

Postinfectious fatigue: prospective cohort study in primary care

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Summary

The idea that chronic fatigue has an infectious origin has become popular, but the main evidence for such an association has come from retrospective case-control studies, which are subject to ascertainment bias. We report a prospective study of the outcome of clinically diagnosed infections in patients presenting to UK general practitioners.

Questionnaires assessing fatigue and psychiatric morbidity were sent to all patients aged 18–45 years in the study practices. The prevalence of chronic fatigue and chronic fatigue syndrome was then ascertained among 1199 people aged 18–45 who presented to the general practitioners with symptomatic infections and in 1167 people who attended the surgeries for other reasons. 84% were followed up at 6 months. 9.9% of cases and 11.7% of controls reported chronic fatigue (odds ratio 1.0 [95% CI 0.6–1.1]). There were no differences in the proportions who met various criteria for chronic fatigue syndrome. No effect of infection was noted when we excluded subjects who reported fatigue or psychological morbidity at the baseline screening. The strongest independent predictors of postinfectious fatigue were fatigue assessed before presentation with clinical infection (3.0 [1.9–4.7]) and psychological distress before presentation (1.8 [1.2–2.9]) and at presentation with the acute infection (1.8 [1.1–2.8]). There was no effect of sex or social class.

Our study shows no evidence that common infective episodes in primary care are related to the onset of chronic fatigue or chronic fatigue syndrome.

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Introduction

The problem of excessive fatigue has attracted much interest in the past few years. Special attention has been paid to the possibility that the condition has an infective origin, and the term postviral fatigue syndrome has become popular. Although the subject of chronic fatigue and infection has a long history,¹ this renewal of interest was stimulated by studies in the 1980s linking chronic fatigue syndromes with Epstein-Barr virus² and the enteroviruses.³ The majority of patients seen in clinics specialising in chronic fatigue syndrome report that their problems began with a viral infection.^{4–8}

Difficulties with this simple story soon became apparent. Markers thought to indicate recent infection with Epstein-Barr virus or enteroviruses were found to be poor guides.^{9,10} Epidemiological difficulties include reliance on retrospective case-control studies to determine exposure to an infective agent often reported as occurring several years previously. One group defined cases of postviral fatigue as “fatigue starting after an acute, apparently viral, infection”.³ However, the average adult in the UK experiences four or five symptomatic viral infections per year. 30% of a population sample¹¹ answered yes to the question “Have you suffered from a virus in the last month?” Chance associations between chronic fatigue and viral infection must be common. Retrospective case-control studies of postinfective fatigue are subject to ascertainment bias, since identification of a case (postviral fatigue) has been made by knowledge of exposure (viral infection), which violates the condition that cases be selected independently of exposure for valid case-control studies. There are psychological reasons why patients might attribute symptoms without a definitive biomedical explanation to a viral cause, thus contributing to recall bias and search after meaning.¹²

To overcome these difficulties, we carried out a study of chronic fatigue that was population based, involved ascertainment of exposure to infection and psychological vulnerability unbiased by the onset of chronic fatigue syndrome, and used controls not exposed to infection recruited at the same time and place.

Subjects and methods

Design (figure)

Stage 1—Before the main study started we sent two questionnaires to all individuals aged between 18 and 45 years registered with the study general practices. Recruitment of the practices has been described elsewhere.¹³ Fatigue was assessed by a self-report questionnaire (fatigue questionnaire), which was developed for a hospital study of chronic fatigue syndrome^{4,14} and refined in primary care.¹⁵ It consists of eleven items covering physical and mental features of fatigue, duration of fatigue, the proportion of the day during which the respondent felt tired, and muscle pain at rest and after exercise. Respondents were also asked why they felt tired. Psychological morbidity was assessed by the twelve-item general health questionnaire (GHQ).¹⁶

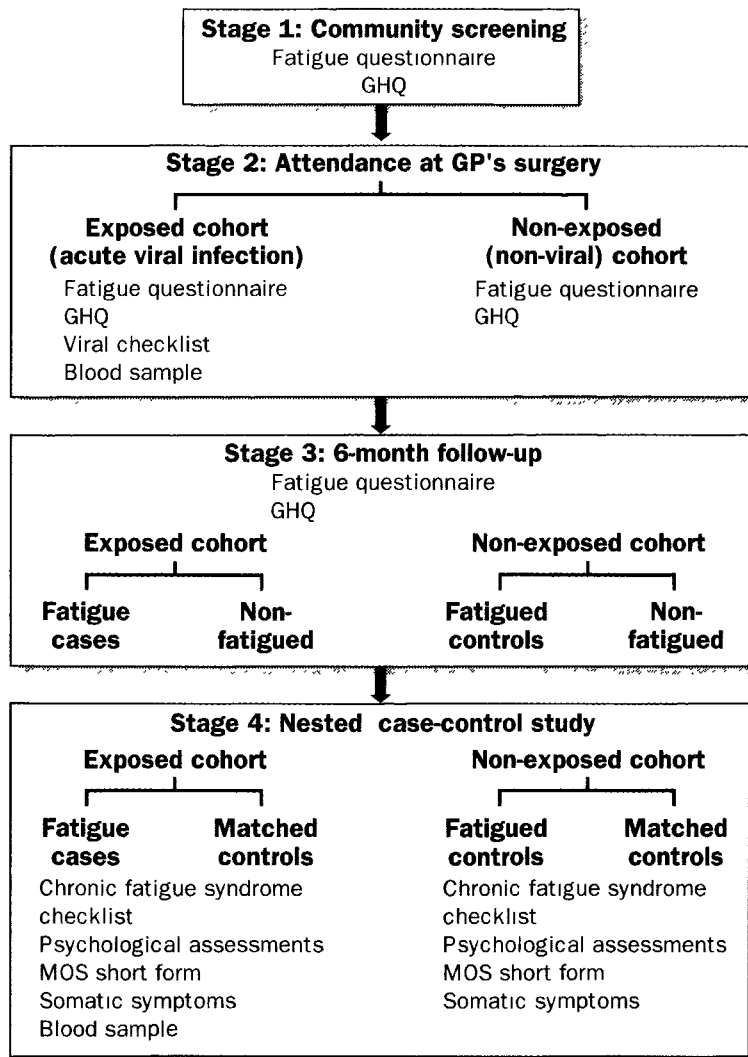


Figure: Study design

Stage 2—The study then followed the traditional design of a cohort study. The exposed cohort were patients aged 18–45 who attended the study general practices with suspected infections. Identification of an infection was at the discretion of the doctor, but guidelines were provided. Local infections such as conjunctivitis, cold sores, fungal nail infections, and vaginal candidosis were not included. Most patients presented with “flu-like” episodes or infections of the upper respiratory tract. Each subject for the non-exposed cohort was the next person within the appropriate age range who entered the general practitioner’s surgery with any complaint not related to a possible infection. All subjects were asked to see the research nurse, who was available in the surgery at the same time. The nurse explained that the study was about the effects of common infection, and obtained written consent. Patients then completed the questionnaires listed on the figure, and blood samples were taken from members of the exposed cohort. (Ethical approval for samples to be taken from non-exposed subjects was not given.) Viral symptoms (including runny nose, phlegm, sore throat, fever, cough) were assessed on the 26-item checklist used by the MRC Common Cold Unit.¹⁷ Each symptom is rated on a 6-point scale. The nurse recorded demographic details, resting pulse rate, and body temperature. Other psychological assessments and allergy questionnaire results will be reported elsewhere.

Stage 3—All subjects were sent the general health questionnaire and fatigue questionnaire 6 months after attendance at the general practitioner’s surgery. The criterion for cases of chronic fatigue was excessive fatigue throughout the preceding 6 months. Subjects who met this criterion were classified as fatigue cases or fatigued controls, depending on whether they belonged to the exposed or non-exposed cohorts.

Stage 4: nested case-control study—All fatigue cases and fatigued controls were asked to return to the general practitioner’s surgery for further investigation and assessment. The same assessments were also carried out in a sample chosen from subjects without fatigue in the two cohorts—equal numbers matched by sex and age to the nearest 5 years (matched

General practitioners' diagnosis	% of exposed cohort
Sore throat	33
Influenza	19
Cold	16
Gastroenteritis	6
Chest infection	4
Tonsillitis	4
Sinusitis	3
Middle-ear infection	3
Chickenpox	1
Glandular fever	1
Urinary tract infection/cystitis	1
Other	6
Missing	2

Table 1: Clinical diagnoses in exposed cohort

controls). The chronic fatigue syndrome questionnaire,¹⁸ a 24-item scale, was used to assess the presence and severity of physical, cognitive, behavioural, and affective components of fatigue. Psychiatric illness was ascertained by the Revised Clinical Interview Schedule (CIS-R¹⁹), which was designed to record psychiatric morbidity in primary care. It is intended to be used by non-psychiatrists, and has a low observer bias. It was completed by the research nurse after appropriate training. It was scored without the fatigue interns. Functional impairment was assessed by the Medical Outcome Study 20-item questionnaire (MOS short form²⁰), scored on a scale of 0–100. We also used a checklist of 32 somatic symptoms, modified from the Somatic Discomfort Questionnaire²¹ and previously used in hospital-based studies of chronic fatigue syndrome.^{4,14} Methods of Coping questionnaire, Life Events inventory and the Hospital Anxiety and Depression scale were also applied. Blood samples were taken from exposed subjects.

Outcome measures

The Oxford,²² Australian,⁶ and USA Centers for Disease Control and Prevention (CDC) 1994²³ criteria for chronic fatigue syndrome were used. The CDC 1988 criteria closely followed the original case definition,²⁴ with the exception of the physical criteria. No measures were made of lymphadenopathy, fever, or pharyngitis because of doubts about reliability.²³

All general practice records were searched for records of any psychiatric admissions, prescriptions of psychotropic medication, and any current medical problems. The number of visits made to the surgery in the year before recruitment to the study was also recorded.

Laboratory investigations

Tests on blood samples were not intended to provide laboratory verification of acute viral exposure, but to study possible viral persistence. All fatigue cases and their stage-4 matched controls were screened with liver and thyroid function tests, haemoglobin, urea, electrolytes, and C-reactive protein.

Statistics

Likert scoring for GHQ and fatigue questionnaires produces a normal distribution in population samples, so parametric statistics can be used. MOS short-form scores produce skewed distributions,²⁵ but these approximated to a normal distribution after log transformation, as did the number of visits to general practitioners. GHQ, CIS-R, and fatigue scores were entered into regression models as continuous variables, but odds ratios are given for categorical variables for ease of comprehension. Social class was entered as a stratified variable with five levels. Parametric comparisons of means were made by *t* tests, non-parametric comparisons by the Mann-Whitney test, and comparison of proportions by the χ^2 test.

The study power was adequate to detect a clinically meaningful difference in the risk of chronic fatigue between cases and controls. With $p=0.05$, the study had 80% power to detect a relative risk of 1.4 between cases and controls. With the same α and β , the figures for more stringent categories of chronic fatigue

	All subjects			Subjects without previous fatigue		
	Exposed cohort (n=1010)	Non-exposed (n=975)	Odds ratio (95% CI)	Exposed (n=386)	Non-exposed (n=407)	Odds ratio (95% CI)
All fatigue cases*	354 (35.0%)	344 (35.2%)	1.0 (0.8-1.2)	87 (22.5%)	84 (20.6%)	1.0 (0.5-2.0)
Chronic fatigue*	100 (9.9%)	114 (11.7%)	0.8 (0.6-1.1)	19 (4.6%)	17 (4.2%)	1.1 (0.8-1.6)
Chronic fatigue syndrome						
Oxford criteria	14 (1.3%)	19 (1.9%)	0.7 (0.4-1.6)	3 (0.8%)	0	..
Australian criteria	7 (0.7%)	13 (1.3%)	0.5 (0.2-1.4)	2 (0.5%)	1 (0.2%)	0.5 (0.2-5.3)
CDC 1988 (modified) criteria	5 (0.5%)	11 (1.1%)	0.4 (0.2-1.3)	0	0	..
CDC 1994 criteria	12 (1.0%)	24 (2.0%)	0.5 (0.3-1.0)	4 (0.9%)	2 (0.4%)	2.0 (0.1-2.6)

*By fatigue questionnaire.

Table 2: **Chronic fatigue and chronic fatigue syndrome 6 months after presentation at surgery (stage 3)**

syndrome were 1.8 (CDC 1994), 1.9 (Oxford), 2.2 (Australian), and 2.4 (CDC 1988).

Results

Response rates

Response rates for stage 1 have been reported elsewhere.¹³ 15 283 replies were received, an overall response rate of 48%. The response rate adjusted for inaccuracies in the inner city practice registers was 67%.

1167 (97%) of the 1199 exposed subjects and 1160 (98%) of the 1177 non-exposed subjects recruited at stage 2 completed all or nearly all of the questionnaires. More refused the blood test. Only 5% refused to be interviewed by the research nurse, usually because of pressure of time. 752 (63%) exposed and 792 (68%) non-exposed subjects had previously completed stage-1 measures. Those recruited at stage 2 who had not replied at stage 1 were slightly younger (33.4 *vs* 31.5 years for the responders), and a larger proportion were male (24.7 *vs* 18.2%, χ^2 test, $p=0.0004$).

At stage 3, 1985 completed questionnaires were received, a response rate of 84% (exposed 84%, non-exposed 83%). 155 patients had moved, 21 refused, and no information was available on 215. Non-responders were more likely to be male (35.8 *vs* 29.7%, $p=0.01$), and at stage 1 more likely to score above the cut-off defining a case for both the GHQ (48.0 *vs* 38.9%, $p=0.02$), and the fatigue questionnaire (46.8 *vs* 42.0%, $p=0.23$).

Of the 214 subjects who met the criterion for chronic fatigue, 185 (86%) were interviewed—89 (89%) exposed and 96 (84%) non-exposed. Of the 214 matched controls, 193 (90%) were interviewed—95 (95%) exposed and 98 (86%) non-exposed.

All patients who met the criterion for chronic fatigue at stage 3 were matched by age and sex with a non-fatigued subject from the same cohort. More than 80% of the matched non-fatigued control subjects were successfully interviewed at the first attempt. Matched controls who could not be contacted were replaced with another. Thus, every fatigued subject interviewed at stage 3 was successfully matched with a control for whom full interview data were obtained.

Clinical diagnoses

The commonest symptoms in the exposed cohort were sore throat (66%), cough (57%), headache (57%), aching muscles (53%), runny nose (49%), fever (38%), and chills (36%). The month of onset followed the expected seasonal distribution for common viral infections. The mean duration of symptoms in the cases was 8 days. The general practitioners' clinical diagnoses are given in table 1. In the non-exposed cohort the reason for attendance was recorded as related to the reproductive

system (25%), musculoskeletal (17%), skin (11%), routine (insurance medicals, repeat prescriptions, &c: 9%), respiratory and cardiovascular (7%), ears, nose, throat, and conjunctivitis (6%), digestive (5%), other eye problems (4%), mental illness (4%), lifestyle advice (4%), nervous system (2%), psychosocial (2%), fatigue (2%), urinary (1%), and endocrine (1%); no reason was recorded in 2%.

Stage 2 sample

The exposed and non-exposed cohorts did not differ in sex distribution; there were more women than men in both cohorts (68%, 70%). The mean age was lower in the exposed than the non-exposed cohort (32.7 [SD 7.5] *vs* 33.5 [7.5] years); this difference was significant because the sample was large, but it is probably unimportant.

There was no difference between the exposed and non-exposed cohorts in the mean fatigue score or the proportions who scored above the cut-off for fatigue cases at stage 1 (before recruitment to the study; 42.4 *vs* 42.7%, $p=0.8$). However, there was a slightly higher proportion of GHQ cases at stage 1 in those later recruited as non-exposed subjects (37.6% exposed *vs* 42.1% non-exposed, $p=0.08$). By contrast at stage 2, 63.5% of exposed subjects scored above the cut-off for fatigue on the fatigue questionnaire compared with 36.1% of non-exposed subjects ($p<0.001$); a greater proportion of the exposed than the non-exposed cohort had psychiatric morbidity according to the GHQ (43% *vs* 36.1%, $p=0.001$).

Postviral fatigue

Similar numbers of exposed and non-exposed subjects complained of fatigue at follow-up (table 2) and similar numbers met criteria for chronic fatigue, scoring above the cut-off already validated in primary care for the previous 6 months (100 *vs* 114). The combined prevalence of chronic fatigue was 10.8%. As we introduced more stringent criteria for chronic fatigue syndrome, the difference in the likelihood of the syndrome between the non-exposed and exposed cohorts increased, although did not reach significance for any set of criteria (table 2). The most likely reason for the slightly higher rates of fatigue in the non-exposed cohort was the slightly higher rates of fatigue and psychological morbidity

Variable	Odds ratio (95% CI)	p
Premorbid fatigue (stage 1)	3.0 (1.9-4.7)	<0.001
GHQ case (stage 1)	1.8 (1.2-2.9)	0.009
GHQ case (stage 2)	1.8 (1.1-2.8)	0.01

Table 3: **Independent predictors of chronic fatigue 6 months after presentation**

at stage 1 in that cohort. Separation of fatigue into physical or mental symptoms^{4,15} revealed no differences between the groups.

Since previous fatigue was strongly associated with subsequent chronic fatigue, it is possible that any association between infection and fatigue was obscured by the high rate of preinfection fatigue in the study sample. We therefore repeated analyses for those without previous fatigue only. Eligibility was defined as a low fatigue score at stage 1, rather than stage 2 since many patients were fatigued at stage 2 because of the acute infection. Even among subjects with no history of fatigue, there was no evidence that infection at stage 2 was associated with chronic fatigue or chronic fatigue syndrome (table 2).

Another confounder is the possibility of further infections during follow-up. 36% of those interviewed at stage 3 recalled such an infection, but there was no difference between exposed and non-exposed cohorts. We restricted analyses to subjects who recalled no infection (no further infection for exposed subjects) during the 6 months of follow-up, and again found no increase in the risk of chronic fatigue in the exposed subjects. 37 (40%) of 93 exposed subjects and 56 (48%) of 118 non-exposed subjects who recalled no infection during follow-up had chronic fatigue (odds ratio 0.7 [95% CI 0.4–1.2]). The odds ratios for other definitions of chronic fatigue syndrome were 0.6 (0.2–1.5) by Oxford criteria, 0.5 (0.1–1.7) by Australian criteria, and 0.2 (0.1–0.8) by CDC 1994 criteria. Thus, there was no difference in the pattern of results, but a slight loss of power reflected in the wider confidence limits.

Stratification by sex, age group, social class, pre-existing psychological morbidity (stage 1 or stage 2), or pre-existing fatigue (stage 1 or stage 2), made no difference to the pattern of results. The stratified (Mantel-Haenzel) odds ratio for the effect of viral infection adjusted for sex was identical to the crude odds ratio shown in table 2. Adjustment for the number of visits to the general practitioner during the year before recruitment also had no effect on the odds ratio for chronic fatigue syndrome.

There were no differences between the exposed and non-exposed cohorts for other outcome measures at stage 3. The proportions who had psychiatric morbidity on the GHQ were similar (49 vs 51%) and the mean GHQ scores were identical. More detailed information was available on the subset recruited for the nested case-control study. There were no differences at that stage between the exposed and non-exposed cohorts in the number of somatic symptoms, depression and anxiety scores, psychiatric disorder assessed by direct interview, previous psychotropic drug use, or previous psychiatric history. (Details will be reported elsewhere.) The only difference between the cohorts at 6-month follow-up was in the total physical limits determined by the MOS short form; the score was greater in the non-exposed cohort (3.5 vs 2.8, $p=0.04$).

Belief that fatigue at stage 2 was due to a physical cause did not influence the risk of subsequent fatigue (odds ratio 1.0 [0.7–1.5]), nor did attribution to a physical explanation for catching the virus (0.8 [0.4–1.4]).

There were no significant differences in the number of symptoms between exposed and non-exposed subjects at stage 3, with the exception of stiffness, palpitations, and tremor, which were commoner in the non-exposed cohort. This may be a chance finding.

Significant variables were entered into a stepwise multiple regression model, with the dependent variable chronic fatigue at stage 3. The data set was the 671 subjects from the exposed cohort with complete data at all three stages of the study. Previous fatigue (scoring above the predefined cut-off on the fatigue questionnaire at stage 1) was the strongest independent predictor of fatigue after viral infection ($p<0.001$). Logistic regression was used to obtain more meaningful measures of effect size with categorical predictor variables (table 3). Independent contributions were made by both fatigue and psychological distress before presentation with the clinical infection, and by psychological distress at the time of presentation. Belief that fatigue was due to a physical cause was not a significant predictor of fatigue (odds ratio 1.6 [0.8–3.3], $p=0.21$).

Acute viral symptoms

Subjects in the exposed cohort who satisfied criteria for chronic fatigue 6 months later were more likely to say that they had most of the general symptoms on the viral checklist when recruited at stage 2. These symptoms included headache, aching muscles, insomnia, joint pain, heaviness of the legs, physical weakness, sore eyes, chills, racing heart, anxiety, tearfulness, sensitivity to noise, sensitivity to light, poor concentration, and poor memory. On the other hand, there was no difference between those who developed chronic fatigue and those who did not in the proportion reporting local symptoms on the checklist (sneezing, runny nose, production of phlegm, earache, hoarseness, nasal stuffiness, sore throat, fevers, sweating, and cough), either in prevalence or severity.

Viral symptoms and psychological morbidity

The association between viral symptoms and postviral fatigue was further explored by studying symptoms experienced during the acute infection and psychological morbidity measured at the same time by the GHQ. Every symptom listed under the viral checklist was commoner in subjects who scored higher than the GHQ cut-off (GHQ cases) than in those who were not cases, except for sore throat (odds ratio 1.0). However, there was a difference between local and general symptoms. Local symptoms that were not associated with the subsequent development of chronic fatigue all had odds ratios of between 1.2 and 1.7. Of those that were associated with chronic fatigue, only chills (odds ratio 1.9) and joint pain (1.9) had odds ratios under 2.0; in most the odds ratio was more than 3.0, which indicates a very strong link.

A similar pattern was observed for the influence of previous (stage 1) psychological morbidity. There was no statistical association between being a GHQ case at stage 1 and ten of the viral symptoms (sneezing, runny nose, phlegm, sore throat, hoarseness, nasal stuffiness, cough, fever, chills, and earache), all of which had odds ratios between 0.8 and 1.2. The other symptoms were all significantly associated with previous GHQ scores. Insomnia, heavy legs, tearfulness, sensitivity to noise or light, poor concentration, weakness, joint pain, fatigue, headache, and memory loss all had odds ratios of more than 2.0, and only racing heart (1.3), sweating (1.5), sore eyes (1.5), and aching muscles (1.9) had significant odds ratios less than 2.

This pattern was confirmed by studying the stage-2 symptomatic profile in subjects without pre-existing psychiatric morbidity (ie, not GHQ cases at stage 1). The

power of the study was reduced, but symptoms with odds ratios of over 2.0 (statistically significant) were again general rather than local symptoms.

Discussion

We found no evidence to suggest that in primary care common viral infections are associated with chronic fatigue syndromes.

The study has several limitations. First, only patients with symptomatic infections were recruited; symptomless infections and those not diagnosed as infections by the general practitioner would be missed. However, most patients seen in specialist care with the diagnosis chronic fatigue syndrome recall a symptomatic episode.^{4-8,26} Second, patients with infections who never presented to their general practitioners would be excluded, although such cases might be expected to be less severe. The cohort design permits study of the outcome of infection and the results can be applied to the general population, unless there is evidence of a selection bias in the choice of cohort. A bias would occur if infections that are associated with chronic fatigue syndrome are also less likely to be seen by the general practitioner. This idea seems implausible. Another possible bias would occur if subjects vulnerable to postinfective fatigue syndromes were unlikely to present to the general practitioner with acute infection. In the self-help literature on chronic fatigue syndrome, sufferers are characterised as over-achievers reluctant to seek medical help. Adjustment for numbers of visits to the general practitioner did not, however, reveal any effect of infection.

Third, as the study progressed some exposed and non-exposed subjects reported new episodes of infection, although there was no difference between the two cohorts in the rate of such infections. However, subjects in the non-exposed cohort who experienced a new infection followed by chronic fatigue would not be false-negatives on follow-up, since they would not be able to complain of the full 6 months of fatigue, and thus would not satisfy the criterion for chronic fatigue cases. Exclusion of subjects who developed further infection revealed no suggestion of any effect on infection on the risk of fatigue or chronic fatigue.

Two internal biases should be considered. The exposed (infection) cohort reported substantially more fatigue at stage 2 than the non-exposed subjects. This difference is almost certainly due to the acute response to infection. At stage 1, before the infection, fatigue scores were identical in the two cohorts, and there was a slight tendency for those who later developed infections to have less psychological morbidity. A more likely source of response bias is the finding that non-responders at stage 3 had slightly higher psychological morbidity at stage 1 than responders. The association between previous psychological distress and postinfectious fatigue may be slightly stronger than that we report.

These criticisms should be set against the strengths of the study design, which are its general practice base, prospective design, and high rates of follow-up. We know of only three similar studies.²⁷⁻²⁹ Imboden et al²⁷ found that among patients who had developed influenza after the 1957 epidemic, psychological vulnerability predicted delayed recovery at 6 weeks. By contrast with our findings, White et al²⁸ found an increase in postinfectious fatigue syndromes, but only in patients with Epstein-Barr and non-Epstein-Barr glandular fevers, not other viral

infections. Epstein-Barr virus is, however, a rare cause of acute viral infection in primary care (only 1% of symptomatic infections in our cohort), and commonly causes no symptoms. Thus, our findings and those of White et al²⁸ accord for upper respiratory tract infections.

Cope and colleagues²⁹ studied subjects defined by a general practitioner as having acute viral infections, but had no control group. At 6 months, 17.5% remained chronically fatigued, a slightly higher proportion than that in a cross-sectional survey of attenders in a single general practice recruited in an earlier study. Our acute infection cohort is similar to that of Cope et al²⁹ in sociodemographic variables and duration and range of presenting symptoms. Cope et al²⁹ acknowledged the need for their results to be confirmed with a control group of non-infected patients. With such a control group recruited prospectively in the same practices and at the same time as the exposed cohort, we found no evidence of any postinfection fatigue effect at 6 months.

The different symptom patterns noted during the acute infection also suggest that acute infection is not an important mediator of chronic fatigue. Local symptoms were common in the acute cases, but did not predict the subsequent development of chronic fatigue. By contrast, general symptoms did predict chronic fatigue. These symptoms were also associated with both current and previous psychological distress, unlike the local symptoms. There are several possible explanations. First, the symptoms may predate viral exposure, but may be confused by the patient with the symptoms of viral malaise. Second, the symptoms may develop during an acute infection because of an underlying trait of somatisation. Cope et al²⁹ reported that somatisation (defined on the basis of attributional style) predicted postviral fatigue. We found no evidence that attribution of the cause of viral infection predicts postviral fatigue, perhaps because we used a cruder measure of direct attribution rather than the measure of global attributional style used by Cope et al. Third, general symptoms represent a general response to acute infection mediated by cytokine release (as opposed to the local symptoms directly related to viral involvement). This mechanism would not explain the firm association with premorbid psychological morbidity. We believe that the different pattern of symptom associations is consistent with the overall lack of an effect of acute infections on the risk of chronic fatigue.

Can these results be applied to chronic fatigue syndrome outside primary care? We believe they can. Most people presenting with chronic fatigue syndrome who claim an infective onset to their symptoms do so without laboratory confirmation at onset, not surprisingly, since most diagnoses of common viral infections are made without laboratory investigation.

We conclude that common infections play little part in the aetiology of chronic fatigue in primary care. This conclusion does not exclude a role for less common infections, caused by Epstein-Barr virus, toxoplasma, or cytomegalovirus, for example. Nor does it exclude a rare complication of a common infection. The study power was adequate to detect small differences in the risk of chronic fatigue, but it had only a 50% power to detect a relative risk of 1.5 for the latest CDC criteria for chronic fatigue syndrome.²³ Overall, we conclude that the population attributable risk of acute infections on the prevalence of chronic fatigue syndrome is low.

Instead, our results suggest a link with previous fatigue and previous psychological disorder. The strong association between previral fatigue and both idiopathic chronic fatigue and chronic fatigue syndrome contrasts with the findings of Cope et al.²⁹ The differences may reflect the limitations of reliance on retrospective reports of fatigability, rather than prospective assessments carried out before the subjects presented with viral infections. Retrospective accounts of previous fatigability, a necessary part of all the case definitions of chronic fatigue syndrome (which require that fatigue must be of new onset), are likely to be even less accurate in the patients with long-standing fatigue who make up most specialist samples of chronic fatigue syndrome.

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