

# The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review

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## Summary

The prognosis of chronic fatigue syndrome and chronic fatigue has been studied in numerous small case series. We performed a systematic review of all studies to determine the proportion of individuals with the conditions who recovered at follow-up, the risk of developing alternative physical diagnoses, and the risk factors for poor prognosis. A literature search of all published studies which included a follow-up of patients with chronic fatigue syndrome or chronic fatigue were performed. Of 26 studies identified, four studied fatigue in children, and found that 54–94% of children recovered over the periods of follow-up. Another five studies operationally

defined chronic fatigue syndrome in adults and found that <10% of subjects return to pre-morbid levels of functioning, and the majority remain significantly impaired. The remaining studies used less stringent criteria to define their cohorts. Among patients in primary care with fatigue lasting <6 months, at least 40% of patients improved. As the definition becomes more stringent the prognosis appears to worsen. Consistently reported risk factors for poor prognosis are older age, more chronic illness, having a comorbid psychiatric disorder and holding a belief that the illness is due to physical causes.

## Introduction

Chronic fatigue syndrome (CFS) is a poorly understood syndrome characterized by physical and mental fatigue, made worse by physical and mental exertion, present 50% or more of the time and lasting at least 6 months.<sup>1,2</sup> The fatigue is accompanied by a range of physical and psychological symptoms, especially myalgia and depression. The prognosis of chronic fatigue is uncertain. Some—particularly the lay literature—suggest a lifelong course with only infrequent recovery, whilst others state that recovery is the norm.<sup>3</sup> Chronic fatigue (CF) is the more common and less severe 'subsyndromal' counterpart to CFS,<sup>4</sup> which we define as severe fatigue present 50% of the time and for at least 6 months, but which is not necessarily associated with functional impairment.

Given the conflicting views expressed over prognosis, and the relatively small size of many studies, we carried out a systematic review of all studies which have followed individuals with fatigue,

chronic fatigue or CFS. The aims of this paper were: (i) to describe the prognosis of fatigue states in terms of the proportion of individuals improved during the course of each study, and any outcomes reported such as additional medical illnesses, or deaths; (ii) to identify factors which may modify prognosis, including age of sufferers, severity and duration of illness at outset, coexistent psychiatric disorder and miscellaneous factors.

## Methods

### Literature search strategy and study selection

Papers giving any clinical follow-up/outcome data subsequent to ascertainment due to a primary diagnosis of CF or CFS from English-language peer-

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reviewed journals between January 1980 and March 1996 were identified from four databases: MEDLINE, EMBASE (BIDS), CURRENT CONTENTS and PSYCHLIT. The search strategy was (chronic\* or persist\* or post?viral) and (fatigue or exhaust\* or tiredness), or any of chronic fatigue syndrome, asthenia, neurasthenia and myalgic encephalomyelitis. All references were checked in title and abstract. The primary exclusion criteria were (i) papers which used mixed target symptoms (e.g. fatigue *and* pain) or mixed diagnostic categories (e.g. CFS *and* fibromyalgia) as entry criteria; (ii) papers whose main theme was the investigation or active treatment of either biological or psychological therapy. Papers which included placebo groups of patients entered for randomized controlled trials were included.

## Data extraction

A standard form was used to obtain information from each study. Studies were classified according to their design, which fell into three main groups: naturalistic studies which simply followed groups of sufferers from CFS over time; comparative cohort studies, where the same measures were used to compare outcome of CFS with that of some other illness; and randomized controlled studies which assigned individuals to placebo groups. Additional details noted related to the social demographic characteristics of the sample, the inclusion criteria for the study, the main outcomes used, and the setting.

Since the studies tended to use different outcome measures, very broad criteria were required to compare the results of studies. It was usually possible to obtain information on the number of individuals who fell into each of the following criteria: (i) recovered or improved; (ii) the same; (iii) worse; (iv) dead. Most studies used different standardized instruments of morbidity, but gave a global outcome measure of fatigue or well-being for the whole group. Information on other measures used was recorded whenever relevant. However, in all but one study,<sup>5</sup> overall objective functional and specific symptomatic measures were not available for the whole group. The number of subjects with new organic or psychiatric diagnoses and any account of treatment over time of follow-up and its length was also noted. Finally, any conclusions on predictors of outcome were noted. Data are presented according to the setting of the study, whether the study followed children or adults and according to the definition of CFS used.

## Results

### Characteristics of samples used

Studies varied in size from samples of 15 to 498 individuals (median 76). A wide variety of definitions

of CF and CFS were used, and relatively few studies used operational criteria for CFS. In eight cohorts, cases were excluded from the rest of the survey if the onset of fatigue had not been clearly defined, whereas in the remainder it was not specified whether onset was new or longer-term. This heterogeneity of case definition severely limits the comparability of these studies. The majority of studies (16/26) were hospital-based. Follow-up duration varied considerably, and some studies only reported a mean or median duration. All the studies which reported gender distribution had more women than men, as might be expected from the epidemiology of CF and CFS. Four studies were restricted to children and adolescents, another four described mixed child and adult groups, and 17 were restricted to adults. The majority of studies (22) achieved >70% follow-up. Three studies followed up 50% or fewer of their patients.

## Outcomes

### Mortality

Only 3 of the 2075 patients in the 19 studies followed with organic exclusions died. In some studies, it was not clear whether the vital status of the non-respondents was checked, hence the death rate could be higher. One of the known deaths was from an unrelated physical illness, another from an unspecified cause, and the other was by suicide.

### Newly-diagnosed physical illness

To assess newly-diagnosed physical illnesses, one needs studies which attempted to exclude current physical illness at their outset. About one quarter of such studies identified one or more cases of new organic illness. In the other 75% of such studies, which did not report new physical morbidity, it was not clarified if this was due to no new onsets or no explicit attempt to re-examine. Buchwald<sup>6</sup> found one case of anaemia, one of hypothyroidism, one onset of breast cancer and one case of sleep apnoea, i.e. four patients out of 74 followed up (5%). Hellinger<sup>7</sup> reported four cases of physical illness out of 30 followed up, but did not give specific diagnoses (13%). Kroenke<sup>8</sup> reported three cases of subclinical hypothyroidism, four of diabetes, one of anaemia and two of cancer (type not given); i.e. 10 cases out of the re-examined group of 102 (10%). Marshall<sup>9</sup> (the only child/adolescent study to report new morbidity) reported one patient with ulcerative colitis i.e. 1/17 (6%). Finally Wilson<sup>10</sup> reported a case of systemic lupus erythematosus and a case of presumed vascular dementia from 103 re-contacted (2%).

## Clinical improvement

Because the studies used widely differing patient populations, we present the results accordingly. First, there are four studies which exclusively assessed outcome in children seen in secondary care. Second, there were four studies which used recognized operational criteria to define cohorts of adult patients with CFS. Third, there was a mixed group of studies which followed CF cases in primary care or cases of fatigue in secondary care. We made the assumption that fatigue seen in secondary care was likely to be chronic, even though some of these studies did not specify the exact duration of fatigue. Finally, there were a number of studies which assessed outcome in adult patients presenting in primary care with fatigue of short duration.

Table 1 shows the outcome in children and adolescents presenting with chronic fatigue. All these studies were based in secondary or tertiary care, and two were in paediatric infectious disease clinics. The outcomes were based on the patient's or their parents' assessment of their clinical condition rated either face-to-face or by a telephone interview. The study with the longest follow-up (up to 6 years<sup>11</sup>) showed that approximately two-thirds of children made a complete recovery, and another quarter make a very substantial improvement. As a whole, these studies show encouraging results: 54–94% of children will make a definite improvement or a complete recovery. There is, however, a small minority of children who appear to have a very poor outcome, remaining bedridden or house-bound, and it is unclear from these studies what factors are associated with such outcomes.

Table 2 shows the outcome of adult cases of CFS defined according to recognized criteria. These studies show that only a small minority of cases (0–6%) recover to premorbid levels over the period of follow-up. There is more variation in the reports of improvement. The study with the longest follow-up<sup>10</sup> reported the highest proportion of patients improved, implying that with time a significant proportion gradually recover. Nevertheless, the overall level of functional impairment reported in this study showed that the majority of cases continued to be impaired carrying out routine activities. Two of the studies also reported a substantial proportion of cases (10–20%) in whom symptoms worsened over the period of follow-up.

The pattern of recovery for the mixed group of studies which followed up cases of fatigue not fulfilling full operational criteria for CFS is shown in Table 3. Some of these studies included patients who met CFS criteria among their cohorts, and some of the cohorts were for chronic fatigue. These studies are very mixed, as some of the cohorts are straightforward clinical series based on consecutive cases of

fatigue, whereas others are defined according to a history of viral illness.

Finally, studies which identify cases from primary care and include cases with fatigue of <6 months duration are described in Table 4. These studies show a good outcome. In all but one of these studies over 40% of patients had made a complete or nearly complete recovery during the duration of follow-up. If the definition is tightened so that only studies with chronic fatigue or those in secondary care are included, the picture is less favourable. There was only one study where more than 40% of patients made a complete or nearly complete recovery during follow-up. Hence it appears that one important determinant of prognosis is chronicity.

## Predictors of outcome

A range of predictors of good and poor outcome were identified in these studies. Most studies defined outcome in terms of current status at follow-up, rather than change in scores on fatigue scales over the follow-up period. Predictors of outcome have been grouped into five broad categories.

### Demographic predictors

We have already seen that children with CFS and chronic fatigue seem to have a good outcome. This is confirmed in these studies: 4/6 studies which tested for age as a predictor of outcome found an association between worsening outcome and increasing age. There were no other consistent patterns for other demographic attributes.

### Features of the initial illness

There were no strikingly consistent trends. In general, markers of a more severe illness (chronic symptoms, severe disability, more severe fatigue and more physical symptoms) tend to be associated with a poor outcome, although such associations were not consistently found.

### Psychological predictors

Psychiatric disorder is consistently associated with a poor outcome. Another consistent feature is the patient's belief in a physical cause of their symptoms, which predicted poor outcome in every study in which it was measured.

### Physical predictors

Apart from a weak association between raised oral temperature and better outcome in one study, there were no associations between physical characteristics

**Table 1** Studies of children with fatigue

Study	Setting and definition	Duration of symptoms at outset	Main outcome used	Detailed notes on outcomes
Carter <i>et al.</i> <sup>30</sup>	Paediatric infectious disease clinic, 31 patients under 18 years with 2 months medically unexplained fatigue	Median 11 mo, range 4–37 mo	Self rating of clinical condition at a median of 17 months	100% followed: 24/31 returned to normal or improved with occasional relapse, 2/31 had got worse
Feder <i>et al.</i> <sup>11</sup>	Clinical sample of 54 patients under 21 presenting to a paediatric outpatient department with at least 3 month medically unexplained severely debilitating fatigue	NK	Telephone contact by doctor 24–72 months later	89% followed: 31/48 reported resolution of symptoms; 14/48 had improvement, but continued to have symptoms; 3/48 had no improvement: one of these was functioning, the other two were home-bound
Marshall <i>et al.</i> <sup>9</sup>	Tertiary care paediatric infectious disease clinic; 23 chronic fatigue patients (aged 4 to 17) according to	Median 6 mo, range 1–60 mo	Telephone contact to family—parent or child's assessment of clinical state at 17–40 months	74% followed: 13/17 reported definite improvement, but six of these still had periodic episodes clinical referral of fatigue; two reported no change; one diagnosed with ulcerative colitis and one bedridden with unexplained fatigue
Smith <i>et al.</i> <sup>31</sup>	Secondary care sample of 15 adolescents (aged 13–17) with	Mean 18.4 mo, range 6–36	Structured telephone interview with patient or parent at 13–32 months	100% followed: 4/15 completely well; 4/15 markedly improved 6 months medically unexplained and 7/15 unimproved or worse. fatigue, plus physical symptoms 7/15 had mild or no activity restriction and 8/15 had moderate or severe restriction. Median of 15 school days missed in previous six months

**Table 2** Studies of chronic fatigue syndrome, defined according to operational criteria

Study	Setting and definition	Duration of symptoms at outset	Main outcome used	Detailed notes on outcomes
Hinds & McCluskey <sup>32</sup>	Immunology clinic. 393 CFS (CDC 1988) patients	NK	Postal questionnaire (unclear about duration of follow-up)	74% followed of which: 54/291 (19%) recovered; 35% 'improving'; 5% getting worse and remainder relapses and remissions
Peterson <i>et al.</i> <sup>33</sup>	Chronic fatigue syndrome clinic;	1–18 years	Postal questionnaire mean follow-up	91% contact: no recoveries; 68 CFS CDC 1988 patients at 12 months 40% improved; 10–20% worsening of symptoms
Tirelli <i>et al.</i> <sup>34</sup>	CFS referral centre. 265 CFS CDC 1988 cases	Median 3 years, range 6 mo-10 years	Followed at mean of 24 months.	100% followed of which: 8/265 method of follow-up unclear (3%) recovery 22/265 (8%) substantial decrease in symptoms, remainder in symptoms persisted.
Vercoulen <sup>13</sup>	Hospital sample of 296 self referred patients with Oxford CFS	Median 4.5 yrs range 2–54yrs	Mean follow up at 18 months. Postal Questionnaire for subjective opinion, BDI, SIP and functional impairment	83% followed of which, 3% reported complete recovery; 17% reported an improvement; 20% had got worse
Wilson <i>et al.</i> <sup>10</sup>	CFS referral centre; 139 patients fulfilling Australian criteria for CFS	Mean 9.2 yrs range 3–30yrs	Mean of 39 months follow-up with patient's self report, Karnofsky score, GHQ-30, and disability benefits received	103 (74%) contacted; 6 completely recovered; 65 improved and 31/103 could not work. Karnofsky rating 76.3 (corresponds to a disability level from 'cares for self, unable to carry on normal activities to normal activity with effort'). Two new diagnoses: one dementia, another SLE.

**Table 3** Chronic fatigue in primary care and fatigue in secondary care

Study	Setting and definition	Duration of symptoms at outset	Main outcome used	Detailed notes on outcomes
Bates <sup>35</sup>	Primary care sample of 22 patients with medically unexplained fatigue of 6 months duration. 17 cases of operationally-defined CFS	NK	Clinical state at mean follow-up of 12 months	86% followed: 5/19 no longer fatigued. 16/17 cases of CFS had remained fatigued
Bombardier & Buchwald <sup>36</sup>	Chronic fatigue clinic in University centre. 498 mixed cases of chronic fatigue (6 months fatigue but not full CFS) and CDC CFS	Mean 5 years for chronic fatigue; mean 5.2yrs for CFS	Postal questionnaire sent 1–31 months after initial visit	89% followed: 10/445 (2%) of total reported complete resolution of symptoms; 281/445 (64%) improved and 107/445 (24%) worse. One third were unable to work and another quarter reported decreased work performance. Over half had impaired family responsibilities
Buchwald <sup>6</sup>	Community survey to identify 74 cases of chronic fatigue: 6 months of new onset fatigue, causing impairment and excluding psychiatric and physical causes of fatigue	NK	Postal questionnaire of clinical symptoms at 12 months	100% followed: 16/74 reported resolution of fatigue. 3 cases of CFS (CDC) of whom none reported improvement
Chalder <i>et al.</i> <sup>1</sup>	116 chronic fatigue sufferers who responded to a community survey	At least 8 months	Postal questionnaire of symptoms and disability	Qualitative outcomes used. Slight overall improvements in fatigue
Clark <i>et al.</i> <sup>37</sup>	78 patients with chronic fatigue (6 months or more) in a CFS clinic (24% met CDC criteria). No systematic psychiatric exclusions	Mean 5.5 years	Postal questionnaire of symptoms and level of functioning at mean of 30 months	100% followed: 1 committed suicide. 32/78 (41%) reported moderate to complete recovery. 7/19 CDC cases recovered
Gold <i>et al.</i> <sup>38</sup>	Viral disease clinic. 26 patients with at least 9 months of fatigue with physical symptoms and raised EBV titres. No systematic psychiatric exclusion	Mean 3.5yrs	Clinical state 3–21 months after visit	81% followed of whom: 4/21 normal; 8/21 significantly improved
Hellinger <i>et al.</i> <sup>7</sup>	60 secondary care patients complaining of chronic fatigue with or without raised EBV titres. No systematic psychiatric exclusion.	NK	Postal questionnaire at 6–17 months	30 followed (50%), of these 2/30 resolved, 14/30 improved & 4/30 worsened. In four there were new medical diagnoses

Levine <i>et al.</i> <sup>5</sup>	31 patients in primary care identified following one of four outbreaks of 'post viral fatigue syndrome' in USA. Cases diagnosed on basis of severe and persistent fatigue	NK	Postal questionnaire at a mean of 24 months	84% followed: 12/26 functioning without limitation at 2yrs; 'almost all' subjects able to return to pre-illness activity at 3 years
Sharpe <i>et al.</i> <sup>12</sup>	177 patients presenting with at least 6 weeks fatigue in an infectious diseases clinic with impaired function and somatic symptoms	NK	Postal questionnaire including measures of functional impairment at 1.5–48 months	81% followed: of those followed for less than one year 62/82 (76%) reported functional impairment. This fell to 69% in those followed 1–2 years and 33% for those followed > 2 years. Only 13% considered selves fully recovered
*Valdini <i>et al.</i> <sup>39</sup>	Primary care: 22 patients with fatigue over one year. Organic not made	Mean 12 yrs	Clinical visits, mean 7 months after	100% followed: 5/22 improved (22%)

measured at baseline and outcome. Studies which had defined cases according to exposure to viruses did not find any associations with viral titres and recovery.

### Other predictors

Very few other predictors were reported, apart from in Sharpe's study,<sup>12</sup> where avoidance of alcohol, belonging to a self-help organization and changing or leaving employment were associated with a poor outcome. Treatments were not widely examined, but Vercoulen reported no association between improvement and treatment by either a medical specialist or alternative practitioners.<sup>13</sup>

### Discussion

Because the literature reviewed in this paper was very varied, in quality and aims, we decided not to proceed with our initial intention of a quantitative synthesis of the literature, preferring to present the main results of individual studies as they stand. The main findings of this paper are first, that CF/CFS is not associated with increased mortality. Second, if subjects are properly investigated at the outset, it is rare for new physical diagnoses to appear. Third, the outcome of chronic fatigue in children appears to be favourable, although a small minority remain chronic invalids. Fourth, the outcome of CFS and chronic fatigue in adults is of concern, with most patients reporting symptoms and disability at follow-up. Fatigue of shorter duration in primary care has a better outcome. Finally the consistently reported predictors of poor prognosis are advancing age, psychiatric disorder and a belief in physical cause of the symptoms.

What are the implications of these findings? The first point is that despite the emotive subject of chronic fatigue and CFS in children, paediatricians seeing fatigued children may be able to reassure parents that the prognosis is better than often reported in the lay literature. Turning to adults, the studies reviewed indicate that complaints of fatigue in primary care are often self-limiting. Chronic fatigue and CFS, however, appear to run a chronic course in many sufferers, and these studies indicate that untreated the prognosis is essentially poor.

Overlap has been reported between CF/CFS and medically unexplained syndromes such as for example fibromyalgia syndrome (FMS).<sup>14</sup> It is noteworthy that FMS patients have similar outcomes, and like CF/CFS patients show better outcome in the one community sample studied<sup>15</sup> than in specialist settings,<sup>16–18</sup> and that children also have favourable outcome relative to adults.<sup>19</sup>

**Table 4** Primary care studies of fatigue of <6 months duration

Study	Setting and definition	Main outcome used	Detailed notes on outcomes
Calder <i>et al.</i> <sup>40</sup>	Primary care: 65 patients positive for coxsackie B virus serology and clinically 'post viral fatigue syndrome'	Patients' report of change at interview at 12 months	100% followed: of which 47/65 (72%) considered self unwell at six months and 36/65 (55%) at one year
Kroenke <i>et al.</i> <sup>8</sup>	102 patients attending primary care who identified fatigue as a 'major problem' for over one month without medical illness.	Postal questionnaire at six months and one year	100% follow up: 2/102 patients developed cancer, 29/102 fatigue improved (28%). 22/102 worsened and remainder unchanged
*Elnicki <i>et al.</i> <sup>41</sup>	52 patients with a chief complaint of fatigue of at least one month's duration. Exclusion only if already established medical cause	Global assessment of change at interview at six months	79% followed: 20/41 reported resolution of fatigue; 17/41 improvement and none got worse
*Nelson <i>et al.</i> <sup>42</sup>	113 patients screened by self report questionnaire in primary care. Fatigue present for one month or longer, and was a major problem. Not excluded if medically ill and no systematic psychiatric exclusion	Telephone questionnaires completed at 3, 6, and 12 months	74% follow up: 51% better; 16% 'substantially improved' at one year. Of those identified as questionnaire fatigue, 35% better at one year
*Teitelbaum & Bird <sup>43</sup>	64 patients presenting with chief complaint of fatigue of at least 2 months duration & functional impairment without initial medical exclusion or systematic psychiatric exclusion	Mean follow-up 15 months: assessed on clinical visits	100% followed: 37/64 patients had almost complete resolution of symptoms and 25/64 showed significant but incomplete improvement. Study looked at treatment of subclinical hypothyroidism and hypoadrenalism
*Valdini <i>et al.</i> <sup>44</sup>	115 patients screened for new onset fatigue of one month on Rand Index of Vitality. No organic exclusions or systematic psychiatric exclusions	Telephone follow up at one year	64% followed: 31/73 not fatigued at follow up
*White <i>et al.</i> <sup>45</sup>	101 patients post glandular fever: fatigue present for 2 weeks, and associated with incapacity	Standardized interview at 1, 2 and 6 months	96% followed: By 6 months 55/97 (57%) were well

Table 5 Predictors of outcome

Study	Demographic	Initial illness	Psychological	Physical
Bombardier <i>et al.</i> <sup>36</sup>	Older age did worse	Longer duration of symptoms and shorter duration of follow up associated with worse outcome	Lifetime dysthymia associated with poor outcome	Raised oral temperature associated with better outcome
Calder <i>et al.</i> <sup>40</sup>	No report	Good outcome if presented with paraesthesiae, dyspnoea or anorexia	No report	No association between recovery and viral titres, lymphocyte levels, or liver function
Chalder <i>et al.</i> <sup>1</sup>	No association	No report	Psychological distress and attributions predict poor outcome	No report
Clark <i>et al.</i> <sup>37</sup>	Older age and less schooling associated with poor outcome	Multiple physical symptoms, longer duration of fatigue associated with poor outcome	Lifelong dysthymia associated with poor outcome	No report
Hellinger <i>et al.</i> <sup>7</sup>	No report	No report	No report	EBV serology not associated with outcome
Hinds & McCluskey <sup>32</sup>	Patients under 20 years had better outcome	No report	No report	No report
Kroenke <i>et al.</i> <sup>8</sup>	Old age associated with poorer outcome but no association for	More disability associated with poorer outcome; non-significant association education with longer duration of fatigue and poorer outcome. No association with fatigue severity or somatic symptoms	BDI not associated	BMI not associated
Sharpe <i>et al.</i> <sup>12</sup>	Gender, age, marital status NOT associated with outcome	Better outcome with increasing duration of follow-up. No association with duration of symptoms at start	Emotional disorder, and belief in viral aetiology associated with poor outcome	No report
Vercoulen <i>et al.</i> <sup>13</sup>	No associations found	Short duration of fatigue and lower fatigue scores associated with a good outcome	Positive self efficacy, and not attributing to a physical cause associated with good outcome	No report
Wilson <i>et al.</i> <sup>10</sup>	Age at onset not associated	Duration of illness not associated	Strength in belief of a physical cause and psychiatric disorder developing during the illness associated with a poor outcome. No association for neuroticism and premorbid psychiatric disorder	No association with cell-mediated immunity

The risk factors for poor prognosis include psychiatric disorder and illness beliefs. We suggest that whatever the original cause of fatigue, there are theoretical reasons to argue that these factors are important perpetuators of the illness.<sup>20–22</sup> These prognostic factors are not unique to CF/CFS. Studies have suggested that depression is an important predictor of poor outcome (expressed both in terms of mortality and quality of life) in many physical illnesses.<sup>23–25</sup> Beliefs about illness are important predictors of behaviour and desire to participate in rehabilitation. Such faulty attributions predict failure to return to premorbid levels of functioning.<sup>26</sup> In CFS, the belief in a solely physical cause for symptoms may be predictive of avoiding exercise or reducing other activities which might prolong disability. If the patient has expectations of failure, it is important not to compound these with uncorroborated predictions of gloomy outcome. On the positive side, the influence of attributional factors indicates an opportunity for effecting change.

This review concerns the prognosis of CF/CFS without treatment. Recent studies have suggested that rehabilitation programmes can alter the short- and medium-term prognosis of the condition<sup>27–29</sup> — further research is needed to determine the long-term effects of such treatment.

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