Psychological Symptoms, Somatic Symptoms, and Psychiatric Disorder in Chronic Fatigue and Chronic Fatigue Syndrome: A Prospective Study in the Primary Care Setting

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Objective: *This study assessed relationships among psychological symptoms, past and current psychiatric disorder, functional impairment, somatic symptoms, chronic fatigue, and chronic fatigue syndrome.* *Method:* *A prospective cohort study was followed by a nested case-control study. The subjects, aged 18–45 years, had been in primary care for either clinical viral infections or a range of other problems. Questionnaire measures of fatigue and psychological symptoms were completed by 1,985 subjects 6 months later; 214 subjects with chronic fatigue were then compared with 214 matched subjects without fatigue. Assessments were made with questionnaires, interviews, and medical records of fatigue, somatic symptoms, psychiatric disorder, and functional impairment.* *Results:* *Subjects with chronic fatigue were at greater risk than those without chronic fatigue for current psychiatric disorder assessed by standardized interview (60% versus 19%) or by questionnaire (71% versus 31%). Chronic fatigue subjects were more likely to have received psychotropic medication or experienced psychiatric disorder in the past. There was a trend for previous psychiatric disorder to be associated with comorbid rather than noncomorbid chronic fatigue. Most subjects with chronic fatigue syndrome also had current psychiatric disorder when assessed by interview (75%) or questionnaire (78%). Both the prevalence and incidence of chronic fatigue syndrome were associated with measures of previous psychiatric disorder. The number of symptoms suggested as characteristic of chronic fatigue syndrome was closely related to the total number of somatic symptoms and to measures of psychiatric disorder. Only postexertion malaise, muscle weakness, and myalgia were significantly more likely to be observed in chronic fatigue syndrome than in chronic fatigue.* *Conclusions:* *Most subjects with chronic fatigue or chronic fatigue syndrome in primary care also meet criteria for a current psychiatric disorder. Both chronic fatigue and chronic fatigue syndrome are associated with previous psychiatric disorder, partly explained by high rates of current psychiatric disorder. The symptoms thought to represent a specific process in chronic fatigue syndrome may be related to the joint experience of somatic and psychological distress.*

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The nature of chronic fatigue syndrome remains subject to controversy. Perhaps the most contentious area is the relation between chronic fatigue syndrome and psychiatric disorder. Several controlled studies have reported high rates of psychiatric disorder in subjects with chronic fatigue syndrome, in excess of rates found in physically ill control subjects (1–3). However, both length of illness and referral to a specialist unit may be associated with increased psychiatric disorder. Confusion also exists about the role of previous psychiatric disorder and/or previous fatigue, reflected in all of the current definitions of the syndrome. Two of the three current sets of criteria insist that fatigue must be of new onset, yet they do not say how this is to be assessed. Studies of se-

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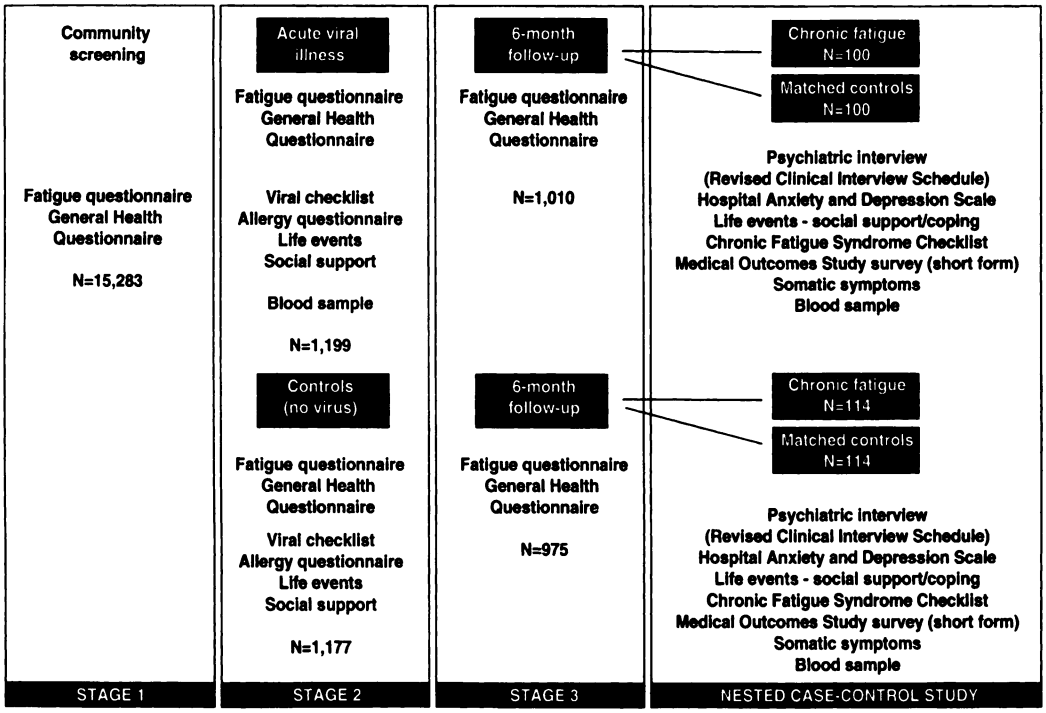
FIGURE 1. Postinfection Fatigue: Plan of the Study



lected referral populations are unlikely to elucidate the true role of previous and current psychiatric disorder in chronic fatigue syndrome.

In this article we report a primary-care-based study of persons not seeking help under the label of chronic fatigue syndrome. The first aim of the study was the relation in primary care between common infections and the various syndromes of chronic fatigue. We reported previously that common community-acquired infections play little role in the development of fatigue, chronic fatigue, and chronic fatigue syndrome in primary care (4). Our second report considered the prevalence, social demography, and public health impact of chronic fatigue and chronic fatigue syndrome (S. Wessely et al., manuscript submitted for publication). In this article we now consider the relations among psychological symptoms, somatic symptoms, psychiatric disorder, chronic fatigue, and chronic fatigue syndrome.

METHOD

This was a three-stage cohort study with a nested case-control study in the final stage. The initial phase (stage 1) consisted of a postal survey of all adults aged 18–34 years who were registered with six general practices in the south of England. The results have been reported elsewhere (5).

The main study then followed the traditional design of a cohort study (4). During the 12 months following the initial screening, all general practice patients in whom the general practitioner suspected a possible viral episode were invited to join the study. Subjects with nonviral illness were recruited from the next persons within the appropriate age band (to the nearest 5 years) presenting to the general practitioner with any complaint not related to a possible infection. The exact diagnoses of these subjects with nonviral illness were presented in our previous paper (4)—they represent the typical range of problems seen in a young adult population in U.K. primary care. All gave written informed consent.

Stage 3 consisted of following up both cohorts, followed by a nested case-control study. All subjects recruited at stage 2, whether the initial illness was viral or nonviral, were sent a further questionnaire 6 months later. Those who had been continuously fatigued during that time, and who scored above a predetermined cutoff for fatigue, were asked to return for a full assessment. Those without alternative medical diagnoses were the chronic fatigue cases. A matched sample of those who were no longer fatigued were also asked to return for a full assessment. All of the subjects with chronic fatigue, and the matched control subjects without fatigue, constituted the subjects for the case-control study that was nested within the larger cohort study.

In the first analysis of this study, we compared the subjects who initially presented with a viral infection to those who presented with any other complaint (4). Since no differences between the two groups were found in any outcome measure, we have now joined the two cohorts, viral and nonviral, to increase the study power.

Instruments

Figure 1 shows the instruments used at all stages of the study. Further details of the instruments relevant to this report are given below.

1. Fatigue questionnaire (6): a self-report measure developed for the study of chronic fatigue syndrome (1). It has been validated by us in primary care (6) but awaits independent validation. It consists of 11 items covering the physical and mental aspects of fatigue. Additional questions concern the duration of fatigue, the percentage of time during the day that the respondent felt tired, and two questions on muscle pain at rest and after exercise.

2. General Health Questionnaire (7): a well-validated questionnaire measure of psychological symptoms. We used Likert scoring, which follows a normal distribution in large samples. Traditional scoring was used, in which "caseness" is a score of 4 or above (8). Those scoring above this cutoff are sometimes called "General Health Questionnaire cases," but we prefer to use the term "subjects with psychiatric disorder (General Health Questionnaire)."

TABLE 1. Current Psychiatric Disorder, According to Data on the General Health Questionnaire, in Subjects With and Without Chronic Fatigue

Subject Group	Subjects With Current Psychiatric Disorder		Comparison With Group With No Chronic Fatigue		General Health Questionnaire Score		
	N	%	Odds Ratio	95% CI[a]	Mean	SD	95% CI[a]
No chronic fatigue (N=1,771)	550	31			24.5	5.9	24.3–24.8
Total with chronic fatigue (N=214)[b]	152	71	5.5*	4.0–7.5	31.5	6.8	30.4–32.6
Idiopathic chronic fatigue (N=149)	107	72	5.5*	3.5–8.7	31.3	6.8	30.2–32.4
Chronic fatigue syndrome (N=36)	28	78	6.7*	3.0–14.7	33.1	7.7	29.8–36.3

[a]CI=confidence interval.
[b]Includes 29 subjects who met the criteria for chronic fatigue but did not receive a standard psychiatric interview.
*p<0.001.

3. Chronic Fatigue Syndrome Checklist (9): a 24-item scale developed to assess the presence and severity of physical, cognitive, behavioral, and affective components of fatigue. The scale was devised for this study, and it also awaits independent validation.

4. Revised Clinical Interview Schedule (10): an interview designed to record psychiatric disorder in community and primary care studies (11). It is used by nonpsychiatric personnel and has a low observer bias. It was completed by the research nurses after appropriate training. Throughout this report, Revised Clinical Interview Schedule scores have been calculated excluding the fatigue item normally contained within the interview.

5. Hospital Anxiety and Depression Scale (12): a self-report questionnaire developed to measure current anxiety and depression in medical settings. Cutoffs are provided for probable and definite depression and anxiety disorders.

6. Medical Outcomes Study General Health Survey—Short Form (13): a 20-item questionnaire measuring functional impairment, scored on a scale of 0–100 (the higher score indicating better health), recommended for studies of chronic fatigue syndrome (14, 15). Although functional impairment is a dimensional measure, it was necessary to choose a cutoff in order to fulfill the latest case definition for chronic fatigue syndrome, which states that functional impairment must be "substantial," without further elaboration (15). We defined impairment as present when a subject answered positively to being limited for 6 months or more on any one of the following four dimensions asked about in the Medical Outcomes Study survey: impairment in moderate activities, walking uphill, or walking 100 yards or needing simple aids to daily living.

7. Somatic symptom checklist: a checklist containing 32 somatic symptoms, modified from the Somatic Discomfort Questionnaire (16) and previously used in hospital-based studies of chronic fatigue syndrome (1, 17).

8. Subjects were also asked about previous episodes of possible psychiatric disorder and previous prescriptions of psychotropic drugs. All general practitioner records were read for any previous mention of psychiatric disorders or psychotropic prescriptions before the current episode. Stage 3 subjects and matched control subjects were interviewed with the Revised Clinical Interview Schedule.

Syndromes

We used three definitions of chronic fatigue: 1) chronic fatigue: all chronic fatigue (idiopathic chronic fatigue and chronic fatigue syndrome), 2) idiopathic chronic fatigue: chronic fatigue failing to meet criteria for chronic fatigue syndrome (15), and 3) chronic fatigue syndrome: chronic fatigue syndrome according to the operational criteria.

Chronic fatigue was defined as fatigue scored above a predetermined cutoff point (6) and lasting for 6 months or more. There are at least three case definitions of chronic fatigue syndrome. We used the 1994 revised Centers for Disease Control (CDC) criteria (15). Data were also collected on three further case definitions: the original CDC 1988 definition ("Holmes criteria") (18), the U.K. ("Oxford") criteria (19), and the Australian criteria (20). No differences emerged in any of the principal analyses for any of the other case definitions, other than a general trend for the CDC 1988 criteria to have the closest association with previous and current psychiatric disorder (data available from the first author on request).

New (incident) cases of chronic fatigue and chronic fatigue syndrome were obtained by restricting the cohort to the minority of those who were not fatigue cases during the community screening (stage 1).

Physical illness was assessed by patient self-report and general practitioner records. All subjects with chronic fatigue and control subjects were also screened with tests of liver and thyroid function, hemoglobin, urea, electrolytes, and C-reactive protein. In contrast to hospital studies, few potential cases were excluded because of coexisting physical illness that could explain the fatigue syndrome (S. Wessely et al., manuscript submitted for publication).

Statistical Analysis

Likert scoring for the General Health Questionnaire and the fatigue questionnaires produces a normal distribution in epidemiological samples, permitting the use of parametric tests. Odds ratios and relative risks are cited with 95% confidence limits.

Because the case subjects and control subjects in the nested case-control study were matched for sex, theoretically, the correct analysis for the calculation of odds ratios involves a discordant pair analysis. However, this analysis did not produce any difference in the pattern of results from that of the more customary methods of obtaining odds ratios and relative risks (because, contrary to expectations, sex was not an important confounding factor). For that reason odds ratios in the case-control study were calculated using all of the available pairs, thus increasing the study power.

Response Rates

Response rates have already been discussed in detail (4, 5). In brief, 2,376 subjects were recruited (1,199 with viral and 1,177 with nonviral illness) at stage 2. Ninety-eight percent (N=2,327) completed all or nearly all of the questionnaire measures. Sixty-five percent (N=1,544) had previously completed stage 1 measures of fatigue and psychological symptoms.

At stage 3, 1,985 completed questionnaires were received, a response rate of 84%. Nonresponders were more likely than responders to be male (35.8% compared to 29.7%; χ^2=5.80, df=1, p=0.01). When previously assessed at stage 1, persons who were nonresponders at stage 3 were more likely to have exceeded the cutoffs on the General Health Questionnaire (48.0% compared to 38.9%; χ^2=5.28, df=1, p=0.02) and the fatigue questionnaire (46.8% compared to 42.0%; χ^2=1.44, df=1, p=0.23).

Of the 214 persons who met the criteria for chronic fatigue, 185 (86.4%) were interviewed. Of the 214 matched control subjects, 193 (90.2%) were interviewed. Those who took part in the detailed interviews did not differ in total fatigue or General Health Questionnaire scores from the nonresponders. Ten subjects completed some or all of the questionnaire measures but did not receive a standardized interview because of time pressures.

TABLE 2. Current Psychiatric Disorder, According to Data on the Revised Clinical Interview Schedule and the Hospital Anxiety and Depression Scale, in Subjects With and Without Chronic Fatigue

Subject Group	Subjects With Current Psychiatric Disorder		Comparison With Group With No Chronic Fatigue		Score on Revised Clinical Interview Schedule			Hospital Anxiety and Depression Scale					
								Depression Score			Anxiety Score		
	N	%	Odds Ratio	95% CI[a]	Mean	SD	95% CI[a]	Mean	SD	95% CI[a]	Mean	SD	95% CI[a]
No chronic fatigue (N=193)	37	19			6.3	6.8	5.2–7.2	4.4	4.1	3.8–5.0	5.8	3.9	5.3–6.4
Total with chronic fatigue (N=185)	111	60	6.4*	4.0–10.1	15.1	9.6	13.7–16.5	9.0	4.5	8.3–9.7	9.9	4.0	9.3–10.4
Idiopathic chronic fatigue (N=149)	85	57	6.1*	3.7–9.8	14.6	9.7	13.1–16.2	8.5	4.5	7.8–9.2	9.8	4.0	9.2–10.5
Chronic fatigue syndrome (N=36)	27	75	5.5*	2.5–12.1	17.4	8.4	14.5–20.2	11.5	4.4	10.0–13.0	10.3	4.3	8.9–11.8

[a]CI=confidence interval.
*p<0.001.

RESULTS

Current Psychiatric Disorder

A variety of measures of previous and current psychiatric disorder and psychological symptoms were available in this study. These are grouped under two headings. The first are variables available for the complete cohort (N=1,985), in which the General Health Questionnaire measured general psychological symptoms. The second are more detailed variables only available within the case-control study. Psychiatric disorder was measured by standardized interview (Revised Clinical Interview Schedule) and both self-report and general practitioner data on previous psychiatric diagnoses and use of psychotropic medication. Anxiety and depressive symptoms were measured by the Hospital Anxiety and Depression Scale.

Psychological symptoms and psychiatric disorders (General Health Questionnaire) as assessed across the whole cohort are shown in table 1. The total (N=185) of idiopathic chronic fatigue and chronic fatigue syndrome does not equal chronic fatigue (N=214) because 29 subjects failed to complete the detailed questionnaires. The General Health Questionnaires and fatigue questionnaires available on these 29 subjects were insufficient to assign them to the category of idiopathic chronic fatigue or chronic fatigue syndrome. There were no differences in psychological symptoms or fatigue between the 185 responders and the 29 nonresponders, and thus the proportions reported are accurate. Subjects with new (incident) cases of chronic fatigue were also more likely than subjects without chronic fatigue to have current psychiatric disorder according to the General Health Questionnaire (79.4% versus 27.5%; odds ratio=10.1, 95% confidence interval=4.0–26.0, p<0.001) or according to the Revised Clinical Interview Schedule (58.1% versus 12.2%; odds ratio=9.9, 95% confidence interval=3.9–25.3, p<0.001).

Further comparisons followed the nested case-control design, in which control subjects were a one-to-one age- and sex-matched sample chosen from the stage 3 subjects without fatigue. Table 2 gives the results of direct psychiatric interviews for the 378 subjects successfully interviewed.

Of the subjects with chronic fatigue, 101 (54.6%) were probably depressed and 56 (30.3%) were definitely depressed according to the depression subscale of the Hospital Anxiety and Depression Scale. These proportions fell to 64 (34.6%) for probable and 31 (16.8%) for definite depression when the fatigue question was removed from the Hospital Anxiety and Depression Scale. Similarly, 113 (61.1%) had probable and 81 (43.8%) had definite anxiety according to the anxiety subscale of the Hospital Anxiety and Depression Scale.

Of the 36 subjects with chronic fatigue syndrome, 29 (80.6%) had probable and 17 (47.2%) had definite depression according to the Hospital Anxiety and Depression Scale subscale. These proportions fell to 16 (44.4%) and 10 (27.8%) when the fatigue question was excluded. Twenty-four (66.7%) had probable and 19 (52.8%) had definite anxiety disorders.

The majority (N=20, 70%) of the chronic fatigue syndrome cases were already probable cases of psychiatric disorder (General Health Questionnaire) at stage 1. Given the close association between fatigue and psychological symptoms, it is not surprising that nearly all of these subjects were also already complaining of excessive fatigue at the same stage. Hence, there were only six incident cases of chronic fatigue syndrome according to the CDC 1994 criteria, three cases according to the Australian criteria, three cases according to the Oxford criteria, and none according to the CDC 1988 criteria. These subjects with new cases of chronic fatigue syndrome (CDC 1994 criteria) were also more likely than subjects without chronic fatigue syndrome to have a current psychiatric disorder according to the General Health Questionnaire (66.7% versus 25.1%; odds ratio=6.0, 95% confidence interval=1.1–32.9, p=0.02) or according to the Revised Clinical Interview Schedule (66.7% versus 22.0%; odds ratio=7.2, 95% confidence interval=1.2–41.3, p=0.01).

TABLE 3. Previous Psychiatric Disorder, According to Self-Report or General Practitioner Notes, in Subjects With and Without Chronic Fatigue

Subject Group	Subjects With Previous Psychiatric Disorder		Comparison With Group With No Chronic Fatigue		Subjects With Previous Psychotropic Prescription		Comparison With Group With No Chronic Fatigue	
	N	%	Odds Ratio	95% CI[a]	N	%	Odds Ratio	95% CI[a]
No chronic fatigue (N=182)	59	32			26	14		
Total with chronic fatigue (N=178)	103	58	2.9**	1.8–4.4	59	34	3.1**	1.8–5.4
Idiopathic chronic fatigue (N=144)	83	57	2.1**	1.4–3.3	46	32	2.1*	1.3–3.4
Chronic fatigue syndrome (N=34)	23	68	2.8*	1.3–6.0	15	43	2.8*	1.4–5.7

[a]CI=confidence interval.
*p<0.01. **p<0.001.

TABLE 4. Relation Between Chronic Fatigue and Previous and Current Psychiatric Disorder

Subject Group	Subjects With Psychiatric Disorder at Stage 1 of Study[a]		Subjects With Previous Psychiatric Disorder[b]		Subjects With Previous Psychotropic Prescription[b]	
	N	%	N	%	N	%
No chronic fatigue, no psychiatric morbidity (N=120)	23	25	27	25	12	11
Chronic fatigue						
No psychiatric morbidity (N=74)	29	52	23	34	6	9
Low psychiatric morbidity (N=91)	45	59	45	51	30	34
Moderate psychiatric morbidity (N=32)	16	76	23	72	11	36
High psychiatric morbidity (N=35)	18	78	26	74	16	50

[a]According to the General Health Questionnaire.
[b]According to self-report or general practitioner records.

Previous Psychiatric Disorder

Subjects with chronic fatigue were more likely than subjects without chronic fatigue to report consulting a doctor for any emotional reason before the current episode (54.8% versus 31.9%; odds ratio=2.6, 95% confidence interval=1.7–3.5, p<0.001) and to report taking psychotropic medication in the past (21.0% versus 6.4%; odds ratio=3.9, 95% confidence interval=1.9–8.0, p<0.001). Their general practitioner records were more likely to indicate a previous psychiatric diagnosis (32.6% versus 13.1%; odds ratio=3.1, 95% confidence interval=1.9–5.5, p<0.01). For the other analyses we combined the self-report and general practitioner data (table 3).

Previous Psychiatric Morbidity and Onset of Chronic Fatigue and Chronic Fatigue Syndrome

Subjects with new (incident) cases of chronic fatigue were more likely than subjects without chronic fatigue to have received psychotropic medication in the past (34.5% versus 9.9%; odds ratio=4.8, 95% confidence interval=1.7–3.4, p=0.001), to have received a previous psychiatric diagnosis (50.0% versus 25.3%; odds ratio=2.9, 95% confidence interval=1.2–7.0, p=0.01), or to have probable psychiatric disorder (General Health Questionnaire) at stage 1 (38.9% versus 21.8%; odds ratio=2.3, 95% confidence interval=1.1–4.6, p=0.01). These results were identical when we adjusted for stage 1 fatigue by the Mantel-Haenszel technique.

Subjects with new (incident) cases of chronic fatigue syndrome were also more likely than subjects without chronic fatigue to have previously received a psychiatric diagnosis (80.0% versus 29.1%; odds ratio=9.8, 95% confidence interval=1.0–90.6, p=0.02) or any psychotropic drug (83.3 versus 12.2%; odds ratio=36.0, 95% confidence interval=3.9–331.6, p=0.01).

Predictors of Psychiatric Comorbidity

We compared the associations of "pure" chronic fatigue (i.e., chronic fatigue without comorbid psychiatric disorder) and comorbid chronic fatigue. Excluding comorbid psychiatric disorder reduced the association between chronic fatigue and previous psychiatric disorder, but only slightly. Pure chronic fatigue remained associated with having probable psychiatric disorder (General Health Questionnaire) at stage 1 (64.4% of subjects with pure chronic fatigue versus 34.8% of subjects without chronic fatigue; odds ratio=3.4, 95% confidence interval=2.1–5.5, p<0.001). The association with any previous psychiatric diagnosis was reduced slightly (43.3% of subjects with pure chronic fatigue versus 26.7% of subjects without chronic faatigue; odds ratio=2.1, 95% confidence interval=1.1–3.8, p=0.02), while that with previous psychotropic prescriptions became nonsignificant (20.6% versus 12.7%; odds ratio=1.8, 95% confidence interval=0.8–3.8, p=0.13).

A more sensitive analysis was possible by grouping the chronic fatigue cases into four quartiles according to General Health Questionnaire score, corresponding to low, moderate, high, and very high psychological distress. We

TABLE 5. Somatic Symptoms in Subjects With and Without Chronic Fatigue

Symptom[a]	Subjects With No Chronic Fatigue (N=193) (%)	All Subjects With Chronic Fatigue (N=185)			Subjects With Idiopathic Chronic Fatigue (N=149)			Subjects With Chronic Fatigue Syndrome (N=36)		
		%	Odds Ratio	95% CI[b]	%	Odds Ratio	95% CI[b]	%	Odds Ratio	95% CI[b]
Headaches	47	67	2.3	1.5–3.4	63	1.9	1.3–3.0	87	3.5	1.5–8.2
Sleep disturbance	31	56	2.8	1.8–4.2	54	2.6	1.7–4.1	64	2.5	1.3–5.2
Neuropsychological disturbance	23	85	18.8	12.8–27.7	83	16.1	10.9–24.1	97	114.4	15.6–837
Myalgia	23	56	4.3	3.2–5.8	50	3.4	2.5–4.7	89	30.2	10.6–85.8
Postexertion malaise	22	29	1.5	0.9–2.3	23	1.1	0.6–1.9	63	5.9	2.8–12.3
Joint pain	19	41	2.9	1.0–13.9	34	1.4	0.9–2.2	72	7.5	3.5–16.1
Muscle weakness	14	68	13.0	9.4–17.7	63	10.1	7.3–14.1	94	92.0	22.0–383.4
Fever/chills	14	24	2.3	1.3–4.1	24	2.3	1.3–3.8	47	4.3	2.0–8.7
Sore glands	7	15	2.4	1.2–4.7	11	1.8	0.8–4.0	31	4.8	2.1–10.7
Daytime drowsiness	41	80	5.6	3.6–8.9	77	4.5	2.8–7.3	90	5.9	2.0–17.2
Back pain	36	55	2.1	1.4–3.2	53	2.0	1.3–3.2	69	3.0	1.4–6.4
Stomach pain	25	34	1.5	1.0–2.4	32	1.5	1.0–2.4	50	2.6	1.3–5.3
Eyestrain	23	42	2.4	1.5–3.7	42	2.8	1.8–4.5	44	1.8	0.9–3.5
Stiffness	22	48	3.1	2.0–4.9	44	2.8	1.8–4.5	64	3.8	1.9–7.8
Nausea	21	41	2.6	1.7–4.1	35	2.1	1.3–3.6	69	6.3	3.0–13.2
Sore throat	21	37	2.3	1.4–3.6	34	2.0	1.3–3.3	53	3.1	1.5–6.2
Dry mouth	20	41	2.8	1.8–4.5	39	2.8	1.7–4.6	53	2.9	1.5–5.9
Palpitations	15	36	3.3	2.0–5.4	35	3.5	2.1–6.0	44	2.7	1.3–5.4
Diarrhea	14	18	1.4	0.8–2.4	17	1.5	0.8–2.7	28	2.3	1.0–5.0
Constipation	14	21	1.7	1.0–2.9	18	1.6	0.9–2.9	36	3.3	1.5–6.8
Tingling in fingers or arms	13	26	2.3	1.4–4.0	25	2.3	1.3–4.0	31	2.0	0.9–4.3
Pain in eyes	13	30	2.8	1.6–4.8	28	2.7	1.6–4.8	42	3.0	1.5–6.2
Light-headedness	13	37	3.9	2.3–6.5	37	4.4	2.5–7.6	42	2.4	1.2–4.9
Increased sensitivity to noise	13	33	3.2	1.9–5.4	31	2.9	1.7–5.0	44	3.0	1.5–6.0
Dizziness	12	25	2.5	1.5–4.3	22	2.1	1.2–3.8	42	3.6	1.8–7.4
Urinating more often	12	29	2.8	1.7–4.8	27	3.1	1.7–5.5	44	3.6	1.8–7.3
Increased sensitivity to light	11	25	2.6	1.5–4.5	24	2.6	1.4–4.7	33	2.5	1.2–5.3
Inability to breathe deeply enough	9	23	2.9	1.6–5.3	22	3.0	1.6–5.6	33	2.9	1.4–6.3
Tingling in legs or feet	8	21	3.1	1.6–5.8	18	2.5	1.3–4.9	31	3.1	1.4–6.7
Chest pain	8	16	2.1	1.1–4.1	18	2.3	1.2–4.3	11	0.8	0.3–2.7
Ringing in ears	7	15	2.2	1.1–4.3	13	2.3	1.1–5.0	31	4.6	2.1–10.2
Tremor	6	14	2.3	1.1–4.8	12	2.8	1.2–6.4	25	3.8	1.6–8.8
Faster breathing than normal	5	19	4.3	2.0–8.9	18	5.8	2.5–13.7	28	3.4	1.5–7.6
Double vision	4	13	4.0	1.7–9.4	12	5.2	1.9–13.7	19	3.2	1.3–8.1
Shortness of breath at rest	4	15	4.0	1.8–8.9	11	3.8	1.5–9.9	33	6.7	3.0–15.0
Pain on urinating	3	9	3.6	1.3–9.9	8	3.9	1.2–12.5	14	3.3	1.1–9.7
Difficulty in urinating	3	5	1.9	0.6–5.8	5	2.2	0.6–7.7	8	2.8	0.8–10.4

[a]From the 1994 Centers for Disease Control criteria for chronic fatigue.
[b]CI=confidence interval.

noted a strong trend for an increase across these groups in probable psychiatric disorder (General Health Questionnaire) at stage 1 (χ^2 for trend=36.1, df=1, p<0.001), previous psychiatric diagnosis (χ^2 for trend=42.6, df=1, p<0.001), and previous psychotropic drug use (χ^2 for trend=33.8, df=1, p<0.001) (table 4).

The subjects with chronic fatigue syndrome were also stratified on the basis of psychiatric disorder into two bands—a minority group of subjects with chronic fatigue syndrome and no current psychiatric disorder (pure chronic fatigue syndrome) (N=8) and the larger number with psychiatric disorder (comorbid chronic fatigue syndrome) (N=28). The associations between pure chronic fatigue syndrome and any previous psychiatric disorder (57.1% of subjects with pure chronic fatigue syndrome versus 31.3% of subjects without chronic fatigue; odds ratio=2.9, 95% confidence interval=0.6–13.5, p=0.14) and previous psychotropic prescription (33.3% versus 14.2%; odds ratio=3.0, 95% confidence interval=0.7–12.7, p=0.11) remained unchanged but were no longer statistically significant. A significant association remained for probable psychiatric disorder (General Health Questionnaire) at stage 1 (75.0% of subjects with chronic fatigue syndrome versus 37.7% of subjects without chronic fatigue; odds ratio=4.9, 95% confidence interval=1.0–24.6, p=0.03).

Somatic Symptoms in Chronic Fatigue Syndrome: Specific or Nonspecific?

Thirty-two somatic symptoms were measured by self-report in the case-control study. By definition, subjects with chronic fatigue syndrome at stage 3 had significantly higher rates of all of the symptoms included in the 1994 CDC case definition. However, these symptoms were not specific to chronic fatigue syndrome. First, subjects with chronic fatigue and idiopathic chronic fatigue also had significantly higher rates of each of the CDC symptoms

FIGURE 2. Psychiatric Morbidity and Symptoms of Chronic Fatigue Syndrome According to the Definition of the Centers for Disease Control (CDC) in a Case-Control Study of Chronic Fatigue

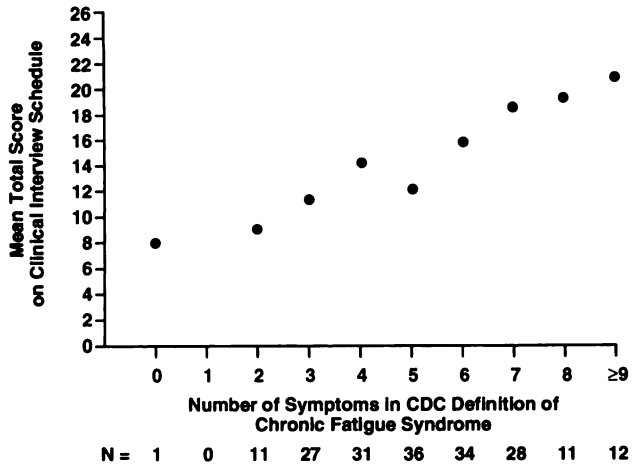
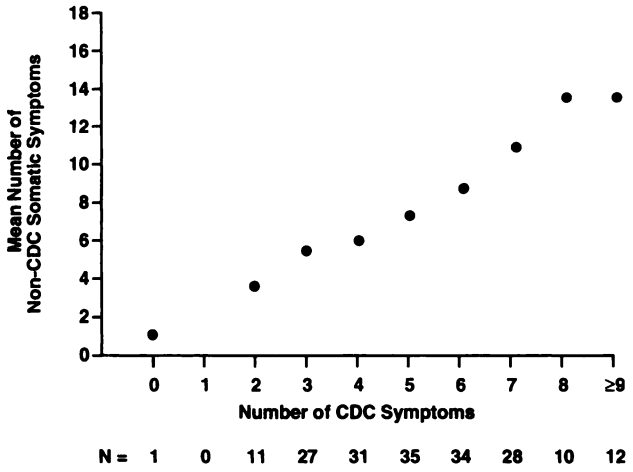


FIGURE 3. Relation Between Symptoms Included In and Excluded From the Definition of Chronic Fatigue Syndrome According to the Centers for Disease Control (CDC) in a Case-Control Study of Chronic Fatigue



than the control subjects without fatigue. Second, subjects with chronic fatigue, idiopathic chronic fatigue, and chronic fatigue syndrome were significantly more likely than subjects without fatigue to complain of 37 out of 38 somatic symptoms, not just those included in the CDC case definition (table 5), the exception being chest pain.

There was a linear correlation between the mean number of somatic symptoms and various measures of psychological symptoms. For chronic fatigue subjects, the total number of somatic symptoms was correlated with Hospital Anxiety and Depression Scale depression scores ($r=0.34$, $N=185$, $p<0.001$) and anxiety scores ($r=0.34$, $N=185$, $p<0.001$). For the subjects without chronic fatigue, the total number of somatic symptoms was also correlated with Hospital Anxiety and Depression Scale depression scores ($r=0.55$, $N=193$, $p<0.001$) and anxiety scores ($r=0.54$, $N=193$, $p<0.001$).

Using the total score obtained on the psychiatric interview as a more sensitive measure of psychiatric disorder, we found that the symptoms included in the original CDC definition of chronic fatigue syndrome (18) were associated with psychological symptoms, again in both the subjects with chronic fatigue ($r=0.41$, $N=185$, $p<0.001$) (figure 2) and the subjects without chronic fatigue ($r=0.53$, $N=193$, $p<0.001$). Overall, there was a strong correlation between total score on the Revised Clinical Interview Schedule and number of CDC symptoms ($r=0.54$, $N=381$, $p<0.001$) and non-CDC symptoms ($r=0.57$, $N=381$, $p<0.001$).

Figure 3 shows the mean number of symptoms excluded from the CDC definition (a maximum of 30) and the number of CDC-included symptoms. A further linear relationship can be seen ($r=0.67$, $N=381$, $p<0.001$).

DISCUSSION

The study had several limitations. First, we merged the two study cohorts (viral and nonviral illness) for this analysis. This was done to increase the power of the study. We have shown no differences in any of the study variables between the two cohorts, and results of all of the analyses reported are the same when the analyses are performed with either cohort.

Second, because of the stage 1 community screening, we are aware that the 16% who did not respond at the stage 3 follow-up had slightly higher rates of psychiatric disorder than the responders. Thus, the strength of the associations between chronic fatigue and psychiatric disorder might be slightly higher than reported here.

Third, we did not carry out all of the laboratory screening tests recommended in the latest CDC criteria (15). We only performed tests of liver and thyroid function, hemoglobin, urea, electrolytes, and C-reactive protein and not tests of calcium, phosphorus, and glucose or urinalysis. This was for reasons of cost. It is thus possible that alternative physical diagnoses were missed. However, investigations of chronic fatigue in primary care are not very helpful, particularly in the 18- to 45-year age group (21). All subjects were also evaluated by their general practitioners. We feel that few, if any, alternative physical diagnoses would have been made in this primary care cohort if more extensive screening had been undertaken.

Fourth, this was a primary care study, not a community study, and was still subject to confounding factors such as the influence of psychological distress on the decision to seek medical care. However, the filter between the community and primary care is very permeable in the United Kingdom; 80% of the adult population visit their general practitioners each year (22), which was the duration of recruitment for this study.

Fifth, nearly all of the subjects recruited in primary care did not present with fatigue as the principal complaint. Instead, chronic fatigue was recorded as present according to predefined criteria, which did not include the requirement for fatigue to be either the principal or

the presenting complaint. We measured the severity of fatigue, the attribution of fatigue, and the severity of functional impairment separately. This was to aid comparison between studies and to reduce the influence of the many factors that determine the choice of which symptom to present to the doctor, which include severity, duration, the culture, illness models, doctor behavior, and others. While chronic fatigue is common in primary care, chronic fatigue as a presenting complaint is less so, and chronic fatigue as a diagnosis is unusual (23–25). We believe that insisting that chronic fatigue be either the presenting complaint or, alternatively, the medical diagnosis, introduces a variety of biases.

Finally, because this study began in the community and continued in primary care, we chose to use instruments that reflect the nature of psychiatric disorder encountered in these settings. Epidemiological research has shown that "the patterns of comorbidity found in treatment settings do not reflect the patterns in the community as a whole" (26). Diagnostic categories developed in specialist samples do not correspond to the pattern of common mental disorder as encountered in the community and primary care, where most psychiatric illness is a combination of depression and anxiety (27). It is more meaningful in the majority of cases to talk about general psychiatric disorder than the specific nuances of psychiatric classification (27). We therefore elected to study the general relationship between psychiatric disorder and the syndromes of fatigue. This approach has been adopted by others working in this setting (28–30) and is in contrast to the strategy we and many others have adopted in studies of specialist samples of chronic fatigue syndrome.

Whether or not psychological vulnerability predisposes to chronic fatigue or chronic fatigue syndrome remains controversial. Previous studies, based on specialist care, report rates of previous disorder that can be less than, the same as, or greater than expected (31). Confusion probably results from differing combinations of referral, selection, and recall bias. We now report that in a nonspecialist, nonreferral setting, there was an association between several measures of previous psychiatric disorder and both chronic fatigue and chronic fatigue syndrome.

Stage 1 of the study consisted of a large community survey of psychological symptoms and subjective fatigue (5). This was carried out to obtain measures of vulnerability to postinfection fatigue before the index infection was acquired (4). It also enabled us to determine the risk factors for new cases of chronic fatigue—to our knowledge, the first time this has been attempted. New cases of chronic fatigue and chronic fatigue syndrome were associated with both self-report and general-practitioner-recorded measures of previous psychiatric disorder.

Turning to the cross-sectional data, we have confirmed previous community and primary care reports of strong associations between chronic fatigue and major depression (32) or chronic fatigue and all psychiatric disorders (21, 28, 29).

Previous studies of chronic fatigue syndrome have also noted a strong association with psychiatric disorder (31). However, all of these studies were of specialist samples, and their findings may be untypical of the disorder. We now report that the link between chronic fatigue syndrome and psychiatric disorder is also found in primary care. Subjects meeting the latest criteria for chronic fatigue syndrome were nearly six times more likely than those without chronic fatigue syndrome to meet criteria for psychiatric disorder on interview, or to have probable psychiatric disorder according to questionnaire measures. We feel that this close association remains an inevitable consequence of the overlap between the criteria used to construct psychiatric diagnoses and those for chronic fatigue syndrome. This remained true even though we modified the standardized interview to exclude fatigue and used questionnaires that avoided the somatic symptoms associated with psychiatric disorder and chronic fatigue syndrome.

Because current psychiatric disorder and chronic fatigue are so closely associated, it is possible that the relationship we observed between previous psychiatric disorder and current chronic fatigue or chronic fatigue syndrome is due to confounding—in other words, previous psychiatric disorder might predict current psychiatric disorder alone, and not chronic fatigue or chronic fatigue syndrome. This was partly confirmed. The associations between chronic fatigue and previous psychiatric disorder were slightly stronger for chronic fatigue and psychiatric disorder combined (comorbid) than for pure chronic fatigue, but the differences were not substantial. However, the more sensitive tests for trend did suggest that previous psychiatric disorder was associated with comorbidity rather than chronic fatigue per se. Similar observations were made for chronic fatigue syndrome. It remains possible that studies of the minority of chronic fatigue syndrome patients without comorbid psychiatric disorder may reveal a different pattern of associations from that of the majority, as is beginning to emerge from studies of neuroendocrinology (33) and life events (34).

CONCLUSIONS

Despite the current interest in chronic fatigue syndrome among the public and professionals, the nosological status of the disorder remains uncertain. Is it an independent entity or, alternatively, does chronic fatigue syndrome simply reflect an arbitrarily defined end of a spectrum of severity? To date no study has reported that chronic fatigue syndrome can be distinguished from chronic fatigue by any particular laboratory, demographic, or psychiatric variable (35, 36).

Is there a particular symptom profile that serves to distinguish chronic fatigue syndrome? Our study suggests that the answer is no. One of the strongest findings of this study was the linear relationship between the experience of somatic and psychological symptoms. This relationship was identical for both the symptoms

included in the current definition of chronic fatigue syndrome and those excluded, which is not surprising, since there was a close association between the two sets of symptoms anyway (figure 3). We thus found no epidemiological justification for stating that certain symptoms are characteristic of chronic fatigue syndrome (and hence form part of the case definition) solely because they resemble those of an infective or immunological disorder held to underlie chronic fatigue syndrome. Most symptoms may instead reflect the joint experience of somatic and psychological distress (35, 37).

We and others have already provided evidence that fatigue is dimensionally and not categorically distributed (5, 38). We found little evidence that the other variables that make up the current concepts of chronic fatigue syndrome can be used to impose a clear cutoff, separating those with severe fatigue from those with chronic fatigue syndrome. Only postexertion malaise, muscle weakness, and myalgia were significantly more likely to be observed in chronic fatigue syndrome than in chronic fatigue or idiopathic chronic fatigue. None of the other 35 symptoms distinguished chronic fatigue, idiopathic chronic fatigue, or chronic fatigue syndrome, nor did the presence or absence of psychological disorder.

The stated desire of all of the current chronic fatigue syndrome case definitions is to attempt to isolate a pure syndrome distinct from other medical or psychiatric categories. We suggest that the current chronic fatigue syndrome case definitions instead achieve the opposite of the intended objective. By insisting on a minimum symptom requirement, these definitions actively select subjects at increased risk of psychiatric disorder. Similar observations have been made previously, but in specialist samples likely to have been influenced by selection bias in favor of psychiatric morbidity (35, 39). We have now confirmed these findings in a primary care sample. We conclude that if it is intended to produce case definitions of chronic fatigue syndrome that distinguish the syndrome from existing categories of psychiatric disorder, it would be more logical to insist on maximum rather than minimum symptom criteria.

A convincing case for heterogeneity in chronic fatigue syndrome has already been made (40). We suggest that current definitions of chronic fatigue syndrome represent an arbitrary imposition where there may be no natural division. Case definitions are obligatory for many types of research into the problems of chronically fatigued patients, including treatment, outcome, and service development. However, at present all such definitions must not be taken as verification of a specific nosological entity.

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