What is chronic fatigue syndrome? Heterogeneity within an international multicentre study

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Objective: We sought to compare the characteristics of patients presenting with chronic fatigue (CF) and related syndromes in eight international centres and to subclassify these subjects based on symptom profiles. The validity of the subclasses was then tested against clinical data.

Method: Subjects with a clinical diagnosis of CF completed a 119-item self-report questionnaire to provide clinical symptom data and other information such as illness course and functional impairment. Subclasses were generated using a principal components-like analysis followed by latent profile analysis (LPA).

Results: 744 subjects returned complete data sets (mean age 40.8 years, mean length of illness 7.9 years, female to male ratio 3:1). Overall, the subjects had a high rate of reporting typical CF symptoms (fatigue, neuropsychological dysfunction, sleep disturbance). Using LPA, two subclasses were generated. Class one (68% sample) was characterized by: younger age, lower female to male ratio; shorter episode duration; less premorbid, current and familial psychiatric morbidity; and, less functional disability. Class two subjects (32%) had features more consistent with a somatoform illness. There was substantial variation in subclass prevalences between the study centres (Class two range 6–48%).

Conclusions: Criteria-based approaches to the diagnosis of CF and related syndromes do not select a homogeneous patient group. While substratification of patients is essential for further aetiological and treatment research, the basis for allocating such subcategories remains controversial.

Key words: chronic fatigue, somatization, latent class.

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Currently, there is little international consensus regarding the pathogenesis of chronic fatigue and related syndromes. As clinical syndromes are traditionally defined by characteristic symptoms and clinical course, over the last decade various national research and/or international committees have set out to define the key features of a more restricted group of patients, now termed as suffering from 'chronic fatigue syndrome' (CFS) [1–5]. Each of the proposed criteria sets for CFS have struggled to come to terms with a range of complex issues including: the relative weights that should be attached to common symptoms such as prolonged mental and physical fatigue, muscle pain, sleep disturbance, poor concentration and mood changes and/or clinical signs; severity of disability; duration of symptoms; acuity of onset; premorbid and/or concurrent psychological morbidity [1,3,5]; and the place of proposed laboratory markers (such as those for immune dysfunction) [2]. Those criteria sets which include many possible symptoms, or require a significant number of different symptoms, are biased towards the inclusion of patients with an increased number of somatic symptoms, longer illness duration and more functional disability. Such factors are, however, more likely to identify patients with a known psychiatric disorder [6–8], rather than a novel syndrome.

An alternative to expert consensus is to use statistical analyses to derive groups of subjects with more homogeneous characteristics [9]. There is no ideal method for the statistical 'clustering' of patients, although latent class analysis (in association with mixture analysis or principal components analysis) may be useful [6,10–12]. Importantly, this approach is free of clinician-bias, and factors such as illness onset, course and treatment response can be used to examine the validity of any derived typology. Given the subjective nature of the diagnosis of CFS and the consequent possibility of significant variation in sample characteristics, we set out: (i) to compare the clinical characteristics and functional disability in patients drawn from CFS research centres in Australia, the USA and the UK; (ii) to re-examine the earlier proposal [6] that relevant subgroups of CFS subjects could be identified empirically on the basis of symptom patterns alone; and (iii) to validate any derived classification against clinical data such as subject age and sex, duration of illness, functional disability, psychological morbidity and family history of psychiatric disorder.

Method

Study centres

Investigators from eight international centres with a known research interest in CFS agreed to participate in this study. Subjects therefore were enrolled from differing geographical and clinical specialty settings (immunology, infectious diseases, rheumatology and psychiatry), although each was predominantly university-based and either a secondary or tertiary referral centre.

Subjects

In order to avoid *a priori* judgements and as a result of the multicentre nature of the study, subjects were selected using the existing CFS diagnostic criteria employed at each centre. Subjects enrolled from Prince Henry Hospital (Australia) all met Lloyd *et al*. [2] clinical criteria (6 months chronic persisting or relapsing fatigue and neuropsychiatric dysfunction), subjects from the National Institutes of Health (USA) and Miami samples met Centers for Disease Control (CDC) criteria [1], whereas subjects from Michigan and Belfast were diagnosed according to 'modified' CDC criteria [4,5]. The study samples from London and Oxford both met UK criteria for CFS [3] and in addition, the sample from London excluded patients that met DSM-III-R [13] criteria for somatization disorder. All patients were evaluated to exclude other medical causes for current symptoms [4,5] and laboratory investigations were carried out in accordance with the practice of each centre. Patients with an identified psychotic disorder and/or a diagnosis of drug or alcohol dependence (premorbid or current) were excluded. One centre (Boston) selected patients who each met clinical criteria for fibromyalgia [14], as well as satisfying Prince Henry criteria [2] for a diagnosis of CFS.

Questionnaire

The subjects were asked to complete a 119-item self-report questionnaire comprising six sections. Section one recorded age, gender, marital status, educational achievement and employment status. Section two determined illness duration, character of symptom onset (sudden *vs* gradual) and factors considered relevant to onset (e.g. a viral or 'flu-like illness'). In Section three subjects rated 48 symptoms as either present or absent. These were the physical, cognitive and neuropsychiatric symptoms considered likely features of the disorder and were an extension of the 38 symptoms utilized in an earlier epidemiological survey [15]. Ten further questions assessed more general, nonspecific somatic symptoms as well as evaluating the effects of sleep, heat, inactivity, emotional stress, mental exertion and vigorous physical activity on fatigue. These were rated on a five-point scale: 0, 'no change or minimal improvement/deterioration'; 1, 'moderate improvement'; 2, 'complete or near complete improvement'; 3, 'moderate deterioration'; and 4, 'severe deterioration'. The extent to which fatigue fluctuated during the day was rated as were (for female subjects) changes in menstrual symptoms following the onset of the disorder, including whether fatigue levels fluctuated with the menstrual cycle.

Specific instructions were given not to rate symptoms that were present only in the first 3 months of the disorder. This was to minimize the reporting of acute symptoms present only following a precipitating event such as a viral infection, and not necessarily part of the ongoing symptom complex. For each positive symptom, subjects then rated the overall severity and frequency of that feature. Severity was rated on a three-point scale: 0, 'mild'; 1, 'moderate'; and 2, 'severe'. Frequency was rated on a four-point scale: 0, 'infrequent'; 1, 'frequent'; 2, 'very frequent/constant symptoms'; and 3, 'cyclical'. The overall severity

and frequency of depressed mood was also rated using the above scales. The relevant questions from the Diagnostic Interview Schedule (DIS) [16] were used to delineate the presence of an episode diagnosis of DSM-III-R major depression [13] and/or panic disorder.

Information on significant past medical history, including health problems which required specialist attention or hospitalization, as well as a previous history of treatment for anxiety or depression were recorded (section four). A family history of treatment for depression or other psychiatric illness was also sought (section five). Functional impairment (section six) was evaluated in several ways. Work participation and social activity were rated on a three-point scale: 0, 'no change or minimal reduction in activity'; 1, 'moderate reduction in activity'; and, 2, 'completely unable to participate'. Subjects recorded the frequency of visits to a medical practitioner as well as levels of current and premorbid physical activity. Data from section three (symptom check-list) were used as the basis for the subclassification of study subjects. Demographic information, course of illness, past and family history and data on levels of functional impairment were used to test its validity.

Statistical methods

The statistical methodology used in the study is similar to that reported previously by Hickie *et al*. [6]. Fifty-five items from section three (symptom check-list) were selected for which a 0–1 coding of 'absent' or 'present' was possible. These were the 48 symptom items and seven items (all coded dichotomously to share the same metric) which assessed the effect of moderating factors (e.g. sleep or inactivity) and fatigue fluctuation.

The analysis had two steps: first, the reduction of the individual 55 items to a small number of scores on continuous dimensions; and, second, the use of combinations of these dimensions to identify patient subclasses. The first step comprised a principal components-like analysis where the matrix analysed contained sums-of-squares and cross-products rather than the usual correlations or covariances. This modification allowed item differences in means and variances to influence the results. The second step used the method called latent profile analysis (LPA) [9], which assumes that the sample comprised a mixture of patients from one or more different classes, that the patients' class memberships are unknown and they have been measured on a number of continuous measures (in this case the dimensions from step one). For a specified number of classes, LPA estimates the proportions in each class, the means of each measure for subjects within a particular class, and allows each individual to be allocated to a particular class. This procedure is similar to latent class analysis in that the underlying variable is categorical, except that instead of categorical measures (manifest variables) there are continuous measures (in this case scores on the principal components).

Results

Subjects and clinical characteristics

Complete symptom data sets were available from 744 patients. The demographic characteristics and comparative length of illness of subjects are shown in Table 1. In the total sample there was little correlation between illness duration and age ($r = 0.17$), but male subjects had a shorter illness duration than females (6.7 years for males *vs* 8.1 years for females, $p = 0.030$). Forty-six per cent of subjects reported that their symptoms began suddenly, with 72% recording a 'viral illness' at onset. Twenty-one per cent believed that a specific environmental factor (e.g. exposure to toxic fumes or physical injury) was associated with their illness onset. The majority of subjects (71%) also reported a fluctuating course, with 21% of these having experienced periods (days to weeks) of complete symptom remission.

Across all centres subjects were predominantly female (mean = 74%, range = 64–96%), middle-aged (mean = 40.8 years, range = 35.0–50.3) and chronically ill (mean illness = 7.9 years, range = 3.9–12.8). This female predominance was especially pronounced in the fibromyalgia patients, however, this centre population did not differ significantly from the other centres across symptom or other illness variables. The key symptoms of fatigue and malaise as well as neuropsychological symptoms (poor concentration and memory impairment) were among the most common features (see Table 1). Two items related to pain (generalized and/or muscular) and two items related to sleep dysfunction (non-restorative sleep and 'global' sleep disruption) were also prominent. Overall, the number of symptoms reported as present at some stage during the illness had a range of 3–47 (mean = 28, median = 27).

For female subjects, 39% reported more painful menstruation during their illness, with 33% noting increased menstrual irregularity. Fifty-two per cent felt that their fatigue worsened premenstrually.

Levels of disability

Subjects across separate study sites reported similar levels of disability, symptom severity and concurrent psychiatric morbidity. Fifty-two per cent reported being unable to work during the course of their illness and 61% stated that they had been unable to complete more than 1 h of daily active work or exercise over the course of their illness. There were highly significant correlations between items which measured various domains of functional impairment (e.g. 'severe' symptoms overall correlating with inability to work $r = 0.62$, $p < 0.001$ and social impairment $r = 0.45$, $p < 0.001$).

Thirty-nine per cent of the sample had had an episode of major depression (MDE) during the illness, with 17% meeting criteria for panic disorder. Twenty per cent of subjects had had previous treatment for depression, however, data from the questionnaire did not allow for specific premorbid psychiatric diagnoses to be made. Surprisingly, an MDE (39% of sample) was not associated with a statistically increased risk of functional impairment: 53% of subjects with MDE were unable to work versus 51% without MDE ($\chi^2 = 3.4$, $p = 0.180$), and 56% with MDE unable to participate in 'normal activities' due to symptoms versus 48% without MDE ($\chi^2 = 4.7$, $p = 0.140$). However, an MDE was strongly associated with more frequent visits to a physician (51% with MDE attending more than four times a year *vs* 34% without MDE; $\chi^2 = 20.9$, $p < 0.001$). An MDE was associated with an average positive symptom report of 25 (SD = 7.5) versus an average positive symptom report without MDE of 31 (SD = 7.0, $p < 0.001$). A previous history of depression was associated with a positive symptom report of 28 (SD = 7.8) whereas those subjects without a history of depression recorded a positive symptom count of 29 (SD = 7.1, p = NS].

Latent profile analysis

From the 55 symptom items, five components were retained after principal components analysis (PCA). Using LPA, initial models assumed that the population included a mixture of two and three subclasses. The three-class solution generated class prevalences of 63%, 29% and 7% respectively meaning that most of the subjects represented one category of symptom profile and two other groups of patients were also represented but progressively less frequently. However, as a result of the inadequate representation of class three across study centres (two centres with no subjects in class three and two centres with less than 5% of their subjects in this class), this model was not pursued. The simpler two-class solution is utilized hereafter.

The means of the first five PCA components are shown in Table 2. Overall, 68% of the subjects were allocated to class one and 32% to class two. Both classes weighted heavily on component one (labelled 'classical CFS symptoms'), which included items considered core features (fatigue, malaise, neuropsychological impairment and sleep disturbance). Class two subjects showed significantly higher mean scores for component two ('multiple somatic symptoms' e.g. swollen joints, dysphagia and painful eyes), component three ('depression and anxiety' e.g. panic attacks, 2 weeks of depression during episode) and

Table 1. Demographic characteristics and symptoms reported in more than 80% of the subjects, latent profile analysis class allocations and history of mood disturbance across study centres

	Overall (n = 744)	Sydney (n = 462)	Boston (n = 47)	London (n = 23)	Oxford (n = 15)	Miami (n = 32)	Belfast (n = 51)	Michigan (n = 25)	NIH (n = 89)
Demographic characteristics									
Mean age (years)	40.8	40.9	43.5	35.0	37.4	50.3	38.4	35.6	39.9
(SD)	(13.0)	(13.9)	(9.8)	(12.2)	(11.4)	(10.5)	(10.3)	(8.7)	(9.8)
% Female	74	72	96	91	87	82	71	76	64
% Single	30	31	9	57	40	21	25	28	33
Length of illness (years)	7.9	7.7	8.8	4.9	3.9	9.3	5.0	12.8	10.4
Symptoms reported by more than 80% of the sample overall (%)									
1. Global fatigue	99	91	100	100	100	100	100	100	100
2. Fatigue after daily activity	96	96	91	96	100	97	96	96	94
3. Malaise	95	96	96	96	100	100	86	92	95
4. Generalized pain	93	93	100	78	93	94	98	100	92
5. Concentration impairment	93	94	83	91	87	94	94	96	90
6. Non-restorative sleep	93	94	96	91	93	100	90	76	96
7. Fatigue at rest	90	92	77	87	100	100	76	96	88
8. Memory impairment	87	86	87	91	93	100	94	96	80
9. Disrupted sleep	85	86	98	87	53	100	76	84	75
10. Fatigue after minor activity	83	82	81	83	93	91	90	88	80
11. Word finding difficulties	83	84	79	91	93	100	82	92	72
12. Muscle pain	82	81	94	69	87	88	90	92	73
Latent profile analysis class allocation (%)									
Class one	68	65	68	83	80	65	94	52	69
Class two	32	35	32	17	20	35	6	48	31
History of mood disturbance (%)									
Past history of depression	20	19	25	32	20	30	20	16	17
Currently meets criteria for major depression	40	44	38	36	6	31	24	36	38

Table 2. Means of 'principal components' utilized in latent profile analysis by class allocation

Component	Class one (68%) Mean scores	Class two (32%) Mean scores
1. 'Classical CFS symptoms'	+4.3	+5.6
2. 'Multiple somatic symptoms'	–0.6	+0.7
3. 'Depression and anxiety'	–0.1	+0.1
4. 'Subjective nodal pain and swelling'	+0.1	–0.2
5. 'Fatigue variability'	0.0	+0.1

For component 4, negative score = increased symptom report.

component four ('subjective nodal pain and swelling' e.g. subjective report of swollen cervical or generalized glands, report of tender cervical or generalized glands). The mean scores obtained for component five ('fatigue variability'), which represented items assessing the effect of various moderating factors on fatigue (e.g. sleep, temperature and emotional stress), did not differ significantly between the two subject groups.

The distribution of classes across centres is shown in Table 1. Comparative clinical characteristics are shown in Tables 3 and 4. Class one was characterized by younger age, lower female to male ratio, a shorter illness duration, reduced prevalence of an episode diagnosis of panic disorder or MDE, lower rates of previous treatment for depression and anxiety and less reported family history of affective or other psychiatric disorder. Class one members also recorded less functional impairment and had a lower rate of previous attendance to a physician for medical problems. There were no reported differences as to whether symptoms commenced suddenly or gradually (47% class one subjects with sudden onset *vs* 44% class two; $\chi^2 = 1.5$, $p = 0.820$).

By contrast, class two subjects reported their symptoms as being less responsive to factors expected to improve fatigue such as sleep and physical inactivity. As well as reporting a high prevalence of typical CFS symptoms (e.g. fatigue, malaise and sleep disturbance), class two subjects also reported high frequencies of 'atypical' symptoms such as loss of vision, incontinence, swollen joints and dysphagia. The mean number of positively rated symptoms for class one subjects was 24 which was significantly lower than the mean of 36 for class two subjects ($p < 0.001$).

Importantly, there were significant intersite differences in class allocation, with the proportion of class one subjects varying from 94% in Belfast to 52% in Michigan (Table 1).

Conclusions

In this study we have shown that patients currently diagnosed with CFS in university-based research centres in Australia, the USA and the UK have similar overall demographic and clinical characteristics and report comparable levels of psychological morbidity and functional disability. By utilizing a multivariate statistical procedure (LPA), however, we were able to identify at least two clinically important subgroups. One group, consisting of approximately one-third of the total sample (class two), displayed characteristics more suggestive of a somatoform disorder, namely: (i) greater numbers of non-specific or 'atypical' symptoms (including those traditionally associated with somatoform disorders such as loss of vision, bladder disturbance and dysphagia); (ii) higher psychological morbidity and health care utilization (both in the past and concurrently); (iii) a longer duration of illness; (iv) a higher female to male ratio; and (v) more functional disability. These international results replicate earlier findings based only on Australian subjects [6]. The significant between-group differences for the prevalence of premorbid (as evidenced by treatment rates) and familial psychiatric disorder argues against the proposition that the groups differ only along some

Table 3. Comparison of symptom report and fatigue modulating factors between Class one and Class two CFS subjects

	Class one (%)	Class two (%)
Episode symptoms		
1. Global fatigue	100	99
2. Fatigue after daily activity	95	91
3. Non-restorative sleep	93	96
4. Malaise	94	98
5. Concentration impairment	91	98
6. Generalized pain	91	99
7. Fatigue at rest	88	96
8. Memory impairment	83	95
9. Globally disrupted sleep	80	95
10. Fatigue after minor activity	80	91
11. Word finding difficulties	77	97
12. Muscle pain	77	94
13. Headache	74	87
14. Muscle pain with minor activity	71	93
15. Poor coordination	64	96
16. Joint pain	63	92
17. Initial insomnia	63	80
18. Enlarged cervical glands	62	89
19. Muscle pain with exercise	61	81
20. Recurrent sore throat	60	82
21. Hypersomnia	58	79
22. Paresthesia	56	86
23. Nightmares	55	83
24. Nausea	54	82
25. Tender glands (cervical)	48	86
26. Early morning wakening	46	72
27. Recurrent fevers	41	76
28. Panic attacks	39	72
29. 2 or more weeks depressed mood	37	69
30. Chest pain	36	77
31. Slurred speech	36	80
32. Painful eyes	36	79
33. Muscle twitching (general)	35	78
34. Tinnitus	35	75
35. 2 or more weeks anhedonia	33	63
36. Dry mouth	32	72
37. Facial muscle twitching	30	76
38. Enlarged glands (general)	27	67
39. Diarrhoea	26	61
40. Dry eyes	23	57
41. Difficulty swallowing	20	55
42. Raynaud's phenomenon	20	56
43. Tender glands (general)	18	64
44. Persistent cough	17	53
45. Incontinence	15	50
46. Swollen joints	15	50
47. Repetitive eye blinking	9	30
48. Loss of vision	6	55
Modulating factors		
49. Fatigue fluctuation	86	96
50. Emotional stress affects fatigue	69	79
51. Vigorous exercise affects fatigue	59	65
52. Mental activity affects fatigue	57	77
53. Inactivity affects fatigue	56	59
54. Sleep affects fatigue	55	56
55. Increased temperature affects fatigue	54	79

Table 4. Latent profile analysis class designation vs. *demographic, psychiatric and disability data*

Validation markers	Class one	Class two	p
1. Age (years)	39.7	42.6	< 0.010
2. Length of illness (years)	6.9	9.6	< 0.001
3. Female to male ratio	2:1	5:1	< 0.001
4. Sudden onset (%)	47	43	NS
5. Concurrent panic disorder (%)	11	29	< 0.001
6. Concurrent major depression (%)	28	65	< 0.001
7. Eight or more symptoms rated 'severe' (%)	15	44	< 0.001
8. Unable to work during illness (%)	48	63	< 0.001
9. Unable to function socially during illness (%)	37	47	< 0.001
10. Frequent medical attendance during illness (more than once/3 months) (%)	35	51	< 0.001
11. More than three past health problems (saw specialist) (%)	8	22	< 0.001
12. Previous treatment for depression (%)	17	26	< 0.010
13. Previous treatment for anxiety (%)	12	13	NS
14. Family history of depression (%)	22	32	< 0.050
15. Family history other psychiatric illness (%)	12	24	< 0.010

shared dimensional factor such as symptom severity, functional disability or concurrent psychological morbidity. Rather, it suggests a constitutional vulnerability to a somatoform disorder in class two subjects. An alternative possibility is that patients with more prolonged disorders develop some (but not all) of these features as a consequence of the chronicity of their condition.

Importantly, the presence of a diagnosis of a major depressive episode, although associated with increased health care utilization, was not associated with greater functional disability, nor did current or premorbid depression predict increased positive symptom reporting. From a traditional psychiatric perspective, these were unexpected findings and suggest that the presence of affective disorder alone does not account for the other symptomatic differences between the two groups. It is consistent, however, with the findings from other aetiological studies which suggest that the liability toward reporting such somatic syndromes is determined by independent genetic and/or environmental factors [17–21]. Previous attempts to explain such syndromes simply in terms of unrecognized depressive disorders are no longer consistent with either these aetiological studies or treatment studies utilizing common antidepressant agents [22,23]. The clinical management of these patients is likely to be enhanced by modes of treatment based on sleep-wake cycle [24] and/or specific cognitive–behavioural approaches [25,26].

This study shows the difficulties which arise when a traditional approach to diagnosis and classification is adopted in this patient group. We used a method without prior clinical assumptions (e.g. the significance of certain clinical symptoms such as fever, lymphadenopathy or course of illness factors such as onset after a 'viral' illness) to define subgroups. Expert-derived classification systems [3,7,27] do not discriminate between subjects, as those in class two (likely somatoform disorder) report 'classical' CFS features as frequently as class one subjects. While such systems (and their inevitable revisions) will continue to drive much clinical and aetiological research [5], it cannot necessarily be assumed that they have yet succeeded in describing distinct or valid entities. Similarly, the use of impaired cell-mediated immunity as an additional laboratory criteria [2] is unlikely to identify a more homogeneous group, given the similar class frequencies of the Australian sample (the majority of whom had some evidence of impaired cell-mediated immunity during their illness). Rather, a multiplicity of non-specific or 'atypical' somatic symptoms in association with higher rates of psychological morbidity may more clearly differentiate patients with a primary somatoform disorder and also predict higher levels of functional disability. This is in keeping with earlier reports [6,7] that current CFS classificatory systems are unfortunately biased towards the inclusion of such subjects, and emphasizes that only sophisticated forms of substratification are likely to reveal critical patient differences. While our findings suggest aetiological heterogeneity within CFS populations, further studies are needed to determine whether the proposed subgroups lie on a continuum (of severity or chronicity) or truly represent aetiologically distinct groups.

In contrast to the comparable clinical characteristics across the centres, there were significant intersite differences in subclass distributions. In particular, the sample from Belfast was characterized by a very low frequency of class two subjects (6% *vs* 35% overall, $p < 0.001$), implying the importance of local selection factors. This

factor is generally ignored in multisite international comparison studies. As a consequence of working in very different health systems and of the different clinical orientations of the investigators, the sites did not generate directly comparable patient groups. That is, while clinicians may assume that they are applying current classification systems any resultant patient cohorts are likely to be quite heterogeneous.

It has been common in the medical literature to speak of 'fibromyalgia' and 'CFS' as different but related conditions. In this study, there were no significant differences in subclass allocations in subjects with a diagnosis of fibromyalgia (68% c1ass one Boston *vs* 65% overall, $p = 0.970$). Although, since all these subjects also met Prince Henry criteria for a diagnosis of CFS, this finding adds weight to the view that the two diagnostic labels are largely interchangeable [28]. This has important implications for patient education, clinical management and aetiological research.

This was a highly selected sample, derived from university-based, secondary- and tertiary-referral centres. Although uniform diagnostic criteria were not utilized, the exclusion of patients with concurrent medical disorders (and, to a lesser extent, those with more overt psychiatric disorder) should have reduced the number of subgroups identified. A CFS sample collected from a primary care setting, however, might identify quite different patient subclasses (e.g. a 'depressive-anxious' subset may be more likely). It is likely that referral to a university-based research centre has a filtering effect, favouring those with a pattern of excess health care utilization, increased care-eliciting behaviour (thereby increasing the female to male ratio), more chronicity and functional disability. All these factors are likely to increase the chances of detecting somatoform disorders.

Although the use of a self-report methodology may increase the number of positive symptom responses, it is the pattern of symptom response which best helps to identify the somatizing patients. The self-report methodology also allowed for a standardized symptom inventory to be collected internationally, independent of interviewer-induced biases. Data pertaining to antecedent factors should be viewed cautiously, although these data do provide a guide as to the approximate prevalence of possible initiating factors. It must also be noted that psychiatric diagnoses were made using self-report data only, and therefore should only be seen as approximating prevalence rates able to be determined by structured diagnostic interview.

The present study suggests that CFS research samples are heterogeneous. Attempts to improve case definition by simply refining clinical features already considered characteristic of the disorder will do little to identify patient subgroups. A definition requiring fewer symptoms would be likely to diminish class two size. Alternative strategies such as subtyping and categorizing CFS patients according to presence of a psychiatric diagnosis, hypothalamic-pituitary-adrenal axis activation or immune abnormality may be of use. Future studies to test aetiological or treatment hypotheses should incorporate specific strategies to identify patient subtypes.

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