Is there a Gulf War syndrome?

Khalida Ismail, Brian Everitt, Nick Blatchley, Lisa Hull, Catherine Unwin, Anthony David, Simon Wessely

Summary

Background UK veterans of the Gulf War report more ill health than servicemen who were not deployed to the Gulf War. We investigated whether the pattern of symptom reporting by veterans of the Gulf War differed from that in active servicemen who had not fought in the Gulf War or who had fought in other conflicts.

Methods We used a population-based cross-sectional design. We sent a standardised survey that asked about 50 physical symptoms to three UK military cohorts; men who had served in the Gulf War, those who had served in the Bosnia conflict, and men who had been in active service but not deployed to the Gulf War (Era cohort). We used exploratory factor analysis to identify underlying factors and describe the factor structure of the symptoms reported in the Gulf War cohort. Confirmatory factor analysis was used to test the fit of this factor structure in the Bosnia and Era cohorts.

Findings Three factors in the Gulf War cohort together accounted for about 20% of the common variance. We labelled the factors mood, respiratory system, and peripheral nervous system, according to the symptoms that loaded on to them. In the confirmatory factor analysis, the factor structure identified in the Gulf War cohort fitted reasonably well in the Bosnia and Era cohorts.

Interpretation Although results from complex modelling procedures need to be interpreted with caution, our findings do not support a unique Gulf War syndrome. The mechanisms behind increased self-reporting of symptoms need further investigation.

Lancet 1999; **353:** 179–82
See Commentary page ???

Gulf War Illness Research Unit, Guy's, King's, and St Thomas's Medical School, London SE5 8AF, UK (K Ismail MRCPsych, L Hull BSc, C Unwin MSc, Prof A David FRCP, Prof S Wessely MD)**; Department of Biostatistics, Institute of Psychiatry, London** (B Everitt PhD)**; and Office of National Statistics seconded to the Ministry of Defence, London** (N Blatchley BSc)

Correspondence to: Dr Khalida Ismail
(e-mail: k.ismail@iop.bpmf.ac.uk)

Introduction

In our first paper (see pages 169–78), we reported that UK military veterans of the Gulf War have higher frequencies of self-reported impaired physical functioning, psychological morbidity, and poor perception of general health than UK servicemen who were not deployed to the Gulf War. In addition, more Gulf War veterans reported non-specific physical symptoms. We investigated whether these findings constitute a new disorder.

For an illness to be recognised as a new disorder it must be sufficiently different from other recognised disorders.[1] There is no formal process to investigate whether a set of symptoms are unique to a new illness. Several different methods can be used.

In our first paper we used the empirical approach with epidemiological evidence. This method may, however, miss rare symptoms that could be specific markers for the illness. Assumptions that common symptoms are clinically important may introduce systematic biases and result in misleading theories about possible biological mechanisms.

An alternative method is an analytical approach by factor analysis. Factor analysis is a generic term for several procedures that aim to identify whether the correlations between a set of observed variables can be explained by a few latent, unobserved variables (factors). Exploratory factor analysis is used for preliminary investigations of a set of observed variables. In a population with diverse symptoms, this method makes no a-priori assumption about the composition of the factors, can potentially identify clinically important factors, and commonly provides a concise description of the data. Specifically, relevant factors, and the variables that load on to them, can be used to suggest a structure that can be tested on a new set of data in confirmatory factor analysis.[2] For confirmatory factor analysis, a specific factor structure is assumed which, after estimation of its parameters, leads to predicted values for the correlations between the observed variables. Whether the specified structure provides an adequate explanation of how the observed variables fit, shown by correlations between them, is determined by how close the predicted correlations are to those observed. Judgment of the fit of models in confirmatory factor analysis is rarely straightforward and various measures of fit are generally used.

Factor analysis has been used in two studies of Gulf-War-related illnesses. Haley and colleagues[3] did an exploratory factor analysis of 52 symptoms in 249 Gulf War veterans selected from one US reserve unit. Six factors accounted for 71% of the variance of observed variables. These factors were: impaired cognition, confusion-ataxia, arthromyoneuropathy, phobia-apraxia, fever-adenopathy, and weakness-incontinence. They

	Factor 1: mood cognition	Factor 2: respiratory system	Factor 3: peripheral nervous system
Percentage variance of each factor	12·0	5·5	4·2
Symptom			
Headaches	42	0	16
Irritability or outbursts of anger	62	16	13
Sleeping difficulties	62	14	17
Feeling jumpy	52	20	14
Feeling unrefreshed after sleep	65	13	18
Fatigue	63	20	14
Feeling distant or cut off from others	65	15	0
Forgetfulness	60	13	0
Loss of concentration	69	15	0
Avoiding doing things or situations	60	15	0
Distressing dreams	48	14	13
Unable to breathe deeply enough	21	71	0
Faster breathing than normal	18	57	11
Feeling short of breath at rest	21	69	11
Wheezing	16	60	0
Tingling in fingers or arms	24	13	78
Tingling in legs or arms	22	17	63
Numbness or tingling in fingers or toes	21	14	69

*Factor loadings >40 are above threshold value used to define factor structure for Gulf-War cohort.

Table 1: **Results of exploratory factor analysis (factor loadings ×100) of symptoms reported in past month in Gulf War cohort (n=3214)**

interpreted their findings as evidence for a unique Gulf War syndrome, despite the lack of a comparison population as a control group. Haley and colleagues' findings and interpretations have heightened the controversy as to whether a unique Gulf War syndrome exists[4–8] and have yet to be replicated.

Fukuda and colleagues[9] did an exploratory factor analysis of 35 symptoms in a random sample of current service personnel from four US Air Force units. Three factors—mood and cognition, musculoskeletal, and respiratory—accounted for 39% of the common variance. A second factor analysis of the symptoms that loaded on to these factors in a separate random sample from the same population identified two factors that they labelled mood-cognition-fatigue and musculoskeletal. The investigators developed a clinical case definition of Gulf-War-related illnesses based on whether symptoms in the whole sample had a chronic course, were commonly reported, and were more frequent than in the non-Gulf-War sample. This definition identified fatigue, difficulty remembering or concentrating, difficulty sleeping, moodiness, joint pains, and joint stiffness as the criteria for case definition. Agreement was good between factor-derived and clinically derived symptoms which suggests acceptable construct validity of the analytical approach. Ex-servicemen were not, however, included, which might have introduced a healthy worker bias.

We aimed to identify underlying factors that explained the correlations among symptoms reported in UK servicemen deployed in the Gulf War, and to assess, by confirmatory factor analysis, the fit of the factor structure in the Gulf War cohort in servicemen deployed to the Bosnia conflict and in active servicemen who were not deployed to the Gulf War (Era) at the time of the Gulf War. We tested whether the factor structure proposed by Haley and colleagues[2] could be replicated in our Gulf War, Bosnia, and Era cohorts.

Methods

We did a population-based cross-sectional postal survey to compare the health profiles of three UK military samples.

Participants

We defined three UK military male populations: all veterans deployed to the Gulf War; all veterans who served in the first four regiments deployed to the Bosnia conflict; and all veterans in active service on Jan 1, 1991, not deployed to the Gulf War. Respondents who had served in the Gulf War and the Bosnia conflict were defined as veterans of the Gulf War. The Ministry of Defence provided three random samples of equal size from each of these populations. Details of stratification, methods of selection and tracing are described in our other paper. In this paper, veterans are current and discharged military personnel.

Methods

We sent a standardised postal questionnaire to 12 592 men that asked whether any of 50 non-specific symptoms had been experienced in the past month. We took symptoms from the Hopkins symptoms checklist, which is reliable and validated,[10] symptom criteria for various functional somatic syndromes (chronic fatigue syndrome, irritable bowel syndrome),[11] and symptoms reported from our pilot studies of Gulf War veterans. We asked participants to score each symptom as present or absent and, if present, to rate its severity as mild, moderate, or severe (0 absent, 1 mild, 2 moderate, 3 severe).

Statistical analyses

For the exploratory factor analysis, we constructed the Pearson's correlation matrix among the 52 symptoms in the Gulf War cohort. We excluded respondents with missing values for any symptom.

Principal factor analysis was applied to the correlation matrix. We used the Kaiser-Guttman rule (eigenvalue >1·0) to find out the number of factors to retain for rotation. The eigenvalue is the amount of total variance explained by each factor. We simplified the initial solution by varimax (orthogonal) rotation. We named factors according to the types of symptoms with a factor loading of 0·40 or more (an arbitrary but conventionally accepted cut-off). To simplify analyses, we included only the first three factors. Although this approach provides limited results, inclusion of additional factors would introduce unnecessary complexity.

Goodness of fit tests	Model 1*	Model 2†	Model 3‡	Model 4§
χ^2 (p)	2802 (<0·001)	2823 (<0·001)	2859 (<0·001)	2891 (<0·001)
Index 1 (Bentler-Bennett normed)	0·90	0·90	0·90	0·90
Index 2 (Bentler-Bennet non-normed)	0·90	0·90	0·90	0·91
Index 3 (comparative fit indices)	0·91	0·91	0·91	0·91
Average residual	0·03	0·03	0·04	0·03

*No constraints in factor structures of Bosnia and Era cohorts. †Correlations between factors fixed to be equal in Bosnia and Era cohorts. ‡Correlations between factors and factor loadings fixed to be equal in Bosnia and Era cohorts. §All parameters of factor structure fixed to be equal in Bosnia and Era cohorts.

Table 2: **Confirmatory factor analysis of factor structure of Gulf War (n=3225), Bosnia (n=1770), and Era (n=2384) cohorts**

Symptom	Factor 1: mood cognition	Factor 2: respiratory system	Factor 3: peripheral nervous system
Headaches	x	0	0
Irritability or outbursts of anger	x	0	0
Sleeping difficulties	x	0	0
Feeling jumpy or easily startled	x	0	0
Feeling unrefreshed after sleep	x	0	0
Fatigue	x	0	0
Feeling distant or cut off from others	x	0	0
Forgetfulness	x	0	0
Loss of concentration	x	0	0
Avoiding doing things or situations	x	0	0
Distressing dreams	x	0	0
Unable to breathe deeply enough	0	x	0
Faster breathing than normal	0	x	0
Feeling short of breath at rest	0	x	0
Wheezing	0	x	0
Tingling in fingers and arms	0	0	x
Tingling in legs and arms	0	0	x
Numbness or tingling in fingers or toes	0	0	x

x=parameter to be estimated; 0=parameter fixed at zero in model 1; in addition, factors were allowed to be correlated in all four models.

Table 3: **Factor structure of Gulf War cohort to be tested in confirmatory factor analysis**

Symptoms	First three factors from Haley and colleagues[2]		
	Factor 1: impaired cognition	Factor 2: confusion-ataxia	Factor 3: arthromyo-neuropathy
Headaches	x	0	0
Irritatability or outbursts of anger	x	0	0
Sleeping difficulties	x	0	0
Fatigue	x	0	x
Shaking	x	0	0
Tingling in fingers and arms	0	0	x
Tingling in legs and arms	0	0	x
Numbness or tingling in fingers or toes	0	0	x
Forgetfulness	x	x	0
Dizziness	0	x	0
Loss of concentration	0	x	0
Burning sensations in the sex organs	0	x	0
Loss of interest in sex	0	x	0
Avoiding doing things or situations	0	x	0
Pain, without swelling, in several joints	0	0	x
Joint stiffness	0	0	x
Distressing dreams	0	x	0

x=parameter to be estimated; 0=parameter fixed at zero; factors were allowed to be correlated in all four models.

Table 4: **Structure of "Haley model" based on our symptoms**

We used results from the three-factor solution in the Gulf War cohort to specify the factor structure to be tested in the Bosnia and Era samples. Confirmatory factor analysis was first applied to the correlation matrix of these symptoms in each cohort separately with no constraints (model 1). Next, we examined a series of models in which increasing numbers of parameters were fixed so they were equal in the Bosnia and Era cohorts. In model 2, we fixed factor correlations. In model 3 we fixed correlations between the factors and the factor loadings. In model 4 we fixed all parameters of the factor structure.

Goodness of fit can be assessed by global measures of fit, commonly with χ^2 statistic. This assessment is, however, generally not adequate on its own because, especially in large samples, non-important differences between observed and predicted correlations of observed variables can lead to large significant values. Other goodness of fit indices have, therefore, been suggested,[11] and we used Bentler-Bennett normed, Bentler-Bennett non-normed, and comparative fit indices. Differences between observed and predicted correlations (residual correlations) should be small, at 0·05 or less, for the model to be acceptable.

In the second confirmatory factor analysis, a factor structure was specified based on symptoms from our questionnaire that had face validity with the symptoms that loaded on Haley and colleagues' first three factors, which we called the Haley model. We constructed a correlation matrix of these symptoms for each cohort. The goodness of fit of the Haley model was tested in each cohort with the same fit measures.

We used SPSS (version 7.5) for the exploratory factor analysis, and EQS[2] for the confirmatory factor analysis.

Results

The response rates and sociodemographic and health characteristics for all men are reported in our first paper, as well as the 15 most commonly reported physical symptoms. Nearly all symptoms were reported most in the Gulf War cohort and decreased progressively from the Bosnia to the Era cohort.

In exploratory principal factor analysis, ten factors with eigenvalues of more than 1·0 accounted for 42·1% of the variance in the Gulf War cohort. 69 (2·1%) questionnaires had missing values. The symptoms that load on to the first three factors are shown in table 1. We labelled these factors according to the symptoms with loadings of more than 0·40: factor 1 was mood-cognition (headaches, irritability, sleep difficulties, feeling jumpy, unrefreshing sleep, fatigue, feeling distant or cut off from others, forgetfulness, loss of concentration, avoiding doing things or situations, and distressing dreams); factor 2 was respiratory system (inability to breathe deeply, fast breathing, shortness of breath at rest, wheezing); and factor 3 was peripheral nervous system (tingling in fingers or arms, tingling in legs or arms, numbness or tingling in fingers or toes).

In the confirmatory factor analysis, model 1 (table 2) had reasonable fit when fitted separately to the Bosnia and Era cohorts (table 3). The fit of the other models did not decrease significantly (table 3). The sizes of the residual correlations were small and they had no obvious pattern. The three tests of goodness of fit produced values of more than 0·9 for all models, which suggested an adequate fit. Goodness of fit tested by χ^2 statistic did not show good fit for the observed correlations and the difference in χ^2 values suggested a progressive deterioration in fit as more constraints were introduced. This measure is, however, sensitive to relatively unimportant differences between observed and predicted correlations in large sample sizes.

The fit of the Haley model (table 4) was poor in all three cohorts, with goodness of fit indices values, for example, of 0·8.

Discussion

The latent dimensions (factors) that underlie the pattern of symptom reporting in the Gulf War cohort seemed to differ little from those in the Bosnia and Era cohorts. Therefore, although the frequency of symptom reporting was higher in the Gulf War cohort, the underlying structure of the correlations between symptoms was similar to that in the other cohorts. This finding seems to provide evidence against the existence of a unique Gulf War syndrome.

Whether the three factors we analysed represent conventionally defined psychiatric disorders such as depression, anxiety or post-traumatic stress disorder, chronic fatigue syndrome, a variation of these, or some other dysfunction of the central nervous system cannot be inferred from our data. These possible explanations are not mutually exclusive. The three factors will require validation against criterion measures for recognised psychiatric and physical disorders.

The six factors identified by Haley and colleagues[8] accounted for a larger proportion of the variance than those in our study and the study by Fukuda and colleagues.[9] We were unable to replicate Haley's model in any of the three cohorts. One explanation is that the factor structure of our hypothesis was, by necessity, an approximation of their model, since we had used different measures. There may have been weaknesses in the methods of Haley's model. Their factors and reported variance may have been incorrect, since they studied a small population (n=606) that had a low response rate (41%) and used 52 symptoms from 249 participants in their exploratory factor analysis. In addition, their sample was not representative of the US military population because it consisted of US reservists from a unit comprised of naval construction workers, already known to have high rates of illness. Most important, they included no control (non-Gulf-War) group to compare the factor structure against.

By contrast, we used randomly selected population-based samples of Gulf War veterans and two control groups. We used military controls instead of general population controls to compare the pattern of symptoms. We also used large samples to ensure adequate power in our findings. The validity of factors derived from factor analysis depends on the use of appropriate epidemiological methods and the use of measures with good psychometric properties.

One weakness in our study was that we analysed only a three-factor model. The exploratory factor analysis of the Gulf War cohort suggests that three factors do not account adequately for the observed correlation structure, since they accounted for only 20% of variance in observations. Nevertheless our finding that this three-factor structure also fits the Bosnia and Era cohorts even after models were constrained shows that the factor structure of all three cohorts is probably similar.

Similar syndromes to those found in our exploratory factor analysis have been reported in one other study of military personnel. In a sample of Gulf War veterans still in service, Fukuda and colleagues[9] identified three factors in their first exploratory factor analysis. Their first factor related to mood, cognition, and fatigue with symptoms of feeling depressed, feeling anxious, feeling moody, difficulty remembering or concentrating, trouble finding words, difficulty sleeping, and fatigue, which was similar to our first factor, mood-cognition. Their third factor consisted of symptoms of wheezing, shortness of breath, coughing, and chest pain, which was similar to our second factor, respiratory system. We did not identify their second factor that related to musculoskeletal symptoms, but this difference may reflect the method of factor selection rather than differences in the patterns of symptom reporting.

Exploratory factor analysis of somatic symptoms by Simon and colleagues[12] in an international primary-care study identified four factors—gastrointestinal, neurological/conversion, autonomic, and musculo-skeletal—that accounted for 42% of the total variance. Symptoms that loaded on to the neurological/conversion and autonomic factors were similar to the symptoms with high factor loadings in our peripheral nervous system and respiratory factors, respectively. Simon and colleagues also observed that these factors were non-differentially associated with symptoms of psychological distress.

One question we did not address is how the three cohorts differ in level on the three factors identified. Since this investigation needs complex statistical procedures, we will report this in a later paper.

We can speculate that other mechanisms, such as altered illness perception, could be involved, or that Gulf War syndrome actually represents the final common pathway for several different health-related processes.

Although illness reporting was more common among men who served in the Gulf War, our evidence did not support the existence of a unique Gulf War syndrome. Explanations for higher frequencies of ill health are still needed. If there is a Gulf War syndrome, it cannot be identified by symptoms alone.

Contributors

Khalida Ismail contributed to generating the study hypothesis, analysis, and the drafting of the manuscript. Brian Everitt helped to generate the study hypothesis, and with analysis and preparation of the manuscript. Catherine Unwin coordinated the study, and was involved in analysis and the writing of the paper. Nick Blatchley gave statistical support and created the study cohorts. Lisa Hull traced veterans and coordinated the study and follow-up. Anthony David and Simon Wessely were the principal investigators and planned, designed, and supervised the study, as well as being involved in the writing of the paper.

Acknowledgments

See page 178.

References

1 Wegman DH, Woods NF, Bailar JC. Invited commentary: how would we know a Gulf War Syndrome if we saw one? *Am J Epidemiol* 1997; **146:** 704–11.

2 Dunn G, Everitt B, Pickles A. Covariances and latent variables using EQS. London: Chapman and Hall, 1993.

3 Haley R, Thomas L, Hom J. Is there a Gulf War Syndrome? Searching for syndromes by factor analysis of symptoms. *JAMA* 1997; **277:** 215–22.

4 Haley R. Point: bias from the 'Healthy-warrior effect' and unequal follow-up in three government studies of health effects of the Gulf War. *Am J Epidemiol* 1998; **148:** 315–23.

5 Gray GC, Knoke JD, Berg W, Wignall S, Barrett-Connor E. Counterpoint: responding to suppositions and misunderstandings. *Am J Epidemiol* 1998; **148:** 328–33.

6 Cowan DN, Gray GC, DeFraites RF. Counterpoint: responding to inadequate critique of birth defects paper. *Am J Epidemiol* 1998; **148:** 326–27.

7 Kang HK, Bullman T. Counterpoint: negligible 'healthy-warrior effect' on Gulf War veterans' mortality. *Am J Epidemiol* 1998; **148:** 324–25.

8 Haley RW. Countercounterpoint: Haley replies. *Am J Epidemiol* 1998; **148:** 334–38.

9 Fukuda K, Nisenbaum R, Stewart G, et al. Chronic multi-symptom illness affecting air force veterans of the Gulf War. *JAMA* 1998; **280:** 981–88.

10 Derogatis L, Lipman R, Rickels K, Uhlenhuth E, Covi L. The Hopkins Symptom Checklist (HSCL): a self report symptom inventory. *Behav Sci* 1974; **19:** 1–15.

11 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:** 953–59.

12 Simon G, Gater R, Kisely S, Piccinelli M. Somatic symptoms of distress: an international primary care study. *Psychosom Med* 1996; **58:** 481–88.