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Searching for a Gulf War syndrome using cluster analysis

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ABSTRACT

Background. Gulf veterans report medically unexplained symptoms more frequently than non-Gulf veterans did. We examined whether Gulf and non-Gulf veterans could be distinguished by their patterns of symptom reporting.

Method. A *k*-means cluster analysis was applied to 500 randomly sampled veterans from each of three United Kingdom military cohorts of veterans; those deployed to the Gulf conflict between 1990 and 1991; to the Bosnia peacekeeping mission between 1992 and 1997; and military personnel who were in active service but not deployed to the Gulf (Era). Sociodemographic, health variables and scores for ten symptom groups were calculated.

Results. The gap statistic indicated the five-group solution as one that provided a particularly informative description of the structure in the data. Cluster 1 consisted of low scores for all symptom groups. Cluster 2 had veterans with highest symptom scores for musculoskeletal symptoms and high scores for psychiatric symptoms. Cluster 3 had high scores for psychiatric symptoms and marginally elevated scores for the remaining nine groups symptom groups. Cluster 4 had elevated scores for musculoskeletal symptoms only and cluster 5 was distinguishable from the other clusters in having high scores in all symptom groups, especially psychiatric and musculoskeletal.

Conclusion. The findings do not support the existence of a unique syndrome affecting a subgroup of Gulf veterans but emphasize the excess of non-specific self-reported ill health in this group.

INTRODUCTION

The debate about the existence of a new 'Gulf War syndrome' continues among the general public and the scientific community. Several population studies have now established that veterans of the Gulf conflict 1990–1991 report physical and psychological symptoms more frequently (Fukuda *et al*. 1998; The Iowa Persian Gulf Study Group, 1997; Unwin *et al*. 1999; Kang *et al*. 2000) and more severely (Cherry *et al*. 2001) than appropriate controls. To date none of these studies have been able to identify a group of symptoms unique to Gulf veterans.

A number of studies have employed various methods of factor analysis that examine the structure of the correlations between a set of symptoms observed in Gulf veterans. Haley *et al*. identified six factors in an exploratory factor analysis of 52 symptoms in 249 Gulf veterans serving in a United States (US) Reserve Naval Unit (Haley *et al*. 1997). While such an analysis was useful in describing the factor structure of the observed symptoms in Gulf veterans, it produced little convincing evidence of a new 'Gulf War syndrome' since it lacked a comparison factor structure from a similar analysis on a military control group that had not been deployed to the Gulf (Gray *et al*. 1998; Landrigan *et al*. 1998). We failed to find any great differences in the three factor structures

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derived from an exploratory factor analysis of 50 observed symptoms between three randomly selected samples of United Kingdom (UK) Gulf veterans, veterans who had served in the Bosnia conflict between 1992 and 1997, and veterans who were in active service at the time of the Gulf conflict but not deployed (Ismail *et al.* 1999). In a population of active duty US Navy personnel, (Knoke *et al.* 2000) the factor solutions were similar in each group although the Gulf veterans had higher scores on most of the factors reflecting that they were reporting more symptoms as opposed to a unique syndrome. Three of the factors represented symptoms suggestive of depression and the remaining two factors represented generalized and multi-system symptoms such as tender glands and pain. Cherry *et al.* (2001) identified a seven-factor solution that seemed to be essentially the same for their Gulf and non-Gulf samples. They too found that most of the factors had higher scores in the Gulf sample. Doebbeling *et al.* (2000) reported a three-factor structure in another randomly selected US Gulf sample that was similar to the non-deployed sample. These factors were also related to depression, anxiety and generalized multi-system symptoms. The correlations between the factor-scoring weights from the deployed and non-deployed samples were highly convergent.

Cluster analysis has been used less widely in the study of ill health in Gulf veterans. The aim of this statistical method is to cluster together individuals who have similar clinical profiles. It may be more useful than factor analysis in this context as it could potentially categorize individuals according to their symptom profile whereas in factor analysis it is the symptoms that are being analysed. It is arguable that if there is a unique 'Gulf War syndrome' comprising of a complex multiple symptom profile, then a cluster analysis of symptom profiles of veterans from different conflicts should result in a cluster consisting of predominately Gulf veterans. Cherry *et al.* did conduct a cluster analysis of randomly selected UK Gulf and non-Gulf samples (Cherry *et al.* 2001). They identified six clusters and each veteran from both samples was assigned to one of them. Most subjects in both cohorts were grouped within the first two clusters, which represented the healthiest subjects. The last four clusters progressively defined more ill subjects, and each cluster had almost twice as many Gulf veterans than non-Gulf veterans but there was no cluster that was predominantly or unique to Gulf veterans. Their findings suggested that although there was no evidence for a unique syndrome, Gulf veterans did seem to be more unwell.

We conducted a cluster analysis of three randomly selected samples of the respondents from Phase 1 of the Health Survey of UK military personnel which compares the health of three military populations, those deployed to the Gulf, those deployed to Bosnia peacekeeping and those who had been in active service at the time of the Gulf conflict but had not been deployed to the Gulf (Era) (Unwin *et al.* 1999). This is the same data that we used to conduct the factor analysis that we reported earlier. We will then examine whether the resulting clusters are associated with cohort status and relevant sociodemographic variables.

METHOD

Design and population

A cross-sectional postal survey was conducted. The study population consisted of three randomly selected military samples from the UK Armed Forces: those who served in the Gulf conflict between 1 September 1990 and 30 June 1991 ($N = 5046$); those who served in the United Nations Bosnia peacekeeping forces between 1 April 1992 and 6 February 1997 ($N = 3450$); and those in the UK Armed Forces during the Gulf conflict but not deployed to the Gulf (Era) ($N = 4248$). A standardized self-report questionnaire requesting sociodemographic, military and health information was sent to these individuals between August 1997 and November 1998. Further details of method of selection, tracing and response rates have been reported in an earlier publication (Unwin *et al.* 1999). The number of veterans who responded to our questionnaire in each cohort was 3529 (Gulf), 2052 (Bosnia) and 2614 (Era). Computationally it was not feasible to apply the *k*-means clustering method to all 8195 veterans. Instead, 500 veterans were randomly sampled from each of the three cohorts giving a total of 1500 veterans on which the analysis was conducted and reported here.

Measures

Each serviceman in the study was given a standardized questionnaire asking about his experiences of 50 non-specific symptoms that are common in the general population (Table 1). The symptom list was derived both from the Hopkins Symptom Checklist which is a well-validated instrument to record somatic complaints (Derogatis *et al*. 1974) and from symptoms which were reported in our pilot studies. Symptoms were chosen to reflect most permutations of somatic distress. Respondents were asked to report whether each symptom had been present or absent in the past month and if present, to rate its severity as mild, moderate or severe leading to a scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe) for each symptom. The symptoms were then re-categorized into 10 groups according to body systems as follows: cardiovascular, respiratory, gastrointestinal, urogenital, ophthalmological, auditory, peripheral-neurological, musculoskeletal, mood and cognitive and generalized symptoms using the same rating scale for severity (Table 1).

Sociodemographic variables of age, sex, marital status, educational attainment and current employment status were also assessed. The following indices of health status were measured; fatigue using the Chalder fatigue scale (Chalder *et al*. 1993), psychological distress using the 12-General Health Questionnaire (Goldberg & Williams, 1998), physical impairment using the Short Form-36 Physical Functioning (Ware & Sherbourne, 1992) and current alcohol intake (number of units per day). These have been reported elsewhere (Unwin *et al*. 1999).

Statistical analysis

The randomly selected 1500 veterans, each having a set of ten scores, were subjected to *k*-means cluster analysis as implemented in S-PLUS 2000 (Everitt *et al*. 2001). When using *k*-means cluster analysis the data are grouped into a number of groups set by the user. This analysis does not, of course, use knowledge of the cohort from which each veteran came. In general a series of values for number of groups is used and one of a variety of *ad hoc* procedures used for deciding on the value that best fits the data, since, unfortunately, there is no completely acceptable method of estimating number of groups. In particular it is often difficult to decide whether the data consist of only a single 'group' so that clustering may not be appropriate. But recently, Tibshirani *et al*. (2001) have proposed a computer intensive approach to this problem based on what they term the 'gap statistic' which does appear to work reasonably well. This statistic was applied in this study to suggest which number of groups or clusters best describe the data. The association between the cluster membership, cohort status and a number of sociodemographic variables was then tested using a logistic regression model suitable for a categorical response with more than two categories (McCullagh, 1980).

RESULTS

The mean profiles of the original 50 symptoms and of the 10 groups of symptoms used in the cluster analysis are given in Table 1 for the original sample. The Gulf veterans had higher means on all the 50 symptoms, with the largest differences being for headaches, irritability, loss of concentration and avoidance. The Era and Bosnia groups had very similar mean values on all the 50 symptoms and the ten groups of symptoms.

The 'gap statistic' suggested that the four, five and eleven cluster solution produced by the *k*-means procedure would be of most interest (solutions available from the authors). For the purposes of parsimony we describe the five-cluster solution here. The mean profiles are displayed graphically in Fig. 1. Cluster 1 consisted of low scores for all symptoms. Cluster 2 had veterans with highest scores for musculoskeletal symptoms and high scores for neuropsychological. Cluster 3 had high scores for neuropsychological and marginally elevated scores for the remaining nine symptom groups. Cluster 4 had elevated scores for musculoskeletal symptoms only and cluster 5 was distinguishable from the other clusters in having high scores in all symptom groups, especially musculoskeletal and neuropsychological.

To assess whether cluster membership was associated with either cohort or any of the sociodemographic or health variables, a stepwise logistic regression was performed. Only cohort

Table 1. *Mean scores (standard deviations) for the original Gulf* (N = 3529), *Bosnia* (N = 2052) *and Era* (N = 2614) *cohorts*

Symptom	Gulf	Bosnia	Era
Neuropsychological symptoms	1·8 (0·7)	1·4 (0·5)	1·3 (0·5)
Headaches	2·0 (1·1)	1·6 (0·9)	1·6 (0·9)
Irritability/outbursts of anger	2·1 (1·2)	1·6 (0·9)	1·5 (0·9)
Sleep difficulties	1·9 (1·1)	1·5 (0·9)	1·5 (0·9)
Feeling jumpy/easily startled	1·4 (0·8)	1·2 (0·6)	1·2 (0·3)
Feeling unrefreshed after sleep	2·0 (1·1)	1·5 (0·8)	1·5 (0·9)
Fatigue	1·9 (1·0)	1·4 (0·8)	1·5 (0·8)
Feeling distant or cut off from others	1·5 (0·9)	1·2 (0·6)	1·2 (0·6)
Forgetfulness	1·8 (1·0)	1·3 (0·7)	1·3 (0·6)
Loss of concentration	1·7 (0·9)	1·3 (0·6)	1·2 (0·6)
Avoiding doing things/situations	1·5 (0·9)	1·2 (0·6)	1·2 (0·5)
Distressing dreams	1·4 (0·9)	1·2 (0·6)	1·2 (0·5)
Respiratory symptoms	1·3 (0·4)	1·1 (0·3)	1·1 (0·3)
Unable to breathe deeply enough	1·4 (0·7)	1·2 (0·5)	1·1 (0·5)
Faster breathing than normal	1·2 (0·5)	1·1 (0·3)	1·1 (0·3)
Feeling short of breath at rest	1·3 (0·6)	1·1 (0·4)	1·1 (0·4)
Persistent cough	1·3 (0·6)	1·1 (0·5)	1·1 (0·4)
Lump in throat	1·1 (0·5)	1·1 (0·3)	1·1 (0·3)
Sore throat	1·4 (0·7)	1·2 (0·6)	1·2 (0·6)
Wheezing	1·3 (0·7)	1·1 (0·5)	1·1 (0·5)
Cardiovascular symptoms	1·3 (0·6)	1·2 (0·4)	1·1 (0·4)
Chest pain	1·4 (0·7)	1·2 (0·6)	1·2 (0·5)
Rapid heartbeat	1·3 (0·6)	1·1 (0·4)	1·1 (0·5)
Opthalmological symptoms	1·3 (0·5)	1·1 (0·3)	1·1 (0·3)
Double vision	1·1 (0·4)	1·0 (0·3)	1·0 (0·2)
Increased sensitivity to light	1·3 (0·7)	1·1 (0·4)	1·1 (0·4)
Itchy or painful eyes	1·4 (0·8)	1·2 (0·5)	1·2 (0·5)
Global	1·2 (0·4)	1·1 (0·2)	1·1 (0·2)
Intolerance to alcohol	1·2 (0·7)	1·1 (0·4)	1·1 (0·4)
Shaking	1·2 (0·6)	1·1 (0·4)	1·1 (0·3)
Dry mouth	1·3 (0·7)	1·1 (0·5)	1·1 (0·4)
Dizziness	1·3 (0·6)	1·1 (0·4)	1·1 (0·4)
Feeling disorientated	1·2 (0·6)	1·1 (0·3)	1·1 (0·3)
Night sweats which soak the bedsheets	1·5 (0·9)	1·2 (0·6)	1·2 (0·6)
Feeling feverish	1·2 (0·5)	1·1 (0·3)	1·1 (0·3)
Loss or decrease in appetite	1·2 (0·7)	1·1 (0·5)	1·1 (0·4)
Unintended weight gain > 10 1b	1·4 (0·8)	1·2 (0·6)	1·2 (0·5)
Unintended weight loss > 10 1b	1·1 (0·5)	1·1 (0·4)	1·1 (0·3)
Peripheral-neurological symptoms	1·3 (0·6)	1·1 (0·4)	1·2 (0·5)
Tingling in fingers and arms	1·4 (0·8)	1·1 (0·4)	1·2 (0·5)
Tingling in legs and arms	1·3 (0·8)	1·1 (0·4)	1·1 (0·5)
Numbness or tingling in fingers or toes	1·4 (0·7)	1·1 (0·4)	1·2 (0·6)
Gastrointestinal symptoms	1·3 (0·4)	1·1 (0·3)	1·1 (0·3)
Constipation	1·2 (0·6)	1·1 (0·4)	1·1 (0·4)
Flatulence or burping	1·6 (1·0)	1·3 (0·6)	1·3 (0·7)
Stomach cramp	1·3 (0·7)	1·1 (0·5)	1·1 (0·5)
Diarrhoea	1·3 (0·8)	1·2 (0·5)	1·2 (0·5)
Nausea	1·1 (0·5)	1·1 (0·3)	1·1 (0·3)
Vomiting	1·1 (0·4)	1·1 (0·3)	1·1 (0·3)
Urogenital symptoms	1·2 (0·4)	1·1 (0·2)	1·1 (0·2)
Pain on passing urine	1·1 (0·4)	1·0 (0·3)	1·0 (0·3)
Passing urine more often	1·3 (0·7)	1·1 (0·4)	1·1 (0·4)
Burning sensation in the sex organs	1·1 (0·4)	1·0 (0·2)	1·0 (0·2)
Loss of interest in sex	1·3 (0·8)	1·1 (0·5)	1·1 (0·5)
Auditory symptoms	1·3 (0·6)	1·1 (0·4)	1·2 (0·4)
Increased sensitivity to noise	1·3 (0·7)	1·1 (0·5)	1·1 (0·3)
Ringing in the ears	1·4 (0·7)	1·2 (0·5)	1·2 (0·6)
Musculoskeletal symptoms	1·7 (0·9)	1·3 (0·6)	1·3 (0·7)
Pain, without swelling in several joints	1·6 (1·0)	1·2 (0·6)	1·3 (0·7)
Joint stiffness	1·7 (1·0)	1·3 (0·7)	1·4 (0·8)

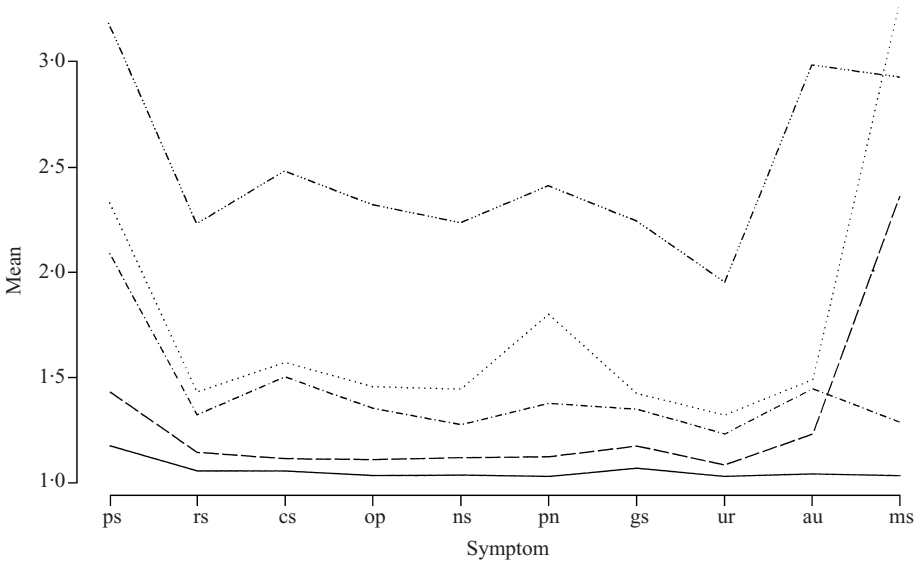

FIG. 1. Five cluster (——, Cluster 1 ($N = 963$); ----, Cluster 2 ($N = 93$); ·–·–, Cluster 3 ($N = 242$); ——, Cluster 4 ($N = 176$); ···–···–, Cluster 5 ($N = 26$)) solution of ten symptom groups in all three cohorts ($N = 1500$) (ps, neuropsychological symptoms; rs, respiratory symptoms; cs, cardiovascular symptoms; op, opthalmological symptoms; ns, generalized (non-specific) symptoms; pn, peripheral neurological; gs, gastrointestinal symptoms; ur, urogenital symptoms; au, auditory symptoms; ms, musculoskeletal symptoms).

Table 2. *Cross-classification of cohort* (N = 500 *in each cohort*) *and cluster*

Cluster	Gulf	Bosnia	Era
1	235	369	359
2	58	15	20
3	123	62	57
4	62	52	62
5	22	2	2

status was found to be associated with cluster membership ($\chi^2 = 83{\cdot}74$, $P < 0{\cdot}001$). A cross-classification of cohort against cluster membership is shown in Table 2. Sociodemographic and health variables were not associated with cluster membership when cohort was already in the model. Most veterans were grouped in Cluster 1 regardless of cohort status. Cluster 2 had three to four times as many Gulf veterans compared to Bosnia and Era veterans. There were eleven times more Gulf veterans in Cluster 5 than Bosnia and Era veterans but the actual numbers were very small.

To assess whether the five cluster solution might largely reflect differences in symptom severity rather than symptom pattern, a further cluster analysis of the data was carried out after standardizing each individual's set of scores by their average score over all ten symptom groups. In this case, the gap statistic estimated that there were two clusters present; the corresponding mean profiles are shown in Fig. 2. Veterans in Cluster 1 had low scores for each symptom group and likewise in Cluster 2 except that they had higher mean scores for musculoskeletal symptoms and neuropsychological. Logistic regression showed that cohort was associated with cluster membership. ($\chi^2 = 12{\cdot}91$, $P = 0{\cdot}002$); 72% of Gulf veterans ($N = 385$) belonged in Cluster 1 compared to 87% of Bosnia ($N = 435$) and 94·2% of Era ($N = 417$) veterans. To a lesser extent marital status was also associated with membership ($\chi^2 = 4{\cdot}91$, $P = 0{\cdot}006$); 82% of married veterans belonged in Cluster 1 compared to 78% of divorced and 88% of single veterans.

DISCUSSION

We carried out a cluster analysis of ten symptom groups for 1500 veterans, 500 from each of three cohorts which suggested that these individuals can be classified into five clusters. This was a

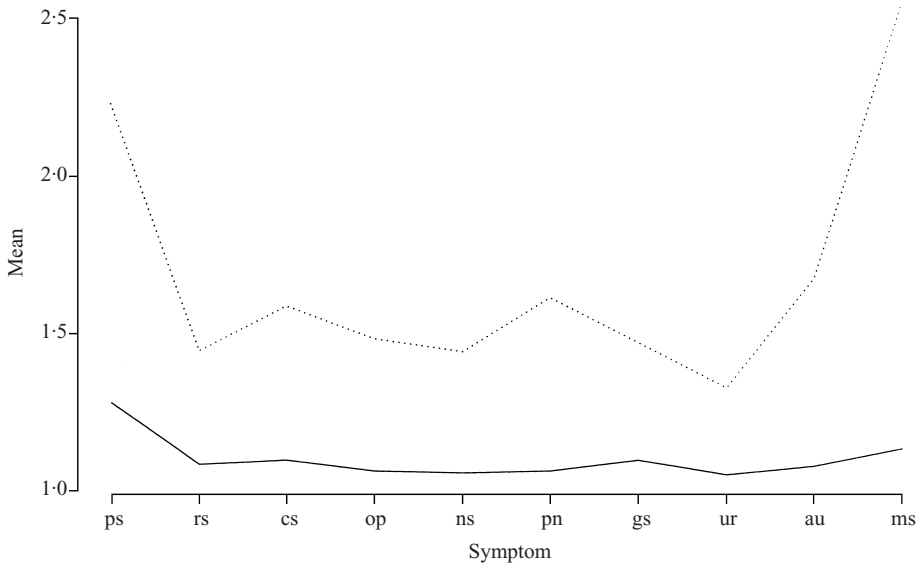

FIG. 2. Two cluster (——, Cluster 1 ($N = 1215$); · · · ·, Cluster 2 ($N = 285$)) solution of ten symptom groups standardized for severity in all three cohorts ($N = 1500$) (ps, neuropsychological symptoms; rs, respiratory symptoms; cs, cardiovascular symptoms; op, opthalmological symptoms; ns, generalized (non-specific) symptoms; pn, peripheral neurological; gs, gastrointestinal symptoms; ur, urogenital symptoms; au, auditory symptoms; ms, musculoskeletal symptoms).

secondary and different analysis to the factor analysis that we have reported earlier on the same sample (Ismail *et al*. 1999). The first, and by the largest cluster, consisted of individuals who were only mildly symptomatic, and contained the majority of Bosnia and Era veterans compared to less than a half of the Gulf veterans. The second cluster had relatively severe neuropsychological and musculoskeletal symptoms with approximately three times more Gulf veterans than Bosnia or Era. The third cluster had severe neuropsychological symptoms with approximately twice as many Gulf veterans as those from each of the other cohorts. The fourth cluster of individuals had more severe musculoskeletal symptoms and almost equal numbers from each cohort. The fifth cluster had severe scores for all symptom groups but it contained only 26 individuals, 85% of whom were Gulf veterans. Belonging to the Gulf cohort was associated with having severe neuropsychological and musculoskeletal symptoms and there was a small group of Gulf veterans who had high scores on all ten symptom groups. There were no sociodemographic characteristics or other health indices that distinguished the clusters.

To remove the effect of severity of symptoms, we standardized the ten symptom group scores by a crude measure of severity and then repeated the cluster analysis. Although Gulf veterans were more likely to a member of Cluster 2, the severity of musculoskeletal and neuropsychological symptoms were now no longer high and there was generally a more equal spread of veterans from each of three cohorts between the two clusters. Marital status was also associated with cluster membership with more divorced and separated veterans belonging to Cluster 2. Standardizing the data in this way is one way of examining whether less frequently reported symptoms such as nausea and more severe symptoms, such as weight loss, may be distinguishing ill health in Gulf veterans.

Our interpretation of these findings is that there is no convincing evidence of a new syndrome unique to Gulf veterans but there are more Gulf veterans who seem to be reporting neuropsychological or musculoskeletal symptoms and a much smaller group of Gulf veterans with multiple symptoms that span all body systems compared to non-Gulf veterans.

Our results partly support the one other study using cluster analysis (Cherry *et al*. 2001) and

indirectly support those studies that have used dimensional latent variable models to study the underlying pattern of ill health in Gulf veterans (Fukuda *et al*. 1998; Ismail *et al*. 1999; Doebbeling *et al*. 2000; Knoke *et al*. 2000). We did not have similar symptom data for a civilian sample to compare the clusters in our military sample. One study of medically unexplained symptoms carried out a hierarchical cluster analysis of eight symptom groups of 41 somatic symptoms in a primary care population (Gara *et al*. 1998). They reported 11 major clusters; their largest cluster had none or few symptoms (similar to our first cluster) and a superset cluster of symptoms from nearly all symptom groups (similar to our fifth cluster). The remaining clusters did have distinct patterns of symptoms but there was no cluster of symptom group(s) that seemed to be predominate, which lends support our findings.

Our finding that divorced veterans were more likely to belong to a cluster group that had more neuropsychological and musculoskeletal symptoms is in keeping with other studies of Gulf veterans (Ismail *et al*. 2000) and in the general population (Richards *et al*. 1997).

The advantage of our study is that the original sample was randomly selected and the symptoms were measured in a standardized manner in all three cohorts. The limitations of our findings that the symptoms were non-specific and may be distorted by reporting bias, although by standardizing in the way we did may have partly addressed this problem. There may have been some misclassification of symptoms into the symptom groups which may have led to an under- or over-estimation of the cluster sizes and their associations with Gulf status. However, we did categorize them into symptom groups similar to those used in other studies (Gara *et al*. 1998) and generally recognized by classification systems (World Health Organization, 1992; American Psychiatric Association, 1994).

In summary, our cluster analysis has identified five cluster groups of veterans according to the way in which their symptom scores are distributed. Gulf veterans are over-represented in clusters with higher neuro-psychological and musculoskeletal symptoms scores but the members in these clusters are relatively small and there is no substantial cluster that consists almost exclusively of Gulf veterans.

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