, may be subject to reporting or recall bias. Other studies have attempted to categorize GW veterans as having illness in various predefined categories (eg, CFS, multiple chemical sensitivities, depression, and neurologic abnormalities). We chose a completely different strategy first to document the presence, magnitude, and duration of various symptoms reported by veterans and nondeployed personnel and then to determine if a meaningful construct could be identified. Although a reporting bias may have contributed to the moderately higher prevalence of symptoms reported by GW veterans in the index unit, the main findings of this study remain valid for the comparison units. In addition, although the participation rate of one of the comparison units (unit A) was low, the findings within that unit were consistent with those from the other units.

Table 6.—Functional Disability Among Long-term Multisymptom Cases and Noncases as Measured by the Medical Outcomes Study Short Form 36 (MOS SF 36)*

MOS SF 36 Subscales	Noncase (n = 59)	Mild-to-Moderate Case (n = 86)	Severe Case (n = 13)	Student *t* Test *P* Value
General mental health	36.4 (3.7)	32.1 (6.3)	28.0 (8.8)	.001
Vitality	17.8 (3.9)	13.4 (3.6)	8.5 (3.4)	.001
Physical functioning	29.5 (0.9)	27.9 (2.4)	24.5 (3.4)	.001
General physical	30.8 (3.0)	25.1 (4.8)	17.0 (3.7)	.001
Physical limit	7.9 (0.5)	6.7 (1.4)	5.5 (1.6)	.001
Emotional limit	5.8 (0.6)	5.4 (1.0)	4.8 (1.4)	<.001

*Values followed by numbers in parentheses are the mean (SD).

The same limitations apply to the clinical evaluation phase of the study. We evaluated GW veterans from one unit in order to establish clinical parameters of the illness we had defined and not to conduct a case-control study. Participants underwent a systematic standardized physical examination by physician assistants, who focused on documenting obvious abnormalities. Thus, this study did not attempt to assess subtle physiologic differences. Furthermore, the number of severe, chronic, multisymptom cases was relatively small, which potentially limited our ability to identify significant findings associated with those cases.

In addition, all clinically evaluated subjects were from a single ANG unit, and only 35% of GW veterans from that unit participated. This participation rate may not adequately represent GW veterans. The extent to which ill GW veterans were underrepresented or overrepresented could influence the findings. A first interpretation may suggest that ill veterans were more likely to have volunteered, because 63% of the clinically evaluated participants were classified as cases in contrast with the 45% prevalence of illness in GW veterans from the cross-sectional survey. However, it was our impression that military personnel with severe illness were less likely to participate for fear of identification and service-related medical consequences. Moreover, it may be that the most seriously affected GW veterans are no longer in the military.

These limitations notwithstanding, our results indicate that a substantial proportion of currently active air force GW veterans have a chronic multisymptom illness, which is accompanied by significant decreases in functioning and well-being. The illness was not associated with physical examination or clinical laboratory abnormalities or with infection by assorted agents that are found in the region or to which troops in combat may have been exposed. Poorly characterized illness, including fatigue, neurocognitive, and musculoskeletal complaints, has affected veterans of many other wars.[45] The empirically based approach described here provides a method for assessing the prevalence of multiple chronic symptoms and exploring the clinical basis of this condition. Other studies should use similarly rigorous analytic methods to classify cases and standardized measures of function and well-being to collect data and should enroll personnel from other branches of the military.

The elevated case prevalence among GW veterans remains unexplained by our study. It is possible that the symptom complex is associated with GW-specific exposures (eg, an as-yet-unidentified chemical or biological agent).[16] Although in our study population the risk of illness was not associated with the dates, season, duration, number of deployments, or military occupational activities, we believe a more plausible explanation is that key risk factors present among both deployed and nondeployed populations were present at higher intensity or greater frequency among GW veterans. It is clear that the distribution of cases among GW veterans and nondeployed personnel in this study cannot easily be explained by risk factors unique to Southwest Asia.

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