

IN-DEPTH REVIEW

Epidemiology of chronic fatigue syndrome

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Background	Chronic fatigue syndrome (CFS) is a controversial disorder with different case definitions, aetiological models and proposed treatments. An epidemiological approach is likely to bring some clarity to the field.
Aim	The aim of this article is to review the literature on the epidemiology of fatigue, chronic fatigue and CFS.
Method	A literature search was conducted using the databases Medline and Pubmed as well as the reference lists of recent reviews to identify the relevant studies. The aim was not to do a systematic review but to review the key studies in the area to highlight the methodological issues.
Results	The review is organized according to the following areas: the prevalence of fatigue and chronic fatigue, the prevalence and incidence of CFS, epidemiological associations such as gender, social class and psychiatric co-morbidity and CFS in special groups such as those recovering from a viral infection, specific occupational groups and Gulf War veterans.
Conclusion	While fatigue as a symptom is very common, CFS is relatively rare. Many of the epidemiological associations seen in specialist clinics are not found in community samples. It is unlikely that one specific causal factor can explain CFS. Future studies should go beyond estimating the prevalence to testing more complex aetiological models.
Key words	Chronic fatigue syndrome; co-morbidity; incidence; post-viral fatigue; prevalence.

Introduction

Fatigue is a common complaint in primary care and hospital settings. But the study of fatigue is beset with problems, starting with its definition [1]. Prevalence rates vary according to whether the symptom sought is tiredness, weakness or exhaustion. The boundary between fatigue, chronic fatigue and chronic fatigue syndrome (CFS) is also quite arbitrary. By common consent, the term chronic fatigue is used for an illness characterized by fatigue as the main symptom lasting for more than 6 months and CFS when criteria for a case definition are met.

There are many definitions for CFS. These include the criteria introduced by the Centres for Disease Control and Prevention (CDC) in 1988, the CDC-1988 definition [4], the Australian [5] and British [6] definitions, and the most recent CDC-1994 definition [7]. Table 1 compares and contrasts various features of these definitions. It will be seen that these definitions

differ on the non-fatigue symptoms needed to make the diagnosis and the medical and psychiatric exclusions.

CFS is often thought of as a modern illness. Taking a historical perspective, Wessely has argued that CFS is only 'old wine in new bottles', having been preceded by other diagnostic labels such as neurasthenia [2]. The nature of CFS as a distinct disorder with well-demarcated boundaries has also been questioned. In fact, there are more commonalities than differences among many medically unexplained syndromes such as CFS, irritable bowel syndrome and fibromyalgia that they may all be considered to belong to a unitary group, functional somatic syndromes [3].

It will be clear to the reader from the above discussion that epidemiological studies and their findings are likely to differ according to the setting in which they were conducted, whether fatigue as a symptom, chronic fatigue or CFS was studied, the definition of CFS used and the rigourousness of the efforts made to rule out alternative medical explanations. These and other methodological issues in the epidemiology of CFS have been discussed in detail by Wessely [8].

With this background, the rest of the chapter looks at epidemiological studies of fatigue and CFS. As most of

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Table 1. Case definitions for CFS

	CDC-1988	CDC-1994	Australian	British
Minimum duration	6 months	6 months	6 months	6 months
Functional impairment	50% decrease in activity	Substantial	Substantial	Disabling
Cognitive or neuropsychiatric symptoms	May be present	May be present	Required	Mental fatigue required
Other symptoms	Six or eight required	Four required	Not specified	Not specified
New onset	Required	Required	Not required	Required
Medical exclusions	Extensive list of known physical causes	Clinically important	Known physical causes	Known physical causes
Psychiatric exclusions	Psychosis, bipolar disorder, substance abuse	Melancholic depression, substance abuse, bipolar disorder, psychosis, eating disorder	Psychosis, bipolar disorder, substance abuse, eating disorder	Psychosis, bipolar disorder, eating disorder, organic brain disease

Reproduced with permission from Wessely *et al.* [1].

the studies are prevalence studies, they will be discussed according to the setting of the study. Later the rarer incidence studies are discussed. This is followed by a section on CFS in special populations where I concentrate on CFS in selected occupational groups, CFS in those recovering from an identified viral infection and CFS in those who served in the Gulf during the first Gulf war. The studies discussed in this paper were identified by a search of the databases Medline and Pubmed and the reference lists of recent authoritative reviews [1,9,10]. The aim was not to perform a systematic review of all the available studies but to critically discuss the key studies.

Prevalence of fatigue and chronic fatigue

Fatigue or 'feeling tired' is a common experience and any measurement of fatigue needs to differentiate between a normal experience and a symptom. Drawing from the distinction proposed between the concepts of disease (with a pathological basis) and illness (a subjective experience), Wessely *et al.* [1] argue that fatigue should be considered abnormal when the fatigued person views him- or herself to be ill. Factors associated with this crossing of the threshold involve the decision to seek help, chronicity and the functional impairment. Thus, it is important, while reading the literature on the prevalence of fatigue, to be aware that drawing boundaries between normal and abnormal fatigue is an arbitrary one.

Fatigue in the community

A large community survey conducted in the UK gives us the opportunity to study the prevalence of fatigue in the community [11]. The OPCS survey of psychiatric morbidity in the UK found that 27% of all adults (a third of all women and a fifth of all men) reported

significant fatigue in the week before interview. Skapinakis *et al.* [12], using the data from this survey, looked at the prevalence of chronic fatigue and unexplained chronic fatigue (a CFS-like illness). This survey used the Revised Clinical Interview Schedule, a structured interview designed to be used by lay interviewers. The point prevalence of chronic fatigue was 13.4% and that of unexplained chronic fatigue was 9%. It has to be borne in mind that this was a secondary analysis of data set collected for other purposes. Self reported 'long-standing illness' was used to differentiate between chronic fatigue and unexplained fatigue. Being a community survey, no review of medical records or medical investigations was carried out. A comparable study from the US, using data from the Epidemiological Catchment Area study reported 1-month prevalence of unexplained fatigue lasting longer than 2 weeks of 6% [13].

Pawlikowska *et al.* conducted a postal survey of people registered with six general practices in southern England [14]. The questionnaires included the 12-item general health questionnaire, a well-validated measure of psychological morbidity, and a fatigue questionnaire. Substantial fatigue lasting 6 months or longer was reported by 18.3% of the respondents. Of the respondents with chronic fatigue, only 1.4% attributed it to CFS. It is probable that it is this group of self-identified patients who attend specialist clinics, thus biasing the sample.

Fatigue in primary care

In an early study from Texas, Kroenke *et al.* found that 24% of patients attending two primary care clinics identified fatigue as a 'major problem' [15]. In a group of studies from South London, it was shown that 10.2% of men and 10.6% of women complained of feeling tired all the time throughout the previous month [16]. It is

important to realize that these were surveys of fatigue as a symptom in primary care attendees and do not necessarily study fatigue as the presenting complaint. In fact, Wessely *et al.* [1] conclude in their review of the epidemiology of fatigue that while fatigue is a common symptom, it is not a common reason for medical consultation. Fatigue is considered as a diagnosis in only 1–2% of primary care attendees—the National Morbidity Survey of 1985 found that only 1% of consultations were listed under the category, ‘malaise, fatigue, debility, tiredness’ [17].

Fatigue in secondary care

It is a common observation of hospital doctors that fatigue is a common symptom. There is a lack of systematic surveys on this topic. Studies by Kroenke and Mangelsdorff [18] in the US have found that fatigue was the second commonest presenting complaint in medical outpatients with 8% of patients presenting with it. They also found that a third of outpatients reported fatigue, making it the commonest overall symptom. The shortcoming of these studies is that they are retrospective analyses.

Prevalence of CFS

Primary care studies

The study by David *et al.* [16] discussed earlier found only one case of a CFS-like illness in a sample of 611 primary care attendees. A later study by the same group [19] used a 2-stage procedure. They screened 686 patients attending primary care physicians and identified 77 individuals with chronic fatigue. Of these, 65 underwent a comprehensive medical and psychological evaluation. Twenty-six percent met the British criteria for CFS. Many of these studies had small sample sizes and inappropriate sampling procedures.

In one of a series of London-based studies, Wessely *et al.* [20] conducted a prospective study to determine the prevalence of CFS in 1199 primary care attendees with symptoms of common infection and 2267 seen for other reasons. They managed a follow-up rate of 84% at 6 months. At 6 months, 9.9% of the infectious group and 11.7% of the control group reported chronic fatigue and there was no difference in the proportions of the case groups fulfilling criteria for CFS. The study also looked at the prevalence of various definitions of CFS. The overall prevalence of CDC-1994, Oxford, Australian and CDC-1988 criteria were 2.6, 2.2, 1.4 and 1.2%, respectively; these values fell further when co-morbid psychiatric disorders were excluded. This compares with an American primary care study which found rates of 0.3, 0.4 and

1% for CDC-1988, British and Australian definitions, respectively [21].

Community-based studies

Price *et al.* [22] used the Diagnostic Interview Schedule (DIS) to assess the presence of CFS according to the CDC-1988 definition. While 23% of the participants reported experiencing persistent fatigue sometime during their lives, only 1 of 13 538 people met a diagnosis of CFS fulfilling all exclusion and inclusion criteria. This gave a prevalence figure of 7/100 000. The study of Price *et al.* [22], though, has numerous methodological problems. The definition of CFS did not correspond to other definitions. The other problem was that symptoms were assessed on a lifetime basis, leading to the possibility that cases where medical or psychiatric conditions existed at a different time may have been excluded. The lack of medical work-up or laboratory analyses was also a failing.

The CDC conducted a community-based survey in San Francisco [23]. Using telephone interviews, 14 627 adults were studied of whom 4.3% reported chronic fatigue. Having excluded cases with medical or psychiatric diagnoses that could potentially explain fatigue, the investigators identified 1.8% of the population as having idiopathic chronic fatigue and 0.2% as having a CFS-like illness.

Jason *et al.* [24] studied the point prevalence of CFS in an ethnically diverse random community sample. The study was a methodologically sophisticated one with a 2-stage procedure. In the first stage, the patients were screened using a questionnaire and those who screened positive for a CFS-like illness were interviewed on the Structured Clinical Interview for the Diagnostic and Statistical Manual (SCID) in the second stage. This was followed by a detailed medical examination and investigations. The final diagnosis of CFS was made by two independent raters. The study found a prevalence of 0.42% in the sample.

The wide disparity in the figures for prevalence of CFS in various studies (see Table 2) is likely to be due to differences in methodology rather than a true difference in prevalence. It seems clear that random community-based samples, an extensive search for a medical abnormality and restrictive case definitions result in lower prevalence figures. It is noteworthy that a recent Australian study found a prevalence rate of 1.5% in the population for neurasthenia, a related disorder [25].

Incidence and follow-up studies

There are few studies which have estimated the incidence of CFS. Lawrie *et al.* [26] resurveyed respondents 1 year after a postal survey and interviewed them again 18–22 months later. Based on that follow-up they estimated the

Table 2. Prevalence of CFS (studies discussed in the text)

Study	Setting	CDC-1988	CDC-1994	Australian	British
Price <i>et al.</i> [22]	Community	0.007%	–	–	–
Lawrie <i>et al.</i> [40]	Community	–	–	–	0.56%
Steele <i>et al.</i> [23]	Community	–	0.2%	–	–
Jason <i>et al.</i> [24]	Community	–	0.42%	–	–
Bates <i>et al.</i> [21]	Primary care	0.3%	–	1.0%	0.4%
Wessely <i>et al.</i> [20]	Primary care	1.2%	2.6%	1.4%	2.2%

annual incidence of CFS as 370 per 100 000 and the prevalence as 740 per 100 000. The sample was non-random and was relatively small. There have been many long-term follow-up studies of CFS and a review by Joyce *et al.* [27] revealed that a majority of patients report some improvement 18 months to 4 years after initial medical evaluation, although substantial recovery occurs in less than 10% of cases. For an updated review on this topic from the same group of researchers, see Cairns and Hotopf ([46], this issue).

Epidemiological associations

Gender

Most studies of gender differences report higher rates in women. It has been suggested that the gender difference is an artefact of recruiting samples from specialist centres and reflect differences in illness behaviour and referral patterns. But many community-based studies confirm this finding. Pawlikowska *et al.* [14] found that the relative risk of fatigue in women compared with men was 1.3, similar to the relative risk found by David *et al.* [16] in a primary care study. It was interesting that excess of psychological disorder in women did not explain the excess of fatigue. Jason *et al.* [24], in their community-based random sample, also found significantly higher prevalence rates of CFS in women (522 per 100 000) compared with men (291 per 100 000). These studies suggest that there may be a true gender difference and various predisposing vulnerabilities have been proposed such as endocrine and stress-related factors.

Social class

The popular epithet ‘yuppie flu’ which was used for CFS reflects the widespread view that it is a disease of the upper classes. Such an impression was created by studies and reports from specialist centres but has been criticized as unrepresentative. In community-based studies of fatigue, the finding is that fatigue is commoner in the lower classes. The Health and Life Survey, a large population-based study from the UK showed that fatigue is commoner in lower socio-economic classes [28]. A

study from French primary care also showed that the group with the highest socio-economic status was the least fatigued [29]. This may reflect the fact that low social class is a proxy for social adversity, a known predictor of fatigue. Community-based studies of CFS show a similar trend.

Psychiatric disorders

Much of the debate in CFS circles about whether it is a physical or psychiatric disorder has revolved around the issue of psychiatric co-morbidity. Studies from primary care and specialist clinics (including studies with normal or medical controls) point to a general pattern: psychiatric disorders, particularly depressive disorders, somatoform disorders and anxiety disorders are common but a substantial minority do not fulfil criteria for any psychiatric disorder [1]. A study from a hospital-based specialist clinic in Cardiff which studied 100 consecutive patients with CDC-1994 CFS and 50 controls is typical of such studies [30]. Forty-five percent of the CFS group and 10% of the control group had depressive disorders, 34% of the CFS group and none of the control group had somatoform disorders and 23% of the CFS group and 9% of the control group had anxiety disorders. A recent meta-analysis of the association of anxiety and depression with functional somatic syndromes confirmed that patients with CFS suffer from major depression or anxiety disorder at rates higher than healthy controls or patients with similar medical diseases [31]. It was also reported by a group analysing data from a WHO study of psychological problems in primary care that patients with stricter definitions of CFS requiring more additional symptoms had higher rates of depression and anxiety [32].

CFS in special groups

Post-viral fatigue

The modern history of CFS, often known in the UK as myalgic encephalomyelitis (ME), emphasizes the post-infectious nature of the illness. This is also reflected in the large immunological literature looking at various

immunological parameters, although recent reviews have not found any consistent findings in these studies [33]. Various infectious agents have been proposed as causes of CFS including *Brucella* Sp., *Borrelia burgdorferi*, Epstein–Barr virus, enteroviruses, retroviruses and human herpes virus 6 [34]. While there are many cross-sectional studies demonstrating such associations, from an epidemiological point of view, the studies that can answer this question best are prospective cohort studies and a study from White's group in London is discussed as an exemplar.

The prospective primary care study of common viral infections discussed earlier from London showed that subjects in the viral infection group were not more likely to develop CFS than controls. But this does not answer the question as to whether specific infections such as EBV have a link with CFS. White *et al.* [35] followed up 250 primary care patients presenting with glandular fever or upper respiratory tract infection (URTI). Forty-four percent had confirmed or probable EBV infections, 34% had non-EBV glandular fever and 22% had URTIs over a period of 6 months. The relative risk for the CDC-1994, the British and the authors' empirical definitions were 5.1, 3.9 and 4.6, respectively. The prevalence was greatest for the British criteria on account of it being least restrictive. The authors also calculated the population attributable risk of 9% in cases of glandular fever.

Cope *et al.* [36] found that the following factors predicted CFS 6 months later in patients who were given a diagnosis of viral infection by their general practitioner: fatigue, a cognitive style of attributing symptoms to psychological causes and sick certification. These factors were different from the predictors of psychiatric 'case-ness' which included past psychiatric history and psychological distress at the time of the viral illness. White *et al.* [37] found a positive Monospot test and lower physical fitness to predict CFS 6 months following glandular fever. They replicated Cope *et al.*'s finding that premorbid psychiatric history predicted post-viral mood disorders, other predictors being social adversity and 'emotional personality'. A recent study by Candy *et al.* [38] adds to this literature by showing that expectations that the individual would take a long time to recover, or that the illness would have serious consequences were associated with a poor outcome at 6 months.

High-risk occupational groups

Some occupational groups have traditionally been held to have higher rates of fatigue than control groups. These include health care workers, shift workers and airline pilots. Since much of this literature refers to fatigue as a symptom, it is unclear how applicable it is to CFS. Jason *et al.* [39] have looked at the epidemiology of CFS in health professionals. Using a multi-stage survey design,

they estimated a point prevalence of 1088 per 100 000 and lifetime prevalence of 1265 per 100 000 in nurses belonging to two nurses' organizations. They concluded that the prevalence of CFS in nurses is high in comparison to other community-based epidemiological studies. They speculate that it may be related to factors such as viruses in the work environment, shift work and other work-related stressors. Another study from the same group, a re-analysis of data from the community-based epidemiological study, showed that 15.6% of the CFS group were health care professionals. Given that the national proportion of health care workers in the US is 7.2%, the authors concluded that individuals with CFS were disproportionately represented in health care professions. It must be pointed out that this finding is by no means universal. Lawrie and Pelosi, in their community-based study, found that health workers were no more likely to be fatigued, chronically fatigued or satisfy CFS criteria than other occupational groups [40].

Gulf war veterans

There is an emerging literature on the Gulf war syndrome, a constellation of medically unexplained symptoms which occur in those who served in the Gulf war in the early 1990s. The current consensus is that while service in the Gulf does increase the risk of developing symptoms, the Gulf war syndrome is not a unique syndrome [41].

Some groups which have studied Gulf war veterans have looked for definitions of CFS in a Gulf war cohort. In a cross-sectional postal survey, Reid *et al.* [42] studied the prevalence of CFS according to a modified CDC-1994 definition derived from their questionnaire. They estimated a prevalence of 2.1, 0.7 and 1.8% in cohorts who had been deployed in the Gulf, in Bosnia and had served during the Gulf war but had not been deployed there, respectively. While the prevalence in the Gulf cohort is higher than in civilian populations, the high prevalence in the non-deployed group raises the question whether the higher prevalence might be related to military service. The authors speculate that the high prevalence may be related to the social class distribution of the military population. Kang *et al.* [43] used a 2-stage health survey to study the prevalence of post-traumatic stress disorder and CFS in 15 000 Gulf war veterans and 15 000 non-Gulf veteran controls. The prevalence in Gulf and non-Gulf veteran cohorts was 5.6 and 1.2%, respectively. The authors did not find differences between deployed groups in combat and non-combat roles.

Conclusion

Fatigue as a symptom is very common both in community and health care settings but medically unexplained

fatigue and CFS fulfilling various case definitions are relatively rare. Many of the reported epidemiological associations appear to be an artefact of the study setting. The epidemiological studies in CFS have so far largely concentrated on estimating the prevalence and associations. Probably due to the unhealthy physical versus psychological debate that has raged within this field and the heterogeneous nature of the samples, researchers have studied aetiological factors in isolation. The recent rapprochement in this area leads to the hope that researchers from various disciplines will pool their expertise to test sophisticated models as happens in other complex disorders [44]. There is also a need to include biological variables and study their interactions with psychosocial factors. Some emerging research also suggests that genetic epidemiology will be another fertile area of research in the future [45].

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