The Prevalence and Morbidity of Chronic Fatigue and Chronic Fatigue Syndrome: A Prospective Primary Care Study

ABSTRACT

Objectives. This study examined the prevalence and public health impact of chronic fatigue and chronic fatigue syndrome in primary care patients in England.

Methods. There were 2376 subjects, aged 18 through 45 years. Of 214 subjects who fulfilled criteria for chronic fatigue, 185 (86%) were interviewed in the case–control study. Measures included chronic fatigue, psychological morbidity, depression, anxiety, somatic symptoms, symptoms of chronic fatigue syndrome, functional impairment, and psychiatric disorder.

Results. The point prevalence of chronic fatigue was 11.3%, falling to 4.1% if comorbid psychological disorders were excluded. The point prevalence of chronic fatigue syndrome was 2.6%, falling to 0.5% if comorbid psychological disorders were excluded. Rates did not vary by social class. After adjustment for psychological disorder, being female was modestly associated with chronic fatigue. Functional impairment was profound and was associated with psychological disorder.

Conclusions. Both chronic fatigue and chronic fatigue syndrome are common in primary care patients and represent a considerable public health burden. Selection bias may account for previous suggestions of a link with higher socioeconomic status. (*Am J Public Health.* 1997;87: 1449–1455)

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Introduction

Chronic fatigue is a common problem in both primary and secondary care patients, with prevalences ranging from 10% to 40%, depending upon definition, duration, and setting.[1–4] Although frequent, fatigue is not always trivial, and it is associated with disability comparable to that found in other chronic illnesses.[2] Nevertheless, little attention has been paid to the epidemiology of chronic fatigue, perhaps because it is nonspecific, nonfatal, and difficult to measure. However, the recent emergence of the controversial condition known as chronic fatigue syndrome (CFS) has led to a reawakening of interest.

The epidemiology of CFS remains obscure. One of the principal causes of confusion is the absence of sound population-based studies.[5,6] Most attempts at providing prevalence data have been extrapolated from patients attending specialist clinics or based on physician identification or recall. Referral to specialist services is probably confounded by illness duration, psychological morbidity, and other aspects of illness behavior.[5–7] Identification by physicians is variable, reflecting the controversial nature of CFS and its frequent lack of acceptance by the medical community. A survey of Scottish general practitioners noted the extraordinary variation in the frequency with which general practitioners made the diagnosis, ranging from never to 1 in 60 new patient contacts.[8]

The first aim of the present study concerned possible links between common infections and the onset of chronic fatigue states. We were unable to demonstrate an effect of common infections encountered in primary care in the development of chronic fatigue and CFS in this sample of primary care patients.[9] In this paper we consider the prevalence of chronic fatigue and CFS. A companion paper considers the role of psychological disorder and somatic symptoms in chronic fatigue and CFS.[10]

Methods

Design

The study design, which has been reported in detail elsewhere,[9] is summarized in Figure 1. The study began in 1992 with a large-scale community screening (stage 1). Its purpose was to study the population prevalence of fatigue and psychological morbidity[11] and to determine preexposure vulnerability factors for the subsequent development of postinfectious fatigue.[9] All adults aged 18 through 45 registered with five general practices—two urban, two semiurban, and one rural, all located in the south of England—took part. In the following year (1993), all patients attending the participating general practices and in whom the general

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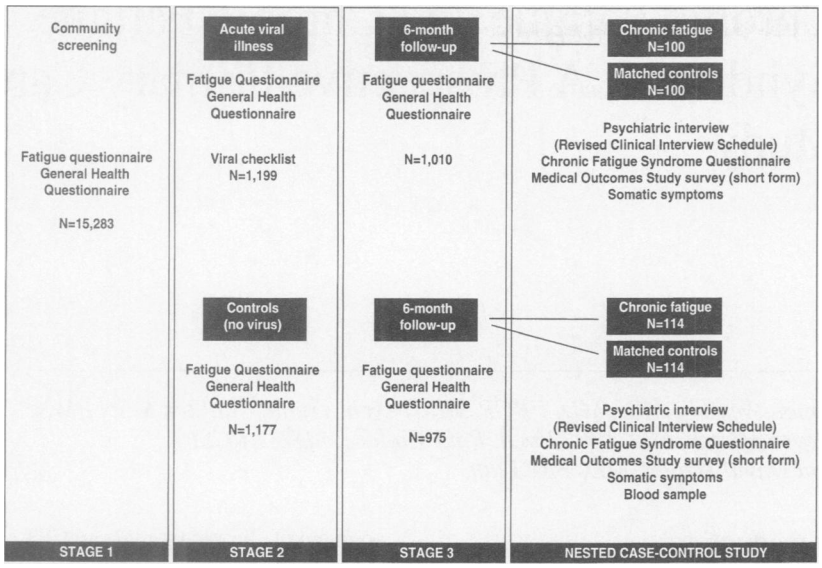

FIGURE 1—Design of a study of chronic fatigue and chronic fatigue syndrome among primary care patients in the United Kingdom, 1992 through 1993.

practitioner suspected a possible viral episode were invited to join the study (stage 2).[9] The next person within the appropriate age range (18 through 45) who presented to the general practitioner with any complaint not related to a possible infection was invited to join the nonviral cohort. Written consent was obtained from all participants.

All of those recruited (viral and nonviral cohorts) were sent a further questionnaire 6 months later. Those who reported fatigue at stage 2 (recruitment) and stage 3 (follow-up), who indicated at stage 3 that they had been fatigued for 6 months or more, and who scored above a predetermined cutoff for fatigue were asked to reattend for a full assessment. A control group, matched for age (to within 5 years) and gender, was recruited from members of both cohorts who were not fatigued 6 months later (data from the control group are not reported in this paper).

In this paper we report on the epidemiology of CFS as defined by a series of criteria and assessed in the final part of the study, the 6-month follow-up. We chose this time interval for several reasons. First, it was only at that stage that we could be certain that subjects were indeed chronically fatigued on the basis of previously obtained direct measures. Second, it was only at that stage that it was practical to carry out the detailed questionnaires, interviews, and laboratory testing necessary to determine whether the criteria for CFS had been met.

Instruments

The instruments used in this study were as follows:

1. *Chronic Fatigue Syndrome Questionnaire.*[12] This instrument is a 24-item scale developed to assess the presence and severity of physical, cognitive, behavioral, and affective components of fatigue.

2. *Revised Clinical Interview Schedule* (CIS-R).[13] This is an interview designed to record psychological morbidity in primary care patients. It is intended to be used by nonpsychiatric personnel and has a low observer bias. It was completed by the research nurses after appropriate training. Throughout this paper CIS-R scores have been calculated excluding the fatigue item normally contained within the interview. The CIS-R is used both to determine the presence or absence of psychiatric disorder and as a continuous measure of psychological morbidity.

3. *Fatigue Questionnaire.*[14] This is a self-report measure consisting of 11 questions measuring the subjective experience of mental and physical fatigability. Although fatigue is a continuous variable, we had previously determined a cutoff point that gave the best discrimination between those with and without clinically significant complaints of fatigue at interview.

4. *General Health Questionnaire (GHQ).*[15] The 12-item GHQ was used throughout the study as a self-report measure of psychological morbidity. There are two methods of scoring the questionnaire. Traditional scoring (0,0,1,1) is popular, and is used with a conventional cutoff of between 3 and 4 to determine the probable presence or absence of psychiatric disorder, conventionally referred to as "GHQ caseness." On the other hand, Likert scoring (1,2,3,4) approximates to a normal distribution in large samples and is thus used in this paper for statistical analysis. The GHQ avoids overlap with the somatic symptoms of psychological disorders.

5. *Medical Outcomes Study (MOS) Health Survey Short Form.*[16] Functional impairment was assessed on this 20-item questionnaire scored on a scale of 0 through 100 (higher scores indicate better health). Like fatigue, this is a continuous variable, but an arbitrary cutoff is required by all the current CFS definitions. A subject who described limitation for 6 months or more in ability to walk uphill, walk 100 yards, or perform activities of daily living without assistance was defined as functionally impaired.

6. *Somatic Symptom Checklist.* A checklist containing 32 somatic symptoms was modified from the Somatic Discomfort Questionnaire[17]; the checklist had previously been used in hospital-based studies of CFS.[18,19]

These instruments allowed data to be collected in a standardized fashion to enable the construction of all the current CFS definitions.

Definitions

We have employed three definitions of chronic fatigue as follows: (1) Chronic fatigue (CF) was defined as all cases of fatigue exceeding the predetermined cutoff with a duration of 6 months or more. It thus included all cases of idiopathic chronic fatigue and CFS. (2) Idiopathic chronic fatigue (ICF) was defined as chronic fatigue failing to meet the criteria for CFS.[20] (3) Chronic fatigue syndrome (CFS) was defined according to the operational criteria.

There is no consensus about case definitions for CFS. Our principal outcome measure was CFS as defined by the latest Centers for Disease Control and Prevention (CDC) criteria,[20] but we also used three other criteria. These were the

first criteria developed by the CDC in 1988,[21] the Oxford criteria proposed by United Kingdom researchers,[22] and the Australian criteria.[23] The 1988 CDC criteria were employed without the physical criteria (lymphadenopathy, pharyngitis, or low-grade fever) because of doubts about reliability.[24] We have also used the 1988 CDC criteria with and without psychological morbidity.

All fatigue case patients and nonfatigued control patients were screened for liver and thyroid function, hemoglobin, urea, electrolytes and C-reactive protein (CRP). All possible cases of CFS underwent a further review of general practice records, supplemented by further interviews with the patient.

Statistics

Likert scoring for the GHQ and the Fatigue Questionnaire produces a normal distribution in population or primary care samples. The MOS Short Form scores are known to produce skewed distributions [25] but approximated to a normal distribution after log transformation for the purpose of logistic regression. Parametric comparisons of means were made by *t* tests; nonparametric means were compared by the Mann-Whitney test. All odds ratios are cited with 95% confidence limits.

The design of this large-scale study (a nested case–control study contained within a larger cohort study) means that one statistical issue needs to be considered in more detail. The original study design called for the recruitment of patients presenting with viral infections and an equivalent random sample of all other clinic attenders matched for age and sex. We have already noted that no difference was found between the two cohorts in the risk of CF and CFS.[9] We therefore felt justified in combining the two cohorts for the purpose of increased power, using the appropriate weighting for sample fraction[26] based on the total expected number of presentations in the two strata (viral and nonviral) obtained from the latest National Morbidity Survey of UK general practice.[27]

Response Rates

A total of 2376 subjects (1199 viral and 1177 nonviral) were recruited at stage 2; 2327 (98%) completed the questionnaire measures and 1544 (65%) had previously completed stage 1 measures of fatigue and psychological morbidity.

At 6-month follow-up, 1985 completed questionnaires were received, a follow-up rate of 84% (viral 84.2%, nonviral 82.8%). Nonresponders were more likely to be male (35.8% vs 29.7%, $\chi^2 = 5.8$, $P = .01$). Nonresponders were also more likely to have psychiatric disorder as measured by the GHQ (48.0% vs 38.9%, $\chi^2 = 5.28$, $P = .02$) and to score above the cutoff on the Fatigue Questionnaire (46.8% vs 42.0%, $\chi^2 = 1.44$, $P = .23$) when studied as part of the community screening that preceded the main study.[11] Of the 214 subjects who fulfilled the criteria for CF (100 viral, 114 nonviral), 185 (86%) were interviewed. Those who took part in the detailed interviews did not differ from nonresponders in total fatigue or GHQ scores. Nonfatigued control subjects (n = 193) were also interviewed as part of the nested case–control study (to be reported elsewhere) and no cases of CFS were found. The response rates for each stage are given in Table 1.

TABLE 1—Response Rates at Stage 2 (Recruitment) and Stage 3 (6-Month Follow-Up and Nested Case–Control Study) of a United Kingdom Primary Care Study of Chronic Fatigue and Chronic Fatigue Syndrome

	Viral Cohort[a]		Nonviral Cohort[b]	
Stage 2: recruitment, n	1199		1177	
Stage 3: 6-month follow-up, no. questionnaires obtained (%)	1010 (84%)		975 (83%)	
	Case Patients[c]	**Control Patients**	**Case Patients[c]**	**Control Patients**
Stage 3: nested case–control study, n	100	100	114	114
Nested case–control study, no. successfully interviewed (%)	89 (89%)	95 (95%)	96 (84%)	98 (86%)

[a]Patients presenting with symptoms of a viral infection.
[b]Patients presenting to the same doctor on the same day for any other reason.
[c]Patients meeting the criteria for chronic fatigue.

All the potential cases of CFS or ICF thus came from the 214 cases of CF. However, 29 of the 214 (14%) were not given the detailed interviews, questionnaires, and physical investigations necessary to establish CFS, usually because they had moved from the area and could not be traced. There were no differences in demographic characteristics, Fatigue Questionnaire scores, or GHQ scores between the 185 subjects who were fully investigated and the 29 who only completed the GHQ and the Fatigue Questionnaire. For calculations of the prevalence and confidence limits for ICF and CFS, where the denominator is the entire cohort (n = 1985), we have assumed that the 29 nonrespondents shared the same characteristics as the 185 fully assessed subjects.

Results

The prevalence of CF was 9.9% (95% confidence interval [CI] = 8.1%, 11.7%) in the viral cohort and 11.7% (95% CI = 9.7%, 13.7%) in the nonviral cohort. The individual numbers for each category in the two strata have already been reported.[9] Table 2 gives the crude total numbers. The overall prevalence figures take into account the weighting of the two strata (see Statistics section), as do the confidence intervals. The overall prevalence of CF is therefore 11.3% (95% CI = 9.6%, 12.9%), weighted according to the stratified sample (viral versus nonviral) and with the confidence interval calculated using the standard errors for a stratified sample. We also present the prevalence of CF without comorbid psychological disorder. Psychological disorder was assessed from the CIS-R scores, adjusted for the missing interviews (13%). Thus 4.1% (95% CI = 3.0%, 5.1%) of the sample were subjects with CF without current psychological disorder. Using the results of the psychological questionnaire (the GHQ) gave a figure of 3.0% (95% CI = 2.3%, 3.7%) for CF in the absence of psychological disorder. The questionnaire is less accurate than a direct interview at classifying psychological disorder, but there were no missing data.

Table 2 contains similar data for ICF and CFS defined by the various criteria. The overall prevalence of CFS (defined by 1994 CDC criteria) was 2.6%

TABLE 2—Prevalence of Chronic Fatigue and Chronic Fatigue Syndrome at 6-Month Follow-up in United Kingdom Primary Care Study (n = 1985)

Criteria	Overall Prevalence, % (95% CI)	Prevalence without Comorbid Psychological Disorder, % (95% CI)
Chronic fatigue	11.3 (9.6, 12.9)	4.1 (3.0, 5.1)
Idiopathic chronic fatigue	9.0 (7.5, 10.5)	3.6 (2.7, 4.6)
Chronic fatigue syndrome		
CDC (1994)[20]	2.6 (1.7, 3.4)	0.5 (0.1, 0.3)
Oxford[22]	2.2 (1.4, 3.0)	0.7 (0.3, 1.1)
Australian[23]	1.4 (0.8, 2.0)	0.2 (0.1, 0.5)
CDC (1988)[21]	1.2 (0.5, 1.8)	0.1 (0.0, 0.5)

Note. Proportions and confidence intervals (CIs) are adjusted for stratified sample and missing values. CDC = Centers for Disease Control and Prevention.

(95% CI = 1.7%, 3.4%), weighted by stratum size and adjusted for missing values. The prevalence of "pure" (noncomorbid) CFS was 0.5% (95% CI = 0.1%, 0.3%).

A weak and nonsignificant negative association was noted between chronic fatigue at stage 3 and social class, assessed by the standard Registrar General's classification,[28] with an excess in the lowest socioeconomic group (social class 5) compared with other categories. The overall test for trend was nonsignificant ($\chi^2 = 1.69$, $df = 1$, $P = .19$). There was a weak but significant negative correlation between age of leaving full-time education (a proxy for social class) and chronic fatigue at stage 3 ($r = -.11$, 95% CI = $-.05$ to $-.16$, $P < .01$). There was, as expected, a strong and consistent negative association between psychological morbidity (measured by the CIS-R) and social class (Mantel-Haenszel test for linear association = 10.12, $df = 1$, $P = .01$).

No social class trend was visible for CFS. There was no suggestion of any excess among the upper social classes (χ^2 for trend = 0.56, $df = 1$, $P = .46$).

At follow-up, 189 men (32%) and 504 women (36%) scored above the cutoff for fatigue of any duration (odds ratio [OR] = 1.2, 95% CI = 1.0, 1.5; $P = .05$). This modest effect disappeared when adjusted for psychological morbidity (OR = 1.0, 95% CI = 0.8, 1.3; $P = .69$). For CF, a larger gender effect was seen: 47 men (8%) and 166 women (12%) fulfilled the criteria for CF (OR = 1.6, 95% CI = 1.1, 2.2; $P = .01$). This effect remained elevated when adjusted for psychological morbidity (OR [Mantel-Haenszel] = 1.4, 95% CI = 1.0, 2.0; $P = .06$). The effect was largest for CFS (OR = 2.8, 95% CI = 1.0, 8.1; $P = .03$). As with CF, this effect decreased (OR = 1.8, 95% CI = 0.6, 5.5; $P = .27$) when adjusted for psychological disorder but was no longer significant. Comparing CFS with CF showed a modest but nonsignificant excess of females among the CFS case patients (CFS by 1994 CDC criteria vs CF; OR = 1.6, 95% CI = 0.6, 4.5).

Functional impairment was measured by the MOS Short Form subscales for role performance, social function, health perception, and physical limitations. Subjects fulfilling criteria for CF, ICF, and CFS all showed worse functional impairment than nonfatigued control subjects (Table 3). Possible confounding of the link between fatigue syndromes and functional impairment by psychological morbidity was investigated by means of stratified analyses. A linear relationship was observed between functional impairment and psychological morbidity as measured by the CIS-R and grouped into four strata (Table 4). Linear regression confirmed the results of visual inspection: there was a substantial and significant association between psychological morbidity and functional impairment within the fatigued group, with significant values for all the regression equations of $P < .001$.

All CF case patients were given a simple biochemical screening. Although a few had results outside the normal range (usually for CRP or thyroid function), in only three were there abnormalities on biochemical screening that potentially could have a role in the etiology of fatigue syndromes—definite hypothyroidism, hyperthyroidism, and possible hypopituitarism. All three were excluded. Three case patients who otherwise fulfilled CFS criteria were excluded on the basis of clinical records (manic depression, recent subarachnoid hemorrhage, hypothyroidism).

Discussion

Prevalence of Chronic Fatigue and Chronic Fatigue Syndrome

CF is common in primary care. Our figure of 11.3% corresponds to the 11.2% reported by McDonald and colleagues in their cross-sectional survey of a single UK practice.[29] CFS, however defined, was less common, with point prevalences ranging from 0.1% (unmodified 1988 CDC criteria) to 2.6% (1994 CDC criteria).

These figures for CFS are between ten and a hundred times higher than most previous estimates of prevalence. Those estimates come mainly from studies based either on medical recognition and referral (tertiary care or sentinel physician studies) or on the recall of known cases by key informants (general practitioners). Hence an example of the former, the CDC study,[30] found prevalences of between 4 and 11 per 100 000, while two examples of the latter in Australia[23] and Scotland[31] found prevalences of 37 and 130 per 100 000, respectively, emphasizing just how few patients who could be classified as having CFS are labeled as having CFS or seek a specialist's help. These results suggest a powerful role of selection bias in previous studies, almost all of which are based on tertiary care samples of patients who have frequently made their own diagnosis before seeking a specialist's help and may be atypical and unrepresentative of CFS patients. We also draw attention to the lack of any socioeconomic gradient for CF or CFS, in contrast to the usual finding of a pronounced excess of upper social classes in tertiary care studies. These social class and attributional differences are explored further in a direct comparison of primary care and specialist samples.[32]

We are aware of only two other published large-scale systematic surveys of the prevalence of CFS. Bates and colleagues[33] screened consecutive attenders in a US urban hospital-based general medicine practice. They found higher prevalences of CF than we found in the present study (27% of those attending a primary care clinic had substantial fatigue lasting more than 6 months and interfering with daily life), but lower prevalences of CFS (0.3% [1988 CDC criteria], 0.4% [Oxford criteria], and 1.0% [Australian criteria]). This may reflect higher rates of

TABLE 3—Functional Impairment among Patients in a United Kingdom Primary Care Study of Chronic Fatigue and Chronic Fatigue Syndrome, as Measured by Scores on the Medical Outcomes Study Short Form[16]

	Role Performance		Social Function		Health Perception		Physical Limitations	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Control patients	89.1	(85.9, 92.5)	77.0	(73.2, 80.8)	73.5	(70.6, 76.3)	89.3	(86.6, 92.0)
Patients with CF	68.8	(63.2, 74.5)	60.8	(56.3, 65.4)	51.4	(47.8, 55.1)	74.4	(70.1, 78.7)
Patients with idiopathic CF	75.2	(69.6, 80.8)	62.6	(57.6, 67.6)	55.2	(51.4, 59.1)	81.6	(77.6, 85.7)
Patients with CFS	40.3	(26.1, 54.5)	50.0	(39.1, 60.9)	34.4	(27.1, 41.7)	39.5	(31.4, 47.6)

Note. Lower scores indicate greater impairment. CI = confidence interval; CF = chronic fatigue; CFS = chronic fatigue syndrome.

TABLE 4—The Association between Psychological Morbidity and Functional Impairment as Measured by Scores on the Medical Outcomes Study Short Form[16] among Patients with Chronic Fatigue in a United Kingdom Primary Care Study

	Role Performance		Social Function		Health Perception		Physical Limitations	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Patients with no CF, no psychological disorder	91.7	(88.8, 95.7)	82.4	(78.2, 86.5)	78.1	(74.7, 81.5)	91.4	(88.1, 94.7)
Patients with CF, no psychological disorder	80.1	(73.8, 88.1)	67.8	(60.6, 75.0)	66.3	(61.1, 71.6)	86.0	(81.3, 90.6)
Patients with CF, low psychological morbidity	77.8	(70.8, 85.8)	64.4	(57.8, 71.0)	56.0	(51.3, 60.7)	79.3	(73.2, 85.3)
Patients with CF, moderate psychological morbidity	61.7	(47.0, 75.6)	67.5	(57.3, 77.7)	44.6	(35.6, 53.6)	69.5	(61.0, 78.1)
Patients with CF, high psychological morbidity	53.6	(38.5, 68.6)	44.6	(34.2, 55.0)	37.6	(30.2, 45.1)	58.3	(45.7, 71.0)
P for trend (linear regression)		<.001		<.001		<.001		<.001

Note. Psychological morbidity was measured by the Revised Clinical Interview Schedule (CIS-R).[13] CI = confidence interval; CF = chronic fatigue.

physical exclusions, which in turn reflect the differences between US ambulatory care patients and UK primary care patients, the latter being closer to a population sample than the former. Buchwald and colleagues[34] studied the prevalence of CFS in members of a single health maintenance organization in Washington State. Using the 1988 CDC criteria, they estimated the prevalence of CFS to lie between 0.07% and 0.4%—very similar to the figures we obtained using the same criteria.

Functional Impairment

Functional impairment in CF patients was considerable, extending the results of Kroenke and colleagues in US ambulatory care patients. Patients with CF had worse mental health, more bodily pain, worse perception of their health, and greater physical impairment than nonfatigued control patients. For comparison, the data from the MOS showed higher scores (indicating better functioning) for subjects with diabetes, hypertension, and arthritis. Only patients with angina and advanced coronary artery disease scored lower than patients with CF.

Functional impairment in patients with CFS was even worse—their mean score of 40 for physical functioning on the MOS Short Form is substantially worse than those recorded in the MOS for patients with a variety of chronic medical conditions.[35] However, that functional impairment in CFS is profound is both unsurprising and tautologous, since one of the main differences between CF and CFS is functional impairment.

We also noted that functional impairment was closely related to psychological morbidity. A similar link between psychological comorbidity and functional impairment was noted in the multinational World Health Organization study of mental disorder in primary care patients,[36] which used the *International Classification of Diseases* (10th revision) diagnosis of neurasthenia, a concept with many similarities to CFS.[37]

Gender

There were more female than male subjects at all stages of the study. This situation was largely influenced by differences in illness behavior, since in this study, as elsewhere, females made up the majority of general practice patients.[38] The female excess among all case patients with fatigue disappeared once adjustment was made for psychological disorder, as in the population study by Chen.[39] A modest female excess was noted for chronic fatigue, even after adjustment for psychological disorder. This finding is broadly in line with the epidemiological literature, in which odds ratios for females compared with males usually lie between 1.2 and 1.7.[6] The modest and nonsignificant increase in the proportion of females among patients with CF as compared with CFS confirms our earlier finding that introducing some of the criteria required for the diagnosis of CFS (such as severity and duration) increased the proportion of females to males.[11] Nevertheless, this

cannot by itself explain the notable excess of female patients with CFS in some specialist studies, which is probably related to selection bias.[40]

Conclusion

Our results add to the growing number of studies confirming the lack of utility of anything other than the most basic physical investigations in diagnosing chronic fatigue, especially in this age group (18 through 45 years).[41–44] Only Elnicki and colleagues differ,[45] perhaps because those authors used a minimum duration of only 1 month, in contrast to the other studies. Alternative diagnoses for chronic fatigue syndrome were also relatively unusual, in contrast to the findings of Bates and colleagues.[33] This probably represents the age restrictions of this cohort and the differences between primary care in the United Kingdom and ambulatory care in the United States. The yield and utility of further investigations in diagnosing CFS is dependent upon setting and duration.

We have confirmed that chronic fatigue is common in primary care patients and presented evidence that chronic fatigue syndrome is far from rare. Both are associated with substantial functional impairment and may thus be important, albeit neglected, public health problems. □

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