

Gulf War Veterans' Health: Medical Evaluation of a U.S. Cohort

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Background: United States military personnel reported various symptoms after deployment to the Persian Gulf during the 1991 Gulf War. However, the symptoms' long-term prevalence and association with deployment remain controversial.

Objective: To assess and compare the prevalence of selected medical conditions in a national cohort of deployed and nondeployed Gulf War veterans who were evaluated by direct medical and teledermatologic examinations.

Design: A cross-sectional prevalence study performed 10 years after the 1991 Gulf War.

Setting: Veterans were examined at 1 of 16 Veterans Affairs medical centers.

Participants: Deployed ($n = 1061$) and nondeployed ($n = 1128$) veterans of the 1991 Gulf War.

Measurements: Primary outcome measures included fibromyalgia, the chronic fatigue syndrome, dermatologic conditions, dyspepsia, physical health–related quality of life (Short Form-36 [SF-36]), hypertension, obstructive lung disease, arthralgias, and peripheral neuropathy.

Results: Of 12 conditions, only 4 conditions were more prevalent among deployed than nondeployed veterans: fibromyalgia (de-

ployed, 2.0%; nondeployed, 1.2%; odds ratio, 2.32 [95% CI, 1.02 to 5.27]); the chronic fatigue syndrome (deployed, 1.6%; nondeployed 0.1%; odds ratio, 40.6 [CI, 10.2 to 161]); dermatologic conditions (deployed, 34.6%; nondeployed, 26.8%; odds ratio, 1.38 [CI, 1.06 to 1.80]), and dyspepsia (deployed, 9.1%; nondeployed, 6.0%; odds ratio, 1.87 [CI, 1.16 to 2.99]). The mean physical component summary score of the SF-36 for deployed and nondeployed veterans was 49.3 and 50.8, respectively.

Limitations: Relatively low participation rates introduce potential participation bias, and deployment-related illnesses that resolved before the research examination could not, by design, be detected.

Conclusions: Ten years after the Gulf War, the physical health of deployed and nondeployed veterans is similar. However, Gulf War deployment is associated with an increased risk for fibromyalgia, the chronic fatigue syndrome, skin conditions, dyspepsia, and a clinically insignificant decrease in the SF-36 physical component score.

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*For a list of the Gulf War Study Participating Investigators, see the Appendix (available at www.annals.org).

Approximately 700 000 U.S. servicemen and service-women were deployed to the Persian Gulf during the 1991 Gulf War. Although only 200 U.S. combat-related deaths occurred, many personnel were subjected to various natural and man-made environmental exposures, including sand flies, molds, infectious agents, vaccines, medical prophylaxis, pesticides, depleted uranium, oil-fire smoke, biological and chemical warfare agents, and psychological stress (1). Within months of their return, many ground-deployed personnel began reporting fatigue, skin rashes, bone and joint pains, symptoms suggestive of the irritable bowel syndrome, cognitive dysfunction, emotional distress, and other symptoms (2–5). Questionnaire surveys of U.S. (6), British (7), and Canadian (8) veterans and more representative veteran cohorts selected from Iowa (9), New England (10), the U.S. Air Force (11), and Great Britain (12) supported individual reports.

In 1995, the U.S. Department of Veterans Affairs funded the National Health Survey of Gulf War Era Veterans and Their Families research project. This study, which compared the health of 15 000 deployed veterans with 15 000 nondeployed veterans through mail and telephone surveys, found that deployed veterans reported a higher prevalence of 29 of 31 self-reported medical conditions and 48 symptoms than nondeployed veterans (13). In

our study, we recruited a subset of deployed and nondeployed veterans who participated in the National Health Survey of Gulf War Era Veterans and Their Families for a medical evaluation to assess and compare the long-term prevalence of selected medical conditions in a national cohort of deployed and nondeployed Gulf War veterans.

METHODS

Study Population and Recruitment

Recruitment for the National Health Survey of Gulf War Era Veterans and Their Families study has been described elsewhere in detail (13) and is summarized in the

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Context

The prevalence and association of medical conditions with deployment to the 1991 Gulf War are controversial.

Contribution

This cross-sectional study, performed 10 years after the 1991 Gulf War, compared the prevalence of 12 conditions between 1061 deployed and 1128 nondeployed U.S. veterans. Only fibromyalgia (2% vs. 1.2%), the chronic fatigue syndrome (1.6% vs. 0.1%), skin conditions (34.6% vs. 26.8%), and dyspepsia (9.1% vs. 6.0%) were more common among deployed veterans.

Cautions

Short-term conditions that resolved weren't assessed. Fifty-three percent of deployed eligible veterans and 39% of nondeployed eligible veterans participated in the study.

Implications

Only a few health conditions seem to be associated with Gulf War deployment.

—The Editors

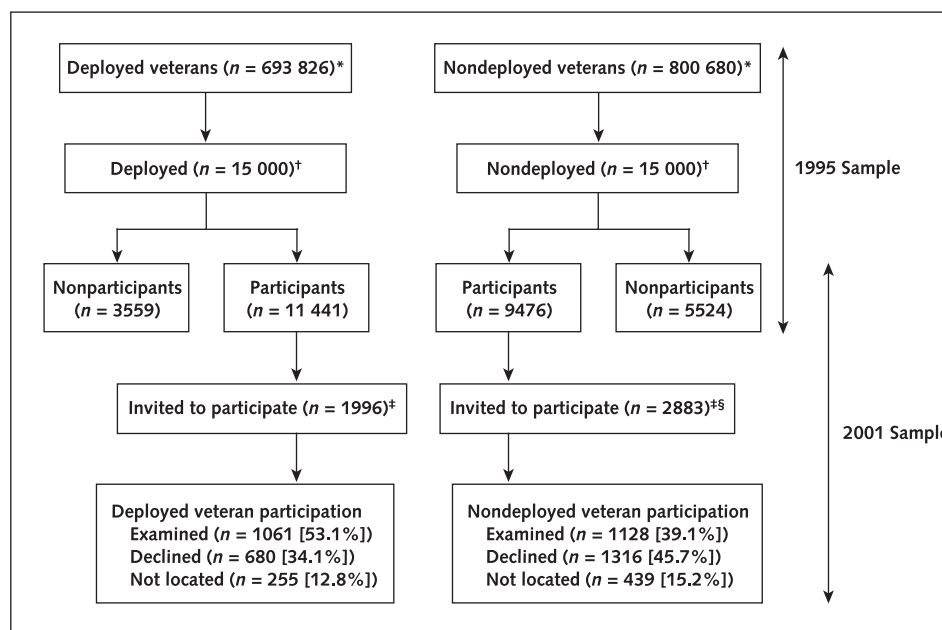
Figure. Briefly, the U.S. Department of Defense's Defense Manpower Data Center, Monterey, California, identified the entire cohort of 693 826 troops who were deployed to the Persian Gulf area during the Gulf War and approxi-

mately half (800 680 troops) of the nondeployed troops who were in military service between September 1990 and May 1991. A total of 15 000 deployed and 15 000 nondeployed veterans were solicited to participate in the study. To ensure that women, reservists, and National Guard members were adequately represented, the investigators applied a stratified random sampling method to each group so that one fifth of each sample were women ($n = 3000$), one third were reservists ($n = 5000$), and approximately one quarter were members of the National Guard ($n = 4000$).

For our study, we created a list of potential participants by randomly selecting from the 11 441 deployed and 9476 nondeployed Gulf War veterans who participated in the 1995 study, stratified by deployment status (deployed or not deployed) and region of last known residence at the time of the original survey based on home telephone area code (**Figure**). We assigned potential participants to the participating Veterans Affairs medical center closest to their home residence. Participating medical centers were in Albuquerque, New Mexico; Baltimore, Maryland; Birmingham, Alabama; Boston, Massachusetts; Cincinnati, Ohio; Hines (Chicago), Illinois; Houston, Texas; Miami, Florida; Minneapolis, Minnesota; New Orleans, Louisiana; New York, New York; Portland, Oregon; Richmond, Virginia; Salt Lake City, Utah; San Diego, California; and St. Louis, Missouri.

We gave each member of the cohort assigned to a

Figure. Sample selection flowchart.



* Cohort obtained from the U.S. Department of Defense Manpower Data Center, Monterey, California. Deployed cohort included all deployed troops, and nondeployed cohort was approximately half of all nondeployed troops in service between September 1990 and May 1991. † Stratified random sampling applied to the U.S. Department of Defense cohort to adequately represent women, reservists, and National Guard members. ‡ Stratified random sampling applied to participants in the 1995 study to select by geographic proximity to 1 of 16 participating Veterans Affairs Medical Centers. § We initially invited 2084 veterans to participate. To achieve examined groups of equal size, we invited an additional 799 veterans to participate in the fourth solicitation wave of 50 veterans per site.

medical center a randomly generated number, and the numbers were sequenced in ascending order. We performed 3 recruitment waves of approximately 40 deployed and 40 nondeployed veterans at approximately 8-month intervals at each site, beginning with the veteran who was assigned the lowest number. In each wave, the veteran received a recruitment package that included an introductory letter, a detailed explanation of the purpose and nature of the study, a letter of intent form, and a preaddressed and stamped return envelope. We asked potential veteran participants to sign and return the letter of intent to participate in the study. Veterans who did not respond within a few weeks received a reminder call. To further encourage study participation, we sent nonrespondents a newsletter and a 12-minute videotape that presented a typical clinical examination day and several testimonies of veterans who had already completed the study. Two research contractors (Gallup Organization, Omaha, Nebraska, for the first wave, and Schulman, Ronca & Bucuvalas, Inc., Silver Spring, Maryland, for successive waves) mailed recruitment packages and made reminder follow-up calls. Because of lower participation rates among nondeployed veterans, we solicited an additional 799 nondeployed veterans to obtain groups of equal size.

The signed letter of intent was returned to the Hines Veterans Affairs Cooperative Studies Program Coordinating Center, Hines, Illinois, which forwarded it to the participating Veterans Affairs medical center to which the veteran was assigned. Site personnel then contacted the veteran and scheduled the examination. The research project provided travel, hotel, and per diem costs and an honorarium of \$200. The Hines Cooperative Studies Program Human Rights Committee and the institutional review board at each individual site approved the protocol and consent form. Participants gave signed informed consent shortly before the start of the examination.

Data Collection

To assess nonparticipation bias, we obtained previously collected data from deployed and nondeployed participants and nonparticipants, including sociodemographic and military service characteristics in 1991 from the U.S. Department of Defense's Defense Manpower Data Center and sociodemographic and self-reported health data collected by the National Health Survey of Gulf War Era Veterans and Their Families in 1995.

For our study, physicians and research nurses performed medical, neurologic, gynecologic, and psychiatric histories and examinations between 1999 and 2001 by using carefully standardized methods. A research nurse solicited histories of symptoms and illnesses in 8 system categories by using a structured interview. Examinations were followed by laboratory, pulmonary function, nerve conduction, and neuropsychological tests. The average examination time was 12 hours performed over 2 days. In this paper, we report the study's medical outcomes. Other

manuscripts will address the psychiatric and neuropsychological results.

Disease Diagnostic Criteria

Fibromyalgia

The diagnosis of fibromyalgia followed the 1990 American College of Rheumatology criteria of diffuse body pain and pain on physical examination on at least 11 of 18 tender points (14).

The Chronic Fatigue Syndrome

The diagnosis of the chronic fatigue syndrome followed the International Chronic Fatigue Syndrome Study Group case definition (15). After data collection was complete, 4 physicians and a psychologist, who were blinded to the participants' deployment status, reviewed medical and psychiatric data on individuals who met the chronic fatigue syndrome inclusion criteria. We identified exclusionary psychiatric disorders by participant responses to the Composite International Diagnostic Interview (CIDI) (16) and self-reported psychiatric diagnoses. We determined exclusionary medical illnesses from history, examination, self-reported diagnoses, and laboratory testing.

Peripheral Neuropathy

The diagnosis of peripheral neuropathy included any idiopathic or unexplained distal sensory, motor, or sensorimotor polyneuropathy based on physical findings, nerve conduction studies, or both. Upper motor neuron findings, alcohol abuse or dependence, HIV or AIDS, hypothyroidism, diabetes, or antineoplastic medications excluded this diagnosis.

Self-Reported Physical Health-Related Quality of Life

We used the physical component score of the Medical Outcomes Study Short Form-36 (SF-36) (17) to provide an overall measure of current self-reported physical health-related quality of life. For the average healthy population, the physical component score was a mean of 50, SD 10.

Dermatologic Conditions

We divided dermatologic conditions a priori into 2 groups. Group 1 conditions were freckles, lentigines, seborrheic keratoses, nevi, moles, cherry hemangiomas, skin tags, and surgical scars detected by research physicians after full-body skin examinations. Group 2 skin diagnoses included all diagnoses that are not included in group 1. A board-certified dermatologist diagnosed these conditions by using teledermatology, at least 2 digital photographs, and the results of a standardized history and physical examination.

Other Illnesses

Dyspepsia criteria included a history or symptoms of dyspepsia (frequent heartburn and recurrent abdominal

pain) and use of antacids, H₂-blockers, or other medications to treat dyspepsia. Hypertension was defined as blood pressure greater than 140/90 mm Hg or history of hypertension and use of antihypertensive medications. Hepatitis was defined as an alanine aminotransferase level greater than 1.5 times the upper limit of normal. We based the diagnosis of symptomatic arthralgias on report of persistent and clinically significant bone or joint symptoms with or without joint effusion and treatment with anti-inflammatory agents, narcotic pain medications, or nonnarcotic pain medications. Obstructive lung disease was defined as a history of lung disease (asthma, bronchitis, or emphysema) or pulmonary symptoms (wheezing, dyspnea on exertion, or persistent coughing with phlegm) and either the use of bronchodilators or at least 15% improvement in FEV₁ after a short-acting bronchodilator. Diabetes was defined as having a fasting glucose level of 6.99 mmol/L or greater (≥ 126 mg/dL) at the research examination or taking a hypoglycemic medication. Hypothyroidism was defined as having an untreated thyroid-stimulating hormone level of 10.0 mU/mL or greater or taking medication for hypothyroidism. Hyperthyroidism was defined as having an untreated thyroid-stimulating hormone level less than 0.1 mU/mL or taking medication for hyperthyroidism.

Laboratory Tests

The following laboratory tests were performed on all participants: complete urinalysis and blood tests to measure hemoglobin, fasting blood sugar, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, albumin, globulins, lactic dehydrogenase, alkaline phosphatase, total and fractionated bilirubin, aspartate and alanine aminotransferases, uric acid, total cholesterol, triglycerides, high-density lipoprotein, and thyroid-stimulating hormone levels; total leukocyte, leukocyte differential, and platelet counts; and erythrocyte sedimentation rate.

Data Quality Assurance

An operations manual provided instructions on the conduct of the study for all 16 sites, supplemented by 3 national training meetings and twice-weekly conference calls. We reviewed all data for accuracy and completeness, entered data into a computer database, and periodically checked data for consistency between variables.

Statistical Analyses

We estimated sample sizes a priori. The target sample size of 1000 persons in each group was sufficient to provide an 80% power to detect prevalence differences of 1.8% for fibromyalgia (assumed prevalences among deployed veterans and nondeployed veterans, 2.3% and 0.5%, respectively), 1.6% for the chronic fatigue syndrome (assumed prevalences among deployed veterans and nondeployed veterans, 1.9% and 0.3%, respectively), 1.5% for peripheral neuropathy (assumed prevalences among deployed veterans and nondeployed veterans, 1.7% and 0.2%, respectively), and a mean difference of 1.5, SD 10, for the physical component score of the SF-36.

We performed all analyses while blinded to deployment status. We based analyses of participation bias (Table 1) on data collected in 1991 and 1995; analyses of current health (Tables 2 to 4) are based on data collected by our present study. Analyses labeled as unadjusted accounted for the stratified sampling design (Figure) on the basis of the sampling probabilities of deployment status, sex, and duty type in the 1995 study and the examination rate of the groups in our study. Logistic regression analyses labeled as adjusted incorporated the stratified sampling design and the following covariates: age, sex, race (white vs. other), years of education (<12 years vs. ≥ 12 years), cigarette history (smoked cigarettes daily for ≥ 1 month during the past 12 months: yes or no), duty type (active vs. reserves or National Guard), service branch (Army or Marines vs. Navy or Air Force), and rank (enlisted vs. officer). We generated the prevalences among deployed and nondeployed veterans in Tables 1 and 2 by using SAS, version 8 (SAS Institute, Inc., Cary, North Carolina). We used the Fisher exact test for comparisons of sociodemographic and military service characteristics and self-reported medical illnesses. We used SUDAAN, release 8.0 (Research Triangle Institute, Research Triangle Park, North Carolina), to obtain population estimates and SEs, odds ratios, and 95% CIs. We based statistical comparisons on the Wald *F* statistic.

Role of the Funding Source

The Cooperative Studies Program of the U.S. Department of Veterans Affairs, Office of Research and Development, sponsored the study. The study's Executive Committee, composed of the principal investigators and several co-investigators (see the Appendix, available at annals.org), had full access to the data files of the study and were responsible for the study protocol, case report forms, statistical analysis plan, progress of the study, analysis, and reporting of the data, regardless of the study's outcome. The U.S. Department of Veterans Affairs had the opportunity to comment on the manuscript before submission, but the final version was the sole responsibility of the authors.

RESULTS

Participation Rates and Participation Bias

The Figure presents the sample selection scheme for the study. Although the percentages of nondeployed (439 of 2883 [15.2%]) and deployed (255 of 1996 [12.8%]) participants who could not be located were similar, a higher proportion of nondeployed (1316 of 2883 [45.7%]) than deployed (680 of 1996 [34.1%]) veterans who were successfully located declined to participate. Because of the lower participation rate by nondeployed veterans, we sought participation from more nondeployed veterans ($n = 2883$) than deployed veterans ($n = 1996$) to attain the minimum recruitment goal of 1000 deployed and nondeployed veteran examinations.

Table 1 evaluates participation bias. Compared with nonparticipants, deployed and nondeployed participants in our study were older and were more likely to be women, white, and in the reserves. In addition, de-

Table 1. Sociodemographic Characteristics in 1991 and Self-Reported Health Characteristics in 1995 of Individuals Who Completed the 1995 Survey according to Their Participation in the Present Study*

Sociodemographic Characteristics and Self-Reported Conditions	Deployed				Nondeployed				P Value†
	Participants (n = 1061)	Nonparticipants (n = 935)	Odds Ratio (95% CI)	P Value	Participants (n = 1128)	Nonparticipants (n = 1755)	Odds Ratio (95% CI)	P Value	
Mean age on 1 January 1991, y‡	30.9, SD 8.8	29.2, SD 8.3		0.001	32.6, SD 9.6	30.1, SD 8.6		<0.01	<0.01
Sex, %‡				0.002				0.02	>0.2
Men	78.0	83.6			78.0	81.7			
Women	22.0	16.4			22.0	18.3			
Ethnicity, %‡				0.001				<0.01	0.03
White	76.5	72.6			80.0	75.3			
Black	19.9	19.7			15.6	18.3			
Other	3.7	7.7			4.4	6.4			
Marital status in 1991, %‡			NA	0.02			NA	0.02	0.02
Married	52.8	49.4			58.7	53.5			
Single	41.5	46.7			36.5	41.4			
Other	5.7	3.9			4.8	5.0			
Rank in 1991, %‡				>0.2				0.005	0.001
Nonofficer	85.7	87.2			80.4	84.6			
Officer	14.3	12.8			19.6	15.4			
Branch in 1991, %‡				0.001				0.13	>0.2
Army	64.6	55.9			62.9	59.5			
Navy	12.0	18.6			13.6	13.7			
Air Force	11.9	15.0			13.7	14.3			
Marines	11.6	10.5			9.8	12.5			
Unit component in 1991, %‡				0.01				0.008	>0.2
Reserve	36.3	32.7			36.9	32.3			
Active	35.2	41.6			35.9	41.4			
National Guard	28.6	25.7			27.2	26.3			
Active duty in 1995, %‡	14.5	22.5	0.59 (0.47–0.74)	<0.001	15.8	18.8	0.81 (0.67–0.99)	0.04	>0.2
Smoked cigarettes in the past 12 mo, %§	34.0	37.6	0.85 (0.71–1.03)		26.2	32.3	0.74 (0.63–0.88)		0.27
Alcohol use, %§				>0.2				>0.2	0.19
None	27.6	29.0			30.6	30.7			
≤1–3 d/mo	34.1	32.9			33.6	30.8			
1–4 d/wk	32.6	31.2			27.3	32.4			
5–7 d/wk	5.7	6.9			8.6	6.2			
≥ 1 health care visit, %§	54.2	50.7	1.15 (0.96–1.38)		46.1	39.5	1.31 (1.13–1.53)		>0.2
≥ 1 hospitalization, %§	8.4	7.0	1.21 (0.87–1.69)		6.6	6.2	1.06 (0.78–1.44)		>0.2
Dermatologic condition, %§	45.3	36.0	1.47 (1.23–1.77)		21.2	17.5	1.27 (1.05–1.54)		>0.2
Numbness or tingling in limbs, %§	37.6	25.3	1.78 (1.47–2.16)		19.9	16.0	1.31 (1.08–1.59)		0.03
Chronic fatigue symptoms, %§	35.5	24.6	1.69 (1.39–2.05)		12.3	7.5	1.73 (1.35–2.23)		>0.2
Hypertension, %§	13.6	11.8	1.18 (0.90–1.54)		7.9	8.0	0.99 (0.75–1.30)		>0.2
Asthma, %§	5.9	4.6	1.29 (0.87–1.93)		3.7	2.9	1.32 (0.87–2.00)		>0.2
Arthritis of any kind, %§	26.5	22.0	1.28 (1.04–1.57)		18.2	14.6	1.30 (1.06–1.59)		>0.2
Heartburn or indigestion, %§	45.8	40.3	1.25 (1.05–1.50)		32.7	25.3	1.43 (1.21–1.69)		>0.2
Hepatitis, %§	1.1	1.1	1.06 (0.46–2.46)		0.8	1.1	0.74 (0.33–1.63)		>0.2
Diabetes, %§	1.4	0.7	2.21 (0.86–5.73)		1.1	1.0	1.10 (0.52–2.32)		>0.2
Bronchitis, %§	14.4	12.8	1.15 (0.89–1.49)		11.1	8.7	1.31 (1.02–1.69)		>0.2

* NA = not applicable.

† P value for the Breslow Day homogeneity of odds ratio test for the hypothesis that the odds ratios of deployed and nondeployed are equal.

‡ Obtained from the U.S. Department of Defense's Defense Manpower Data Center, Monterey, California.

§ Self-reported in 1995.

ployed and nondeployed participants in our study were statistically significantly more likely than nonparticipants in 1995 to report a dermatologic condition, numbness or tingling in hands or feet, symptoms suggestive of the chronic fatigue syndrome, arthritis of any kind, and heartburn or indigestion. Only nondeployed participants were statistically significantly more likely

than nondeployed nonparticipants to have an officer rank (19.6% vs. 15.4%, respectively) and to report at least 1 clinic or physician visit in the year before 1995 (46.1% vs. 39.5%, respectively). Deployed participants were statistically significantly more likely than deployed nonparticipants to be in the Army (64.6% vs. 55.9%, respectively).

Table 2. Sociodemographic and Military Service Characteristics of Deployed and Nondeployed Participants at the Research Examination

Characteristic	Deployed (n = 1061)	Nondeployed (n = 1128)	P Value
Mean age, y	38.9, SD 8.8	40.7, SD 9.6	0.001
Highest education, %			0.001
Not a high school graduate	1.8	2.0	
High school graduate	65.7	56.0	
College graduate	19.8	22.1	
Postgraduate	12.7	19.9	
Marital status, %			0.02
Married	67.5	72.3	
Never married	17.0	12.2	
Divorced	12.5	12.5	
Other	3.0	2.9	
Active military duty, %	7.8	8.5	>0.2
Mean income, \$	46 800, SD 32 600	52 000, SD 44 300	0.003

Participant Characteristics

At the research examination, deployed participants were slightly younger (38.9 years vs. 40.7 years; $P < 0.01$), were less educated (32.5% vs. 42.0% were college graduates or postgraduates; $P < 0.01$), were less likely to be married (67.4% vs. 72.3%; $P < 0.02$), and reported a lower annual family income (\$46 800 vs. \$52 000; $P < 0.01$) than nondeployed participants. The percentages of deployed and nondeployed veterans still on active military duty did not differ (7.8% vs. 8.5%, respectively; $P > 0.2$) (Table 2).

Population Prevalence of Self-Reported Illnesses at the Research Examination

For our study, we first compared the prevalence of self-reported illnesses among deployed and nondeployed veterans (Table 3). Unadjusted and adjusted results statistically significantly differed only in the prevalence of self-reported skin rash and the chronic fatigue syndrome. At the examination, 39.8% of deployed veterans reported having a skin rash versus 27.6% of nondeployed veterans (odds ratio, 1.74 [95% CI, 1.35 to 2.23]), and 2.3% of deployed veterans reported the chronic fatigue syndrome

Table 3. Population Prevalence of Illnesses or Symptoms Reported by the 1061 Deployed and 1128 Nondeployed Gulf War Veterans Who Participated in the Research Examination*

Medical Illness or Symptom†	Deployed, %	Nondeployed, %	Unadjusted		Adjusted‡	
			P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)
Veterans with ≥1 health care visit in previous 12 mo	58.3	57.3	>0.2	1.04 (0.82–1.33)	>0.2	1.10 (0.85–1.41)
Veterans with ≥1 hospitalization in previous 12 mo	4.6	6.3	>0.2	0.73 (0.44–1.20)	>0.2	0.83 (0.50–1.39)
Fibrositis or fibromyalgia	0.6	0.8	>0.2	0.73 (0.23–2.33)	>0.2§	1.21 (0.36–4.10)§
Chronic fatigue syndrome	2.3	0.4	0.005	5.61 (1.71–18.42)	0.0041	8.05 (1.94–33.43)
Skin rash	39.8	27.6	<0.001	1.74 (1.35–2.23)	<0.001	1.74 (1.34–2.26)
Gastritis	5.9	4.2	>0.2	1.43 (0.82–2.49)	0.13	1.57 (0.88–2.78)
High blood pressure or hypertension	10.2	11.0	>0.2	0.92 (0.63–1.34)	>0.2	1.18 (0.79–1.77)
Chronic hepatitis	0.6	0.2	>0.2	3.09 (0.32–30.13)	>0.2	2.40 (0.24–23.74)
Arthritis	12.3	12.3	>0.2	1.00 (0.70–1.44)	0.14	1.34 (0.90–2.00)
Asthma, bronchitis, or emphysema	5.9	6.3	>0.2	0.93 (0.57–1.53)	>0.2§	1.07 (0.65–1.77)§
Diabetes	2.4	1.8	>0.2	1.37 (0.63–2.99)	0.19§	1.69 (0.77–3.72)§
Peripheral neuropathy (damage to nerves in arms or legs)	2.8	3.5	>0.2	0.78 (0.39–1.57)	>0.2	0.86 (0.40–1.85)
Underactive thyroid condition	0.9	0.7	>0.2	1.28 (0.45–3.68)	0.20§	1.83 (0.73–4.60)§
Overactive thyroid condition	0.3	0.2	>0.2	2.22 (0.26–19.08)	0.18¶	4.13 (0.53–32.43)¶

* Population prevalences were calculated by using SUDAAN (Research Triangle Institute, Research Triangle Park, North Carolina) to account for the stratified random sampling with unequal probabilities of selection in various strata (deployment, sex, and unit component). Sample sizes ranged from 1018 to 1061 deployed veterans and from 1096 to 1128 nondeployed veterans.

† Refer to the Methods section for definition of each illness or symptom reported by history.

‡ Adjusted for differences in age, sex, race (white vs. other), years of education (<12 y vs. ≥12 y), cigarette smoking, duty type (active vs. reserves or National Guard), service branch (Army or Marines vs. Navy or Air Force), and rank (enlisted vs. officer), unless otherwise noted.

§ Model does not include adjustment for years of education.

|| Model does not include adjustment for race.

¶ Model does not include adjustment for years of education or rank.

Table 4. Population Prevalence of Illnesses Present on Clinical Evaluation among the 1061 Deployed and 1128 Nondeployed Gulf War Veterans Who Participated in the Research Examination*

Medical Illness or Symptom†	Deployed	Nondeployed	Unadjusted		Adjusted‡	
			P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)
Mean self-reported general health (SF-36) physical component scale	49.26 ± 0.42	50.79 ± 0.32	0.0037	NA	<0.001	NA
Fibromyalgia syndrome, %	2.0	1.2	0.19	1.74 (0.76–3.94)	0.04§	2.32 (1.02–5.27)§
Chronic fatigue syndrome, %	1.6	0.1	<0.001	17.68 (4.63–67.57)	<0.001§	40.6 (10.2–161.15)§
Skin conditions, %						
≥1 group 1 condition	57.7	63.0	0.07	0.80 (0.63–1.02)	>0.2	0.87 (0.68–1.12)
≥1 group 2 condition	34.6	26.8	0.005	1.44 (1.11–1.87)	0.02	1.38 (1.06–1.80)
Dyspepsia, %	9.1	6.0	0.05	1.57 (1.00–2.47)	0.01	1.87 (1.16–2.99)
Hypertension, %	9.1	12.6	0.07	0.70 (0.48–1.03)	>0.2	0.90 (0.60–1.33)
Hepatitis, %	6.5	5.2	>0.2	1.27 (0.75–2.15)	>0.2	1.11 (0.64–1.91)
Symptomatic arthralgias, %	6.4	6.8	>0.2	0.93 (0.58–1.48)	>0.2	1.15 (0.70–1.89)
Obstructive lung disease, %	4.5	5.9	>0.2	0.75 (0.44–1.29)	>0.2	0.91 (0.52–1.59)
Diabetes mellitus, %	4.2	3.5	>0.2	1.21 (0.65–2.25)	0.19§	1.52 (0.81–2.85)§
Peripheral neuropathy, %	4.8	5.9	>0.2	0.80 (0.47–1.36)	>0.2	1.08 (0.64–1.84)
Hypothyroidism, %	1.6	1.2	>0.2	1.34 (0.55–3.27)	0.20§	1.70 (0.75–3.87)§
Hyperthyroidism, %	0.3	0.1	0.15	5.72 (0.52–63.12)	0.11¶	4.86 (0.68–34.58)¶

* Population prevalences were calculated by using SUDAAN (Research Triangle Institute, Research Triangle Park, North Carolina) to account for the stratified random sampling with unequal probabilities of selection in various strata (deployment, sex, and unit component). Sample sizes ranged from 1018 to 1061 deployed veterans and from 1096 to 1128 nondeployed veterans. Values presented with a plus/minus sign are means ± SE. NA = not applicable; SF-36 = Short Form-36.

† Refer to the Methods section for definition of each illness or symptom reported by history.

‡ Adjusted for differences in age, sex, race (white vs. other), years of education (<12 y vs. ≥12 y), cigarette smoking, duty type (active vs. reserves or National Guard), service branch (Army or Marine vs. Navy or Air Force), and rank (enlisted vs. officer), unless otherwise noted.

§ Model does not include adjustment for years of education.

|| Group 1 conditions include nevi or moles, freckles or lentigines, scars, hemangiomas, skin tags, and seborrheic keratoses. Group 2 conditions include conditions other than the 6 conditions included in group 1.

¶ Model does not include adjustment for years of education, service branch, or rank.

versus 0.4% of nondeployed veterans (odds ratio, 5.61 [CI, 1.71 to 18.42]).

Population Prevalence of Illnesses Diagnosed at the Research Examination

Our most important objective was to compare the prevalence of illnesses among deployed and nondeployed veterans on the basis of direct physical and laboratory evaluation (Table 4). The prevalence of the chronic fatigue syndrome was substantially higher among deployed than nondeployed veterans (1.6% vs. 0.1%; odds ratio, 40.6 [CI, 10.2 to 161]). Of the 38 deployed veterans who self-reported the chronic fatigue syndrome at the research examination, only 3 received this diagnosis. Of 8 nondeployed veterans who self-reported the chronic fatigue syndrome, only 2 received this diagnosis (data not shown). Therefore, self-report of the chronic fatigue syndrome among both deployed and nondeployed veterans has low validity.

Deployed veterans received a diagnosis more often than nondeployed veterans with the aggregate variable of 1 or more group 2 skin condition (that is, all dermatologic diagnoses except freckles or lentigines, seborrheic keratoses, nevi or moles, cherry hemangiomas, skin tags, and surgical scars) (34.6% vs. 26.8%; odds ratio, 1.38 [CI, 1.06 to 1.80]) (Table 4). The most common group 2 skin conditions in this veteran cohort were onychomycosis (4.1%), folliculitis (4.0%), tinea pedis (3.5%), acne vulgaris (2.5%), contact dermatitis (2.2%), and seborrheic derma-

titis (2.1%). In adjusted analyses of individual group 2 skin conditions, atopic dermatitis (1.2% vs. 0.3%; odds ratio, 8.1 [CI, 2.4 to 27.7]) and verruca vulgaris (1.6% vs. 0.6%; odds ratio, 4.02 [CI, 1.28 to 12.6]) (data not shown) were statistically significantly more commonly diagnosed among deployed than among nondeployed veterans.

Two percent of deployed veterans received a diagnosis of fibromyalgia versus 1.2% of nondeployed veterans (odds ratio, 2.32 [CI, 1.02 to 5.27]), and 9.1% of deployed veterans received a diagnosis of dyspepsia versus 6.0% of nondeployed veterans (odds ratio, 1.87 [CI, 1.16 to 2.99]).

The mean Physical Component Summary score (±SE) of the SF-36 for deployed veterans (49.3 ± 0.42) was statistically significantly lower than that for nondeployed veterans (50.8 ± 0.32) ($P < 0.001$). The prevalence of physical examination abnormalities did not differ between deployed and nondeployed veterans. Specifically, the prevalence of palpable liver (3.8% deployed vs. 2.8% nondeployed; $P > 0.2$); palpable spleen (0.1% deployed vs. 0.4% nondeployed; $P > 0.2$); or cervical, supraclavicular, axillary, epitrochlear, or inguinal lymphadenopathy (prevalence ranged from 0.02% for epitrochlear lymphadenopathy to 2.4% for cervical lymphadenopathy among deployed veterans and from 0.3% for epitrochlear lymphadenopathy to 2.6% for cervical lymphadenopathy among nondeployed veterans) did not differ. In addition, mean values on all 40 laboratory tests were normal among deployed and nondeployed groups and did not statistically

significantly differ between deployed and nondeployed except as follows: blood urea nitrogen level (5.03 mmol/L [14.1 mg/dL] vs. 5.18 mmol/L [14.5 mg/dL]; $P = 0.04$), magnesium level (0.81 mmol/L [1.95 mg/dL] vs. 0.82 mmol/L [1.98 mg/dL]; $P = 0.003$), prevalence of 2+ or greater proteinuria (1.04% vs. 0.45%; $P = 0.02$), and leukocytes on urinalysis (18.0% vs. 15.8%; $P = 0.05$).

DISCUSSION

One decade after the 1991 Gulf War, our study compared the medical health of a national cross-section of U.S. veterans who were deployed to the Persian Gulf with a control group of nondeployed veterans. Among the study's primary outcomes, fibromyalgia and the chronic fatigue syndrome were significantly more common among deployed than nondeployed veterans. Deployed veterans also demonstrated a higher prevalence of dyspepsia and skin conditions (particularly atopic dermatitis and verruca vulgaris) than nondeployed veterans. The small decrease of 1.53 in the mean self-assessed physical health-related quality of life score of the SF-36 is not clinically important (18). The differences in blood urea nitrogen level, magnesium level, prevalence of proteinuria, and leukocytes on urine examination were small and were not associated with diagnosable disease. We previously reported that detailed analyses of neurologic (19) and pulmonary (20) data collected from this cohort did not demonstrate differences between deployed and nondeployed veterans.

Although we made extraordinary recruitment efforts by using informational mailings, telephone calls, and a videotape, only 53% of eligible deployed and 39% of eligible nondeployed veterans participated. Nevertheless, nonparticipation bias is unlikely to explain our results because nonparticipation bias within the deployed and nondeployed cohorts is similar (Table 1) and because fibromyalgia, the chronic fatigue syndrome, and an aggregate measure of dermatologic conditions are the only medical illnesses that were statistically significantly more common among deployed than nondeployed veterans on examination. If the increased prevalence of these conditions among deployed veterans resulted from nonparticipation bias, we would expect an association between deployment and the diagnosis of many other illnesses. Also, the increased risk among deployed veterans for the chronic fatigue syndrome is 40.6 (CI, 10.2 to 161). This substantial odds ratio is unlikely to be explained entirely by nonparticipation bias. Finally, the mean prevalence of the chronic fatigue syndrome in our nondeployed cohort (0.1%) is similar to that reported for the general U.S. population (5, 21, 22). Of note, the age, education attainment, marital status, and annual income differences between deployed and nondeployed veterans (Table 2) are similar to true differences between deployed and nondeployed service personnel during the Gulf War (23).

Our study's strengths are that 1) the sample was se-

lected independently of veteran medical or psychiatric illness or disability; 2) the stratified sampling method provided enough women and members of the reserves and National Guard to examine the contribution of these subgroups to Gulf War-related illnesses; 3) diagnoses were made with computer-based algorithms developed by researchers who were blinded to the deployment status of participants and were based on a comprehensive health assessment; 4) the extensive clinical assessment permitted the diagnosis of the chronic fatigue syndrome without confounding by psychiatric disorders (21); and 5) because sociodemographic, military service, and self-reported health data were available for all eligible veterans who participated in the 1995 study, we could address the issue of nonparticipation bias by comparing data available from both participants and nonparticipants.

Our study has potential weaknesses. Without a strong theoretical basis for predicting which medical diseases may be caused by the Gulf War experience, data collected focused on the major symptom groups reported by Gulf War veterans (that is, musculoskeletal pain, fatigue, skin rashes, and neuropathic symptoms). The most relevant data to identify differences between deployed and nondeployed veterans may not have been collected. The study's cross-sectional design precludes making cause-and-effect conclusions. Some veterans who were not deployed to the Persian Gulf during the Gulf War may have visited that region between 1992 and the time of the research examination, thereby potentially confounding exposure group assignment, although this is highly unlikely. We did not blindly collect data, which may have introduced observer bias. Although a blinded dermatologist made dermatologic diagnoses by using data from standardized physical examination forms and digital photographs provided by the examining physician, additional or different diagnoses may have been made if the dermatologist had directly examined each participant. The sample size was not sufficient to detect an adverse health outcome resulting from a specific exposure experienced by some veterans or a moderate increase in risk for rare diseases. We did not determine differences in death rates and causes of death among eligible veterans who did not participate in research. The low study participation rate may have biased the results, since the effect of the health status of potential participants on their likelihood to participate is unknown.

Gulf War veterans reported fatigue shortly after their return from the Persian Gulf region in 1991 (2–4, 9, 11, 24–26) and after delays of up to several years (1, 27). Recent studies suggest that the chronic fatigue syndrome among Gulf War veterans may be a different disorder than the sporadically occurring syndrome in the United States (28–30). The mechanisms by which deployment increased the risk for the chronic fatigue syndrome in Gulf War veterans are still unknown. Viscerotropic leishmaniasis from desert sand flies, other oligoparasitic diseases, human herpesvirus (6, 31) Epstein-Barr virus (32), *Mycoplasma*

infections (33), or silicates from the desert sands may precipitate immune activation, abnormally low natural killer cell activity, and impairment of selective lymphocyte functions (34–38). A polyclonal-activating infection or immunization may initiate a sequence of events in genetically susceptible individuals (39–41). Other studies link autonomic and hypothalamic–pituitary axis dysregulation to the chronic fatigue syndrome and suggest physiologic (42, 43) and biological mechanisms (44, 45).

While many dermatologic conditions affected service personnel during deployment to the Persian Gulf (46), several dermatologic conditions are still more common. Perhaps the Persian Gulf region's harsh, desiccating climate or sand silicates themselves precipitated the development of secondary atopic dermatitis. Dermatologic conditions, such as psoriasis, that are known to worsen with stress were not increased statistically among deployed veterans.

The significance of the higher prevalence of dyspepsia among deployed Gulf War veterans is unclear. Of note, similar to combatants of other modern wars (47), deployed veterans in our study reported higher population prevalences of a broad range of gastrointestinal symptoms in the year before the examination compared with nondeployed veterans: nausea (12.5% vs. 8.5%; $P = 0.02$), appetite loss (6.4% vs. 2.2%; $P < 0.001$), dysphagia (4.5% vs. 2.2%; $P = 0.02$), diarrhea (19.1% vs. 12.6%; $P = 0.004$), constipation (7.9% vs. 4.3%; $P = 0.007$), bloody stool (6.1% vs. 4.7%; $P > 0.2$), and vomiting (7.5% vs. 5.3%; $P = 0.11$).

In summary, 10 years after the 1991 Gulf War, the physical health of deployed veterans is similar to that of nondeployed veterans. However, deployment is associated with an increased risk for fibromyalgia, the chronic fatigue syndrome, certain skin disorders, and dyspepsia. Health care providers should be particularly alert for these conditions when examining veterans who served in the Persian Gulf region during either the 1991 Gulf War or the current conflict. More field studies are needed, perhaps with prospective monitoring of U.S. personnel deployed in the Middle East for the development of these conditions. Continued research, particularly directed at elucidating mechanisms for these associations, is warranted.

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References

1. Presidential Advisory Committee on Gulf War Veterans' Illnesses. Final Report. Washington DC: U.S. Government Printing Office; 1996.
2. Korényi-Both AL, Korényi-Both AL, Molnár AC, Fidelus-Gort R. Al Eskan disease: Desert Storm pneumonitis. *Mil Med.* 1992;157:452-62. [PMID: 1333577]
3. Oster CN, Sanford JP. Febrile illness in a Desert Storm veteran. *Hosp Pract (Off Ed).* 1992;27:145-8, 151, 155-60. [PMID: 1331138]
4. Magill AJ, Grögl M, Gasser RA Jr, Sun W, Oster CN. Visceral infection caused by *Leishmania tropica* in veterans of Operation Desert Storm. *N Engl J Med.* 1993;328:1383-7. [PMID: 8292114]
5. Unexplained illness among Persian Gulf War veterans in an Air National Guard Unit: preliminary report—August 1990-March 1995. *MMWR Morb Mortal Wkly Rep.* 1995;44:443-7. [PMID: 7770029]
6. Kippen HM, Hallman W, Kang H, Fiedler N, Natelson BH. Prevalence of chronic fatigue and chemical sensitivities in Gulf Registry Veterans. *Arch Environ Health.* 1999;54:313-8. [PMID: 10501146]
7. Coker WJ, Bhatt BM, Blatchley NF, Graham JT. Clinical findings for the first 1000 Gulf war veterans in the Ministry of Defence's medical assessment programme. *BMJ.* 1999;318:290-4. [PMID: 9924053]
8. Robinson A. Veterans worry that unexplained medical problems a legacy of service during Gulf War. *CMAJ.* 1995;152:944-7. [PMID: 7697587]
9. Self-reported illness and health status among Gulf War veterans. A population-based study. The Iowa Persian Gulf Study Group. *JAMA.* 1997;277:238-45. [PMID: 9005274]
10. Proctor SP, Heeren T, White RF, Wolfe J, Borgos MS, Davis JD, et al. Health status of Persian Gulf War veterans: self-reported symptoms, environmental exposures and the effect of stress. *Int J Epidemiol.* 1998;27:1000-10. [PMID: 10024195]
11. Fukuda K, Nisenbaum R, Stewart G, Thompson WW, Robin L, Washko RM, et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA.* 1998;280:981-8. [PMID: 9749480]
12. Unwin C, Blatchley N, Coker W, Ferry S, Hotopf M, Hull L, et al. Health of UK servicemen who served in Persian Gulf War. *Lancet.* 1999;353:169-78. [PMID: 9923871]
13. Kang HK, Mahan CM, Lee KY, Magee CA, Murphy FM. Illnesses among United States veterans of the Gulf War: a population-based survey of 30,000 veterans. *J Occup Environ Med.* 2000;42:491-501. [PMID: 10824302]
14. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33:160-72. [PMID: 2306288]
15. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med.* 1994;121:953-9. [PMID: 7978722]
16. Andrews G, Peters L. The psychometric properties of the Composite International Diagnostic Interview. *Soc Psychiatry Psychiatr Epidemiol.* 1998;33:80-8. [PMID: 9503991]
17. Ware JE Jr. SF-36 Health Survey: Manual and Interpretation Guide. Boston: The Health Institute, New England Medical Center Hospitals, Inc.; 1993.
18. Wyrwich KW, Tierney WM, Wolinsky FD. Further evidence supporting an

- SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. *J Clin Epidemiol*. 1999;52:861-73. [PMID: 10529027]
19. Davis LE, Eisen SA, Murphy FM, Alpern R, Parks BJ, Blanchard M, et al. Clinical and laboratory assessment of distal peripheral nerves in Gulf War veterans and spouses. *Neurology*. 2004;63:1070-7. [PMID: 15452300]
20. Karlinsky JB, Blanchard M, Alpern R, Eisen SA, Kang H, Murphy FM, et al. Late prevalence of respiratory symptoms and pulmonary function abnormalities in Gulf War I Veterans. *Arch Intern Med*. 2004;164:2488-91. [PMID: 15596641]
21. Natelson BH. Chronic fatigue syndrome. *JAMA*. 2001;285:2557-9. [PMID: 11368714]
22. Price RK, North CS, Wessely S, Fraser VJ. Estimating the prevalence of chronic fatigue syndrome and associated symptoms in the community. *Public Health Rep*. 1992;107:514-22. [PMID: 1329134]
23. Kang HK, Bullman TA. Mortality among US veterans of the Persian Gulf War: 7-year follow-up. *Am J Epidemiol*. 2001;154:399-405. [PMID: 11532780]
24. Murray-Leisure KA, Daniels MO. Visceral and skin aspects of "Persian Gulf mystery disease" associated with sand exposure in a Pennsylvania military unit. In: Program and Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, 4-7 October 1994, Orlando, Florida. Washington, DC: American Society for Microbiology; 1994. Abstract J159.
25. Murphy FM, Kang H, Dalager NA, Lee KY, Allen RE, Mather SH, et al. The health status of Gulf War veterans: lessons learned from the Department of Veterans Affairs Health Registry. *Mil Med*. 1999;164:327-31. [PMID: 10332170]
26. Kang HK, Natelson BH, Mahan CM, Lee KY, Murphy FM. Post-traumatic stress disorder and chronic fatigue syndrome-like illness among Gulf War veterans: a population-based survey of 30,000 veterans. *Am J Epidemiol*. 2003;157:141-8. [PMID: 12522021]
27. Magill AJ, Grogl M, Johnson SC, Gasser RA Jr. Visceral infection due to *Leishmania tropica* in a veteran of Operation Desert Storm who presented 2 years after leaving Saudi Arabia [Letter]. *Clin Infect Dis*. 1994;19:805-6. [PMID: 7803664]
28. Kennedy G, Abbot NC, Spence V, Underwood C, Belch JJ. The specificity of the CDC-1994 criteria for chronic fatigue syndrome: comparison of health status in three groups of patients who fulfill the criteria. *Ann Epidemiol*. 2004;14:95-100. [PMID: 15018881]
29. Khan F, Kennedy G, Spence VA, Newton DJ, Belch JJ. Peripheral cholinergic function in humans with chronic fatigue syndrome, Gulf War syndrome and with illness following organophosphate exposure. *Clin Sci (Lond)*. 2004;106:183-9. [PMID: 14503920]
30. Cook DB, Nagelkirk PR, Peckerman A, Poluri A, Lamanca JJ, Natelson BH. Perceived exertion in fatiguing illness: Gulf War veterans with chronic fatigue syndrome. *Med Sci Sports Exerc*. 2003;35:569-74. [PMID: 12673138]
31. Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. *Ann Intern Med*. 1992;116:103-13. [PMID: 1309285]
32. Straus SE. Studies of herpesvirus infection in chronic fatigue syndrome. *Ciba Found Symp*. 1993;173:132-9; discussion 139-45. [PMID: 8387907]
33. Endresen GK. Mycoplasma blood infection in chronic fatigue and fibromyalgia syndromes. *Rheumatol Int*. 2003;23:211-5. [PMID: 12879275]
34. Korényi-Both AL, Korényi-Both AL, Juncer DJ. Al Eskan disease: Persian Gulf syndrome. *Mil Med*. 1997;162:1-13. [PMID: 9002695]
35. Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbiol*. 1990;28:1403-10. [PMID: 2166084]
36. Landay AL, Jessop C, Lennette ET, Levy JA. Chronic fatigue syndrome: clinical condition associated with immune activation. *Lancet*. 1991;338:707-12. [PMID: 1679864]
37. Straus SE, Fritz S, Dale JK, Gould B, Strober W. Lymphocyte phenotype and function in the chronic fatigue syndrome. *J Clin Immunol*. 1993;13:30-40. [PMID: 8095270]
38. Nicholson GL, Nicolson NL. Diagnosis and treatment of mycoplasmal infections in Persian Gulf War illness-CFIDS patients. *International Journal of Occupational Medicine, Immunology, and Toxicology*. 1996;5:69-78.
39. Keller RH, Lane JL, Klimas N, Reiter WM, Fletcher MA, van Riel F, et al. Association between HLA class II antigens and the chronic fatigue immune dysfunction syndrome. *Clin Infect Dis*. 1994;18 Suppl 1:S154-6. [PMID: 8148444]
40. Hickie IB, Bansal AS, Kirk KM, Lloyd AR, Martin NG. A twin study of the etiology of prolonged fatigue and immune activation. *Twin Res*. 2001;4:94-102. [PMID: 11665341]
41. Buchwald D, Herrell R, Ashton S, Belcourt M, Schmalting K, Sullivan P, et al. A twin study of chronic fatigue. *Psychosom Med*. 2001;63:936-43. [PMID: 11719632]
42. Naschitz JE, Sabo E, Naschitz S, Shaviv N, Rosner I, Rozenbaum M, et al. Hemodynamic instability in chronic fatigue syndrome: indices and diagnostic significance. *Semin Arthritis Rheum*. 2001;31:199-208. [PMID: 11740800]
43. Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, et al. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab*. 1991;73:1224-34. [PMID: 1659582]
44. Visser J, Graffelman W, Blauw B, Haspels I, Lentjes E, de Kloet ER, et al. LPS-induced IL-10 production in whole blood cultures from chronic fatigue syndrome patients is increased but supersensitive to inhibition by dexamethasone. *J Neuroimmunol*. 2001;119:343-9. [PMID: 11585638]
45. Patarca-Montero R, Antoni M, Fletcher MA, Klimas NG. Cytokine and other immunologic markers in chronic fatigue syndrome and their relation to neuropsychological factors. *Appl Neuropsychol*. 2001;8:51-64. [PMID: 11388124]
46. Oumeish OY, Oumeish I, Parish JL. Gulf War syndrome. *Clin Dermatol*. 2002;20:401-12. [PMID: 12208628]
47. Jones E, Hodgins-Vermaas R, McCartney H, Everitt B, Beech C, Poynter D, et al. Post-combat syndromes from the Boer war to the Gulf war: a cluster analysis of their nature and attribution. *BMJ*. 2002;324:321-4. [PMID: 11834557]

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APPENDIX: GULF WAR STUDY

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Hines Cooperative Studies Program Coordinating Center, Hines, Illinois: William G. Henderson, PhD, Director; Domenic J. Reda, PhD, Acting Director; David J. Semlow, Assistant Director; Tammy Nydam, MA, Project Manager; Renee Alpern, MS, Statistician; Coleen Hall, MBA, MS, Statistician; Weichun Xu, PhD, Statistician; Ken Bukowski, Database Programmer; Mike Kerr, Database Programmer; Rosemarie DeNicolo, Statis-

tical Assistant; Barbara Christine, Statistical Assistant; Tom Sindowski, Statistical Assistant; Sheldena Heard, Statistical Assistant; Victoria Barillas, Statistical Assistant; Joyce Jimenez, Budget Analyst.

Brockton Psychometrics Laboratory, Brockton, Massachusetts: Rosemary Toomey, PhD, Director; Lisa James, Research Assistant; Zachary Warren, Research Assistant.

Chairpersons' Offices: St. Louis, Missouri: Seth Eisen, MD, MSc; Joyce Hunter, RN, MSN, Coordinator. Washington, DC: Han Kang, DrPH; Leila Jackson, PhD, Coordinator; Frances Murphy, MD, MPH, Veterans Affairs Central Office.

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Blood Laboratory, Massachusetts Veterans Epidemiology Research and Information Center, Boston, Massachusetts: Michael Gaziano, Director; Nancy Pelligrino, Technician; Erin Lopez, Technician.

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