The prognosis of different fatigue diagnostic labels: 
a longitudinal survey

William T Hamilton\textsuperscript{a}, Arlene M Gallagher\textsuperscript{b}, Janice M Thomas\textsuperscript{c} and 
Peter D White\textsuperscript{b}


\textbf{Background.} Several different diagnostic labels exist for the fatigue syndromes, including chronic fatigue syndrome (CFS), myalgic encephalomyelitis (ME) and postviral fatigue syndrome (PVFS). An allied condition is fibromyalgia. No study has examined prognostic differences across these different labels.

\textbf{Objective.} To compare the prognoses of patients labelled with different fatigue syndromes in primary care.

\textbf{Methods.} We performed a longitudinal survey, using electronic records from the General Practice Research Database. All 18 122 patients diagnosed by their GP with a fatigue syndrome from 1988–2001 with a minimum of one year of records after diagnosis were collated into four groups: CFS, ME, PVFS and fibromyalgia. CFS and ME were combined for the main analysis as no code for CFS was available until 1995. The length of illness was calculated as the interval between the diagnosis and the last recorded fatigue symptom, expressed as days per year, to account for differing lengths of record after diagnosis.

\textbf{Results.} Patients with CFS/ME combined had a worse prognosis (median length of illness 80 days per year; interquartile range 0–242) than fibromyalgia (51; 0–244) or PVFS 0 (0–108), a significant difference, \(P < 0.001\). In a subgroup analysis, ME had a worse prognosis (median length of illness in days per year 106; interquartile range 0–259) than CFS (33; 0–170), \(P < 0.001\), in spite of a better course before diagnosis. Secondary outcome measures were consistent with these results.

\textbf{Conclusion.} There were important differences in outcome between the various fatigue labels, with ME having the worst prognosis and PVFS the best. This could be an adverse effect of the label ME itself. Alternatively, patients who are destined to have a worse prognosis may preferentially attract the ME label. Our data support the first interpretation.

\textbf{Keywords.} Chronic fatigue syndrome, primary health care, prognosis.

\section*{Introduction}

Chronic fatigue syndrome (CFS) is a relatively new name for a condition that has probably always existed. Other names are used, such as postviral fatigue syndrome (PVFS) or myalgic encephalomyelitis (ME). Whether these different labels represent separate conditions or the same disorder is hotly debated. Each label is unsatisfactory in some way: for example, fatigue is not the only component of CFS, making this label unattractive to some. Equally, myalgic encephalomyelitis implies a pathological abnormality that has not been demonstrated, and postviral fatigue gives emphasis to what may have been only a triggering event. Fibromyalgia is characterised by widespread pain and muscle tenderness, but also has prominent fatigue and is closely related to CFS.\textsuperscript{1–3} These different labels may have arisen in part from medical specialism, in that particular labels are favoured by certain specialists.\textsuperscript{3}

Giving a condition a name helps to guide treatment and to advise on prognosis. It may also influence outcome.\textsuperscript{4–6} There have been few prognostic studies of
CFS and none has compared prognoses across the different fatigue syndrome labels.\textsuperscript{7–12} One report of the duration of prolonged fatigue in primary care patients found equal durations of illness between patients who satisfied the international criteria for CFS, and those who did not.\textsuperscript{13,14} Other reports on the duration of illness have focused on features such as illness beliefs, but not examined the effect of the illness label itself.\textsuperscript{15} Therefore, we designed a study to investigate the prognosis of fatigue syndromes with different labels.

Methods

This was a cohort study based on pre-existing medical records. All patients with a diagnostic label of a fatigue syndrome were identified from the UK General Practice Research Database (GPRD) for the years 1988–2001 inclusive. In GPRD practices all patient consultations are recorded on computers using one of two coding systems, Oxmis or Read.\textsuperscript{16} These systems allow recording of both symptoms and diagnoses. When the GPRD began, all systems used Oxmis. Although the Read system was developed in the early 1990s, its adoption by practices was usually linked to upgrades to the practice’s software, and so there was very little use of Read codes before 1995. Since then Read coding has progressively increased and Oxmis decreased. The data are subjected to regular quality checks. Many studies have used the GPRD as their data source.

Identification of fatigue syndromes and symptoms

A list of fatigue syndromes was compiled from the library of Oxmis and Read codes (Table 1). We categorised the syndrome codes into four groups: CFS, ME, PVFS, and fibromyalgia. The first occurrence of a syndrome code was identified and called the date of diagnosis. The full, anonymised records for all these patients were extracted. Patients with a subsequent diagnosis in a different group were classified by their first diagnosis. A list of 32 codes for fatigue symptoms was also compiled. It was largely comprised of the terms tiredness, fatigue, lethargy and their synonyms. This list is available from the authors. All fatigue diagnoses or symptoms recorded after the initial diagnosis were identified. Only patients whose records extended for at least one year after diagnosis were studied, to reduce biases caused by temporary residents (who register temporarily with a doctor when away from home) and to produce a period for study free from potential bias by the different length of records across the different labels.

<table>
<thead>
<tr>
<th>Description</th>
<th>Oxmis (O) or Read (R)</th>
<th>Group</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postinfluenza asthenia</td>
<td>O</td>
<td>PVFS</td>
<td>21</td>
</tr>
<tr>
<td>Postinfluenza debility</td>
<td>O</td>
<td>PVFS</td>
<td>687</td>
</tr>
<tr>
<td>Post viral debility</td>
<td>OR</td>
<td>PVFS</td>
<td>2421</td>
</tr>
<tr>
<td>Post viral (asthenic) syndrome</td>
<td>OR</td>
<td>PVFS</td>
<td>6224</td>
</tr>
<tr>
<td>Post viral fatigue syndrome</td>
<td>OR</td>
<td>PVFS</td>
<td>6530</td>
</tr>
<tr>
<td>Myalgic encephalomyelitis</td>
<td>OR</td>
<td>ME</td>
<td>1200</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>R</td>
<td>CFS</td>
<td>159</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>OR</td>
<td>Fibromyalgia</td>
<td>880</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>18122</td>
</tr>
</tbody>
</table>

In both systems, the same group of words may be arranged differently and given a different code. For instance, post viral fatigue syndrome, postviral fatigue syndrome and PVFS have different codes. All the variations were identified, and are available from the authors, but for brevity are not shown above.

Outcome measures

The duration of the illness was defined as the time interval between the date of initial diagnosis and the final occurrence of a fatigue symptom or diagnosis. There were differences in the duration of medical records after diagnosis among the groups, so the primary outcome measure was the duration of illness as a proportion of the total record duration.

Secondary measures of outcome included proportions of each group with a subsequent fatigue code in the records, the median number of fatigue records and consultations (for any reason) each year after diagnosis. In order to examine whether different diagnostic labels were influenced by illness characteristics before diagnosis, we also measured the number of fatigue records in the year before diagnosis for all those patients who had at least one year of pre-diagnosis data.

Additionally, to remove potential bias from the differing lengths of records after diagnosis, we reanalysed the data for the period from seven to 12 months after diagnosis. As entry to the study required a minimum of one year in the records, the different lengths of record after this will not have affected these analyses. This analysis measured the number of consultations, and the proportion of patients with at least one fatigue code recorded during this six-month period.

Statistical analysis

Firstly, CFS was combined with ME to create CFS/ME, because of the widely held consensus that the two terms are interchangeable (although we also examined whether this is true).\textsuperscript{17} Furthermore, over half of the total dataset was from Oxmis coded data, which has no code for CFS. CFS/ME was compared with both PVFS and fibromyalgia using the whole dataset. The Read-only dataset was used for the CFS versus ME comparison.

None of the measured outcomes was normally distributed. Satisfactory transformations could not be found, so non-parametric methods were used for the
analyses. The Kruskal-Wallis test was used to compare the three groups CFS/ME, fibromyalgia and PVFS in the whole dataset. Where there were only two comparison groups, these were compared using the Mann–Whitney test. Comparisons of proportions were performed by chi-squared tests. Analyses were performed with Stata, version 8.18

**Results**

We identified 18 122 patients with a fatigue syndrome and at least one year of records after diagnosis. Details of the age and sex distributions for each group are shown in Table 2. Of the CFS group 27 (17%) had a subsequent diagnosis in a different group (11 ME, 2 fibromyalgia, 14 PVFS); of the ME group 226 (19%) had a subsequent diagnosis in a different group (61 CFS, 22 fibromyalgia, 143 PVFS); of the fibromyalgia group 74 (8%) had a subsequent diagnosis in a different group (12 CFS, 19 ME, 43 PVFS) and of the PVFS group 668 (4%) had a subsequent diagnosis in a different group (158 CFS, 391 ME, 119 fibromyalgia).

Table 3 shows the main outcome measures and the overall significance test results. Pair-wise comparisons showed the following differences. For CFS/ME versus PVFS all the outcome measures were significantly different ($P < 0.001$). For CFS/ME versus fibromyalgia, all differences in outcome measures, except length of illness ($P = 0.07$) and number of subsequent fatigue

<p>| Table 2 Details of patients with the fatigue syndromes and the coding system they appeared under |
|-------------|--------|--------|--------|--------|-----------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Number female (%)</th>
<th>Median age (IQR)</th>
<th>Number in Oxmis (%)</th>
<th>Number in Read (%)</th>
<th>Median (IQR) length of records after diagnosis, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS</td>
<td>159</td>
<td>97 (61)</td>
<td>36 (26–47)</td>
<td>0 (0)</td>
<td>159 (2.0)</td>
<td>768 (575–1127)</td>
</tr>
<tr>
<td>ME</td>
<td>1200</td>
<td>853 (71)</td>
<td>40 (30–48)</td>
<td>679 (6.6)</td>
<td>521 (6.6)</td>
<td>1768 (1042–2678)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>880</td>
<td>685 (78)</td>
<td>47 (38–56)</td>
<td>202 (2.0)</td>
<td>678 (8.6)</td>
<td>971 (634–1441)</td>
</tr>
<tr>
<td>PVFS</td>
<td>15883</td>
<td>10428 (66)</td>
<td>39 (27–53)</td>
<td>9355 (91.4)</td>
<td>6528 (82.8)</td>
<td>1823 (1035–2777)</td>
</tr>
<tr>
<td>Total</td>
<td>18122</td>
<td>12063 (66)</td>
<td>40 (28–53)</td>
<td>10236</td>
<td>7886</td>
<td>1757 (987–2720)</td>
</tr>
</tbody>
</table>

The difference in length of records across the four diagnoses is significant ($P = 0.001$: Kruskal-Wallis test).

| Table 3 Comparison of CFS/ME with fibromyalgia and PVFS |
|---------------|----------|----------|----------|-----------|
| Outcome measure | CFS/ME ($n = 1359$) | Fibromyalgia ($n = 880$) | PVFS ($n = 15883$) | Significance |
| Median (IQR) length of illness in days per year followed | 80 (0–242) | 51 (0–244) | 0 (0–108) | $P = 0.001$ |
| Number (%) with a subsequent fatigue symptom or diagnosis | 913 (67.2) | 530 (60.2) | 6672 (42.0) | $P < 0.001$ |
| Median (IQR) number of subsequent fatigue symptoms or diagnoses per year | 0.29 (0–0.78) | 0.31 (0–0.89) | 0.00 (0–0.29) | $P = 0.001$ |
| Median (IQR) number of primary care consultations per year after diagnosis | 6.9 (3.8–11.0) | 9.9 (5.7–15.7) | 6.0 (3.3–9.9) | $P = 0.001$ |
| Number (%) with a fatigue symptom or diagnosis in months 7–12 after diagnosis | 330 (24.3) | 677 (23.1) | 1610 (10.1) | $P < 0.001$ |
| Median (IQR) number of primary care consultations in months 7–12 after diagnosis | 4 (2–8) | 5 (3–10) | 3 (1–6) | $P < 0.001$ |
| Number (%) with a fatigue symptom in the year before diagnosis | 275 (34.9) | 67 (8.7) | 2258 (19.4) | $P < 0.001$ |

IQR = interquartile range.
Statistical testing: Chi-squared for measures expressed as a percentage; Kruskal-Wallis for measures expressed as medians.

* For this measure, only patients with a minimum of one year’s records before diagnosis were studied (CFS/ME $n = 788$, fibromyalgia $n = 774$, PVFS $n = 11639$).
症状或诊断数每年 \( (P = 0.76) \) 是显著的 \( (P < 0.001) \)。患有CFS/ME的患者在诊断前一年有更显著的疲劳编码数，而PVFS和纤维肌痛则不然。

表4展示了CFS和ME的比较。对于持续健康状况的三个度量，ME显著差于CFS。患有ME的患者在诊断前一年有更少的疲劳编码数，但这一差异是边缘性的 \( (P = 0.09) \)。

**讨论**

**主要发现**

患者对不同疲劳综合征标签有不同的预后。PVFS是标签中预后最好的，其次是纤维肌痛，然后是CFS。ME的预后最差。这在我们测量的任何情况下都是如此。标签间的差异在统计学和临床学上都是显著的。

**优点和局限性**

第一个问题是我们的结果可能因方法中的偏差而产生。显然，将初始诊断码和最终疲劳症状码之间的间隔作为疾病持续时间的代理是过简化的。患者可能有持续的症状，但不再向医生报告。疲劳症状在社区中非常常见，但很少被患者向医生报告。19%—2.5%的患者每年在初级卫生保健记录中记录疲劳症状。20,21 然而，没有理由认为不同的标签应该诱导不同的初级卫生保健使用模式，或报告疲劳。其他潜在偏差与我们使用最终症状码代表的疾病结束有关，患者如果有更长的记录则可能有更多的机会报告一个症状（这可能与他们最初的疾病无关）。我们使用疾病持续时间调整了记录，这在一定程度上克服了这一潜在偏差。对于结果7–12个月后诊断，结果是相似的，因此，如果有的话，这个潜在偏差的影响是小的。

**标签选择**

有几个方面会决定GP使用特定标签。首先，在ICD编码之前，医生无法使用CFS标签，我们不知道他们当时使用的是什么标签。其次，患者可能更偏好其中一个标签：事实上，他们可能在咨询医生之前已经自诊了自己的条件。2同样，医生可能有偏好，这可能受到他们对患者最近病史的了解的影响，尽管我们没有找到显著的差异在诊断前的疲劳报告之间。CFS和ME的标签变化比例相当低（4%至19%），这表明一旦给定一个特定的标签，患者和他们的医生就会照搬到使用。一些医生认为利用任何疲劳综合征标签的便利性，而其他人则有个人偏好。22 最后，有世间的改变——或者说它更多
simply, fashions—for particular labels. We cannot know how much any of these factors influenced the choice of label.

Interpretation of the findings
ME had the worst prognosis of the fatigue syndrome labels. The simple explanation that ME is a different illness which carries a poorer prognosis is hard to accept as this would imply that GPs are able to differentiate it from the other conditions. This may be true when comparing ME with PVFS, since ME is by definition a chronic illness, whereas PVFS need not be. But this would not explain the difference between ME and CFS, since both conditions are chronic.

More likely are two competing explanations. The first explanation is that the label itself confers a worse prognosis. Giving a disease label can lead to increased illness behaviour, as has been seen with hypertension. A study comparing matched fatigued patients found that those who attributed their fatigue to ME had a worse prognosis than patients who attributed their fatigue to psychological or social factors. It is possible that the label ME with its suggestion of an untreatable pathological process may somehow render the patient less able to combat their symptoms and disability than other labels. The second explanation is that those who are destined to have a worse prognosis preferentially attract the label ME, perhaps by self-diagnosis. Previous studies have shown that belief in a physical cause for the illness is linked with a worse prognosis. More patients diagnosed with ME believe the illness has a physical cause than those not so labelled. It is possible that patients with these beliefs reject the alternative labels in favour of ME, and the GP accepts this.

Significantly more patients with CFS/ME had fatigue symptoms recorded before diagnosis than those with PVFS or fibromyalgia (Table 3). As PVFS has a triggering illness implied in its name this is not surprising. It is likely that the diagnosis of CFS or ME is deferred until the condition has been present for some time: indeed some doctors may be reluctant to give the disease label until six months have passed, as this time period is given in the international research criteria for diagnosis. However, premorbid illness cannot explain the worse prognosis of ME when compared to CFS, as the premorbid reporting of fatigue was higher in the CFS group, albeit with marginal significance.

PVFS had the best prognosis, with over half of patients making no further complaint of fatigue. It is likely that the simple explanation is the correct one: that fatigue syndromes after a recognisable viral infection have a better prognosis. Most patients with a fatigue syndrome can identify a triggering event in the months before development of their condition. In a prospective primary care study of ‘postviral’ fatigue the worse prognosis occurred in those with less evidence of an initial viral infection. Our results suggest that the condition may be more benign if the trigger is a definite viral infection.

Fibromyalgia is defined by muscular tenderness and widespread pain rather than fatigue. Considering we used fatigue symptoms to identify continuing ill health it is remarkable that the prognosis of fibromyalgia was so poor. Our results are further evidence that fibromyalgia can be included within the rubric of fatigue syndromes. However, fibromyalgia appears different from the other labels in this study, by occurring in individuals on average seven years older, in a higher proportion of women, and in having an intermediate prognosis. The remarkably higher consultation rate after diagnosis with fibromyalgia cannot be explained by the age difference, as female consultation rates change relatively little between the ages of 16 and 74.

There is considerable debate in the patient and researcher communities about whether fatigue syndromes are essentially one illness with several synonyms, or whether there are distinct subgroups which should be studied separately. This is the first study to show an important difference among the groups. However, caution should be exercised before using this study to strengthen the case for there being distinct subgroups. This is because we cannot be sure which came first: the different prognosis or the different label, although finding no significant difference in recorded fatigue before the diagnosis of CFS and ME suggests the latter interpretation. This can only be answered by a study examining the process by which patients and doctors agree their specific fatigue syndrome labels. The worse prognosis of the label ME needs further investigation.

Acknowledgements
We would like to thank our patients and colleagues, including Michael Sharpe, Nicola Wiles and Pat Mathewson who commented on earlier drafts of the paper.

Declaration
Funding: this study was funded by the Department for Work and Pensions. The research was conducted independently from the funding source. WTH is funded through RCGP/BUPA and NHS Fellowships, and his practice is funded through the NHS R&D General Practice scheme.

Ethical approval: obtained from the Scientific and Ethical Advisory Group of the GPRD.

Conflicts of interest: none.

References


Stata Statistical Software: Release 8.0 [program]. College Station, TX: Stata Corporation, 2001.


