

# Recovery from infectious mononucleosis: a case for more than symptomatic therapy? A systematic review

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## SUMMARY

*Infectious mononucleosis is usually an acute, transiently incapacitating condition, but for some sufferers it precipitates chronic illness. It is unclear which patients are at risk of a prolonged state of illness following onset of infectious mononucleosis and if there are any useful preventive measures that would facilitate recovery. The aim of this study was to review all cohort studies and intervention trials that provide information on: (a) the longitudinal course of ill health subsequent to the onset of infectious mononucleosis; (b) the relationship between psychosocial and clinical factors and recovery rate; and (c) the effect of interventions on recovery.*

*A systematic review was conducted, based on a search of the PSYCHINFO, MEDLINE, EMBASE and CINHAL databases up to October 2001, and ISI Science and Social Sciences Citation Indices up to 22 November 2001. Eight papers were identified that gave data on illness following onset of infectious mononucleosis. The best evidence concluded that there is a distinct fatigue syndrome after infectious mononucleosis. Eight papers explored risk factors for prolonged illness following acute infectious mononucleosis. Results varied on the association of acute illness characteristics and psychological features with prolonged ill health. Poor physical functioning, namely lengthy convalescence and being less fit or active, consistently predicted chronic ill health. Three trials reported on interventions that aimed to shorten the time taken to resolve symptoms after uncomplicated infectious mononucleosis. None of the drug trials found any evidence that drug therapy shortens recovery time. The trial that compared the effect of activity with imposed bed rest, found that those patients allowed out of bed as soon as they felt able reported a quicker recovery.*

*More information is needed on the course of ill health subsequent to the onset of infectious mononucleosis. Certain risk factors associated with delay may be amenable to a simple intervention in primary care.*

**Keywords:** *infectious mononucleosis; recovery rate; chronicity; systematic review.*

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## Introduction

It is estimated that, in a general practice of 10 000 patients, an average of seven new cases of infectious mononucleosis (IM, often referred to as glandular fever) will be seen per year (personal communication with the Birmingham Research Unit, on data from the Royal College of General Practitioners' 1% sample of general practices in England and Wales, 1996 to 1998). For practices with a high number of young persons the incidence is greater. In four studies of student populations, the incidence ranged from 110 to 480 cases per 10 000 population per year.<sup>1-4</sup>

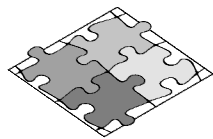
In 1948, Issacs<sup>5</sup> used the term 'chronic IM' to describe patients who reported symptoms lasting more than three months. Since 1948 there have been many studies that have reported symptoms, particularly fatigue or tiredness, persisting for months after onset of IM.<sup>6-16,18</sup> Some of these studies, particularly the older ones, are of poor methodological design and/or small sample size. They report a wide variation in time length of ill health following IM, but generally most patients recovered within a month. However, as IM is more common between the ages of 15 to 25, any delay in a return to health occurs at a crucial time when there is often personal, parental, and peer pressure to perform well in examinations and at sport, and to work hard at establishing a career.

Research papers on the management of IM have often focused on the effect of drug therapies, particularly acyclovir (ACV) and steroids, on oropharyngeal symptoms<sup>19</sup> or on rare complications, such as incipient airway obstruction.<sup>20</sup> Generally, the literature on the management of the illness has been based on clinical experience, rather than formal research. The focus has often been on the acute phase, rather than prevention or management of any lingering symptoms. The literature tends to give guidance on symptomatic relief,<sup>21-27</sup> on identifying and treating complications (such as severe pharyngeal oedema) on patients avoiding activity,<sup>26</sup> particularly vigorous activity<sup>22,27</sup> (because of the rare risk of splenic rupture), and on the need to rest.<sup>22,24-27</sup> However, one popular medical textbook writes that the therapeutic efficacy of rest and a slow return to normal activities has not been established.<sup>28</sup> The theme of most advice regarding chronic ill health following IM has been to promote positive expectations of a short illness,<sup>29,30</sup> although a classic medical textbook stressed the need after acute illness resolution for a prompt return to usual activities, to help prevent lingering symptoms.<sup>31</sup> Yet despite this our impression is that many patients are advised to rest by doctors and close relatives.

In this review paper we aim to answer three questions:

**HOW THIS FITS IN***What do we know?*

Some patients with glandular fever take a long time to recover and report persistent symptoms.

*What does this paper add?*

This systematic review shows that while there are major gaps in the evidence, 9.22% of the sufferers have chronic fatigue syndrome six months following acute glandular fever. Physical deconditioning may play a key role in causing prolonged symptoms, and GPs should probably avoid advising rest for patients recovering from glandular fever.

1. How frequent are chronic symptoms following IM?
2. Are there any risk factors for such symptoms?
3. Do any interventions prevent chronicity of symptoms?

**Method***Literature search strategy and study selection*

The review was limited to cohort or intervention studies that explored the longitudinal course of ill health beyond six weeks after onset in uncomplicated IM and gave data on duration and predictors of, or interventions to prevent, delayed recovery/chronic ill health. Because of the limited number of prospective studies, retrospective cohort studies (in which patients were identified from available case notes or research) were also included.

Papers were extracted from English language peer-reviewed journals up to October 2001 from the PSYCHINFO, MEDLINE, EMBASE and CINAHL databases. The ISI Science and Social Sciences citation indices were searched up to 22 November 2001. The search criteria were 'infectious mononucleosis' or 'glandular fever', with 'prognosis' or 'recovery' or 'risk factors' or 'duration/time factors' or 'anxiety disorder' or 'depression' or 'depressive disorder' or 'stress, psychological' or 'drugs/drug therapy' or 'anti-inflammatory agents, steroidal' or 'glucocorticoids' or 'prednisolone' or 'acycolovir'. References were checked for relevance in the title and abstract. References in the papers found were also checked. The search criteria were devised by two reviewers (BC and MH); papers were selected and read by one author (BC).

A standard form was used to obtain information from each study. Studies were classified according to their design and conduct, the setting, sample characteristics, aim of study, definition of IM, ill health and recovery, predictors of delayed recovery/ill health, and the main study outcomes. Standardised checklists were not used to assess quality but, rather, to provide a critical appraisal of included studies in the discussion.

**Results***Characteristics of studies*

Over 700 abstracts were found by initial subject search. Ninety-eight per cent were discarded from the examination of the title or abstract, because they did not give data on the

longitudinal course of ill health following onset of IM and/or outcome predictors. These studies were often non-clinical and either explored immunological or endocrine aspects of the illness or the aetiological agent of heterophile-positive IM, Epstein-Barr virus (EBV). Some were not included because they explored recovery for less than six weeks from the onset of IM. Others were not included — although they reported beyond six weeks after onset — because they did not quantify how many individuals had a protracted recovery or chronic ill health. One trial was included for its data on an intervention, but not for its data on duration. It recorded the course of three features (weight loss, absence from school or work and sore throat) whose return to normal does not imply complete recovery.<sup>32</sup> Finally, studies were not included if they explored treatment of IM complicated by severe problems, such as incipient airway obstruction. Of the remaining 16 papers for which full texts were retrieved, three were trials,<sup>6,32,33</sup> eight were prospective,<sup>8,14-18,34,35</sup> and five were retrospective cohort studies<sup>7,13,36-38</sup> (Table 1).

Eight studies gave data on the duration of symptoms and ten studies gave data on risk factors for prolonged ill health. Studies varied in sample size, from 25 to 337. Diagnosis of IM was by various laboratory evaluations, in addition to clinical features. Features of illness and recovery were generally measured by patient report. Some studies used validated scales for certain features, such as fatigue, psychological symptoms, life events, and physical functioning. The intervention studies mostly used hospital inpatients. The cohort studies generally used student populations. Three studies used a primary care population; one of these compared their main outcome between the primary care and student sample groups and found no difference.<sup>14</sup> The duration of follow-up from onset ranged from two months to two years. Most studies reported that the sample was from a consecutive series. Not all reported response rates.

*Poor outcome*

Table 2 shows details of the studies that explored the longitudinal course of ill health six months or longer after the onset of IM. White and colleagues' prospective study used controls, who either had clinical features of IM (pharyngitis, cervical adenopathy and fever) but no serological evidence of a recent EBV infection, or who had symptoms of an upper respiratory tract infection (URTI).<sup>14,15</sup> They found that, six months after the onset of illness, two symptoms were significantly more common in IM subjects. Physical fatigue was present at six months in 40% of subjects in the IM group, compared with 15% of subjects who had suffered an URTI. Hypersomnia was present in 22% of subjects with EBV, compared with 2% of subjects with an URTI.<sup>14</sup> White's team concluded, after principal component analysis, that IM was a specific risk, both for a discrete acute fatigue syndrome and chronic fatigue syndrome (CFS) at six months after illness onset.<sup>15</sup> This syndrome was associated with such features as physical and mental fatigue, hypersomnia, poor concentration, irritability, transient sore throat, and swollen glands.<sup>15</sup> The prevalence of CFS six months after IM, depending on how the fatigue syndrome was defined (the definitions used for CFS were those of the Center for Disease Control, the Oxford criteria, and one specially designed for this study)

Table 1. Descriptions of studies.

Reference	(1) Aim(s) of study. (2) Design	Sample	Main outcome assessment(s)	(1) Month of follow-up/review. (2) Participation and response
Andersson et al <sup>22</sup>	(1) To explore the effect of oral acyclovir on recovery in IM. (2) Double-blind placebo RCT	n = 56 Inpatients (Sweden)	Clinical, laboratory, self-report, and days off sick	(1) 6. (2) None reported
Bruce-Jones et al <sup>24a</sup>	(1) To explore the effect of social adversity on the fatigue syndrome, psychiatric disorders, and physical recovery in IM. (2) Prospective cohort	n = 207 Primary care patients with IM, IM-like illness or URTI (UK)	CFS measured by the Oxford criteria, empirically defined criteria, and the Center for Disease Control criteria	(1) 2, 6. (2) Lost to follow-up = 7%
Buchwald et al <sup>17</sup>	(1) To determine how often IM precipitates chronic illness and a description of the risk factors for delayed recovery. (2) Prospective cohort	n = 150 US hospitals and outpatient clinics	Self-report and Symptom Checklist-90	(1) 2, 6. (2) 45% participated, lost to follow-up = 75%
Cadie et al <sup>28</sup>	(1) To determine how often IM is followed by anxiety and depression. (2) Prospective cohort	n = 36 General population (UK)	Middlesex Hospital Questionnaire	(1) 12. (2) 84% participated
Chang and Bittner <sup>26</sup>	(1) To determine what is the frequency of persistent fatigue following IM. (2) Retrospective review of medical records	n = 337 Student health centre (US)	Persistent fatigue beyond the second month, or fatigue of sufficient severity to require a return clinic visit or withdrawal from studies	(1) Not reported. (2) n/a
Chretien et al <sup>8</sup>	(1) To explore the predictors of the duration of IM. (2) Prospective cohort	n = 122 Student health centre (US)	Self-report of symptoms	(1) Until asymptomatic. (2) 23% lost to follow-up
Dalrymple <sup>6</sup>	(1) To investigate the relation of bed rest and activity to prognosis. (2) Quasi-randomised controlled trial	n = 131 Student health service (US)	Clinical, laboratory and self-report	(1) Until asymptomatic. (2) None reported
Greenfield et al <sup>27</sup>	(1) To test the hypothesis that there will be a positive relationship between psychological health and rate of recovery. (2) Retrospective cohort	n = 38 University students (USA)	Minnesota Multiphasic Personality Inventory	(1) 6. (2) None reported
Katon et al <sup>25</sup>	(1) To study the prevalence of psychiatric disorder and psychological distress in acute IM and during recovery. To examine the relation between baseline biopsychosocial factors with distress post-illness. (2) Prospective cohort	n = 144 Population-based (US)	Composite score for anxiety, depression and additional item subscales of the Symptoms Checklist-90	(1) 2, 6. (2) Response rate = 45%
Lambore et al <sup>13</sup>	(1) To explore acute and chronic symptoms of IM. (2) Retrospective cohort with matched controls	134 students with IM, and 105 with URTI (Canada)	Symptom recall and resumption of normal activities	(1) 24. (2) 67% participated
Rea et al <sup>18b</sup>	(1) To assess symptoms, clinical and functional measures in IM. (2) Prospective cohort	n = 150 In and outpatient clinics (US)	Standardised scales including the Symptom Checklist-90	(1) 2, 6. (2) 45% participated, lost to follow-up = 75%
Thompson et al <sup>7</sup>	(1) To explore the duration and nature of symptoms, and the association of acute phase factors with poor outcome. (2) Retrospective cohort	n = 25 University students (US)	Self-report of symptoms	(1) 8 to 14. (2) None reported
Tynell et al <sup>23</sup>	(1) To test what is the combined effect of acyclovir and prednisolone (oral and IV) on clinical, immunological and virological makers, and duration of IM. (2) Double-blind placebo RCT	n = 94 In and outpatients with IM (Sweden and UK)	Clinical, laboratory, self report and days off sick	(1) 6. (2) 4 withdrew
White et al <sup>14-16</sup>	(1) (a) To explore the incidence, risk and prognosis of acute fatigue, CFS and psychiatric disorders after IM. (b) To explore the predictions and associations of fatigue syndromes and mood disorders that occur after IM. (2) Prospective cohort	Primary care patients 103 with IM, 83 with a IM-like illness and 54 with a URTI (UK)	CFS measured by the Oxford criteria, empirically defined criteria, and the Center for Disease Control criteria	(1) 2, 6. (2) 53% participated. Lost to follow-up = 4%

<sup>a</sup>Study was a subsample of White et al study; <sup>b</sup>study was a subsample of Buchwald et al study. RCT = randomised controlled trial; URTI = upper respiratory tract infection; CFS = chronic fatigue syndrome.

Table 2. The prevalence and symptoms of ill health six months and beyond after the onset of IM.

Reference	Prevalence	Main symptom(s)
Buchwald <i>et al</i> <sup>17,18</sup>	12% at 6 months reported failure to recover	Fatigue and mononucleosis specific symptoms
Cadie <i>et al</i> <sup>38</sup>	At 12 months 65% of women had depression and 25% had anxiety (pre-IM 25% had depression and 15% anxiety) In men no excess post-infection	Not tested
Lambore <i>et al</i> <sup>13</sup>	6% reported symptoms persisting over a year	Tired more easily, daytime sleepiness, painful neck swelling and depression
Thompson <i>et al</i> <sup>7</sup>	56% at 6 months recalled being symptomatic and 16% at 11 months	Fatigue
White <i>et al</i> <sup>14</sup>	At 6 months 40% of IM subjects had fatigue, 22% hypersomnia, and 9 to 22% had a CFS The prevalence of psychiatric disorders rose in all illness groups at onset (by 55%) but was no longer elevated by 6 months	Fatigue and hypersomnia

ranged from 9% to 22%, compared with 0% to 6% after URTI.<sup>14</sup> Buchwald and colleagues in Seattle found in their cohort that 38% of subjects at two months and 12% at six months reported non-recovery.<sup>17</sup> Fatigue and hypersomnia abated more slowly than other symptoms.<sup>18</sup> In an intervention trial that explored the effect of bed rest on the course of IM, Dalrymple found that, in most cases, fatigue was the symptom of longest duration and that 10% reported not to have recovered by six weeks.<sup>6</sup>

Three retrospective studies assessed prevalence of prolonged illness. In the largest study, Lambore *et al* matched IM patients with controls with URTI. IM patients were found to recall more severe symptoms that lasted longer. Symptoms that persisted were: becoming tired more easily; daytime sleepiness; painful neck swelling; and depression. Eleven per cent of those who had IM reported persistent symptoms for longer than three months and 6% had symptoms that persisted over a year.<sup>13</sup> A smaller study found that 56% at 24 weeks, and 16% at 48 weeks, recalled having symptoms.<sup>7</sup> Again, the symptom most frequently persisting or recurring was fatigue. A substantially lower rate of delay in recovery from fatigue was found in Chang and Bittner's review of case notes at a student health clinic.<sup>36</sup> They found that 1.5% had persistent fatigue two months after onset, which is well under the expected levels of chronic fatigue in a general primary care population.<sup>39</sup>

The longitudinal course of psychological symptoms and the prevalence of psychiatric disorder subsequent to the onset of IM was explored in three studies. The best evidence is from the two prospective cohort studies.<sup>14,35</sup> Both studies found an increase in psychological morbidity early in the course of IM; one also found at this time a high prevalence of psychiatric disorder,<sup>14</sup> the other a prevalence similar to that found in the general population.<sup>35</sup> Neither found an increased prevalence of psychological morbidity at two and six months. In contrast, a small retrospective study found, at 12 months after the onset of IM, an excess of anxiety and depression in the women in their sample.<sup>38</sup>

### Predictors of poor outcome

Table 3 shows details of studies that explored possible predictors of poor outcome.

(a) *Clinical features.* Seven studies explored the association of prolonged illness with the presence or severity at onset or diagnosis of various signs, symptoms, and laboratory determinants of morbidity. Two found no association<sup>6,36</sup> and four found some features to be predictive.<sup>7,8,16,17,35</sup> Chretien *et al*; explored the widest range of symptoms. They found that gastrointestinal symptoms and palatal petechiae during the acute phase were associated with delayed recovery, but the best predictor was prolonged duration (greater than 11 days) of pre-diagnosis illness.<sup>8</sup> None of the other studies explored these factors. Neither Chretien *et al* nor Dalrymple<sup>6</sup> found delay associated with splenomegaly, whereas a smaller study did.<sup>7</sup> Katon *et al* found clinical (less severe onset symptoms) and biological features (higher aspartate aminotransferase levels) to be predictive of poor psychological outcome at two months, but not at later follow-up.<sup>35</sup> Enlarged cervical glands were found by White's group to be associated with poorer outcome at one and two months after onset<sup>16</sup> and Buchwald's group explored a range of symptoms and objective disease makers. After multivariate analysis they found that the only predictive clinical feature of self-reported non-recovery was a higher temperature during the acute phase of the illness.<sup>17</sup> This association was not found in the other studies that explored this.<sup>6,8</sup>

(b) *Psychological factors.* The influence of a range of psychosocial variables on recovery has been studied. In a review of case notes, a past history of depression was not found to be associated with delayed recovery.<sup>36</sup> Significant symptoms of depression and anxiety (measured by subscales from the Symptom Checklist-90) in recovery were not found to be associated with delay in one study.<sup>17</sup> White *et al* in his cohort found some psychological factors (mood disorders and personality) to be predictive of a CFS,<sup>16</sup> while a retrospective cohort study found an association between psychological co-morbidity (measured by the Minnesota Multiphasic Personality Inventory) and delayed recovery at six months after illness onset.<sup>37</sup> The available evidence on life events is also confused. The group in Seattle found in one study a clear association between self-reported failure to recover and life events (measured by the List of Threatening Experiences) prior to infection.<sup>17</sup> In another study they found an association with psychological distress six months after the onset of IM and adverse events (mea-

Table 3. Risk factors for poor outcome.

Reference	Psychological	Clinical features	Demographic	Behavioural
Bruce-Jones <i>et al</i> <sup>34</sup>	At 2 months there was a weak effect of life events with CFS. Social adversity was predictive of psychiatric diagnosis at 2 and 6 months. Social adversity was not predictive of length of time off sick.	Not tested	Not tested	Not tested
Buchwald <i>et al</i> <sup>17</sup>	Greater family support and more life events were predictive of self-reported delay in recovery at 6 months. No association found with current psychological disorder.	Higher temperature predicted delay at 2 months. Other baseline clinical and biological evaluations were <i>not</i> associated with recovery delay.	At 2 months being older and at 6 months being female predictive of delay.	Poorer physical functioning at baseline predictive of delay at 2 months
Cadie <i>et al</i> <sup>35</sup>	Not tested	Not tested	Female sex associated with psychological distress in recovery	Not tested
Chang and Bittner <sup>36</sup>	History of depression <i>not</i> associated	Acute IM hospitalisation <i>not</i> associated	Not tested	Not tested
Chretien <i>et al</i> <sup>6</sup>	Not tested	Gastrointestinal symptoms and palatal petechiae predicted self-reported delayed recovery. Baseline features <i>not</i> associated were other clinical signs of IM and WBC.	Not tested	Greater number of days from onset to diagnosis best-predicted delay
Dalrymple <sup>6</sup>	Not tested	Clinical features of IM were <i>not</i> predictive	Not tested	Bed rest associated with delayed recovery
Greenfield <i>et al</i> <sup>37</sup>	Psychological morbidity at 6 months associated with self-reported delay	Not tested	Not tested	Not tested
Katon <i>et al</i> <sup>35</sup>	Greater psychological distress at 2 months associated with lower social functioning at onset of IM, and less confidence in health care. At 6 months distress associated with past adverse life events.	Distress at 2 months associated with milder symptoms at IM onset, and higher SGOT/AST concentrations	Age or sex <i>did not</i> predict.	At 6 months distress associated with reduced activity around onset.
Thompson <i>et al</i> <sup>1</sup>	Not tested	Splenomegaly at onset was predictive of delay. Level of heterophil antibodies was <i>not</i> .	No sex difference	Longer convalescence associated with delay
White <sup>16</sup>	Pre-morbid mood disorder predictive of fatigue syndrome at 6 months	Cervical lymphadenopathy associated at 1 month and predictive at 2 months of fatigue syndrome. Other clinical features were <i>not</i> associated.	Not tested	Physical deconditioning associated at 1 month, and at 2 months predicted fatigue syndrome. Physical deconditioning at 2 months predicted CFS at 6 months.

CFS = chronic fatigue syndrome; WBC = white blood cell count.

sured also by the List of Threatening Experiences) that occurred after developing IM.<sup>35</sup> In London, White's team found a strong association between adverse events (measured by the Life Events and Difficulties Schedule) and psychiatric disorder following IM, a weak and transient association between adverse events and fatigue syndrome, and no association with physical recovery.<sup>34</sup>

(c) *Demographic features.* The Seattle group found older age and female sex to be associated with protracted recovery or distress post acute phase.<sup>17</sup> In a small retrospective study, Cadie *et al* found a higher prevalence of psychiatric distress following IM in their female group.<sup>38</sup> A retrospective study found no sex difference in recovery rate.<sup>7</sup>

(d) *Functional status.* In addition to Dalrymple's trial, whose results are presented below, four cohort studies explored the association between factors relating to functional status and prolonged illness. They found that, around onset and during the recovery phase, poorer physical functioning, as measured by patient report,<sup>17,35</sup> lower physical fitness,<sup>16</sup> and a longer absence from work/school,<sup>7</sup> were found to be associated with prolonged illness.

### *Intervention trials to prevent poor outcome*

For uncomplicated IM no evidence of benefit was found from the drug therapies acyclovir only, and acyclovir combined with prednisolone, in the trial by Anderson *et al*<sup>32</sup> and in the trial by Tynell *et al*.<sup>33</sup> The other trial, by Dalrymple, was quasi-randomised by alternative allocation and explored the effect of restricted activity on recovery.<sup>6</sup> The restricted activity group were inpatients on bed rest who were only allowed up for bathroom privileges until they had passed the acute phase (defined as becoming afebrile and having a substantial reduction in lymphocytes). There were two ambulatory groups (one inpatient, the other outpatient) who were both advised to pursue activities as desired. Those with poorer physical functioning, namely the bed rest group, took significantly longer to recover.

## Discussion

The main findings were:

1. The prevalence of prolonged illness after IM varies, from 1.5% to 56%. The symptom consistently reported to have longest duration was fatigue. One of the two largest prospective studies found that, six months after onset of IM, physical fatigue was present in 40% of subjects and 9% to 22% had a CFS. The other prospective study found that 12% of subjects reported not to have recovered by the same time.
2. No single clinical or psychological factor was consistently associated with poor recovery, but poor physical functioning consistently predicted prolonged illness.
3. The drug interventions of acyclovir only and acyclovir combined with prednisolone were found to be ineffective in reducing recovery time in uncomplicated IM. A single intervention trial exploring the effects of bed rest found that reducing physical activity delayed recovery.

### *Methodological issues*

Most of the studies of IM have inherent biases. Nearly all sampled university students. Therefore, although the illness is more frequent in higher socioeconomic groups<sup>39</sup> this sample choice would have under-represented adolescent sufferers (an age group with high incidence<sup>40</sup>) and lower socioeconomic groups. The intervention trials are inevitably skewed towards more severe cases. Only White *et al*,<sup>14</sup> Buchwald *et al*,<sup>17</sup> and Lambore *et al*<sup>13</sup> fully report participation and response rates. In two of these samples only around half agreed to participate.<sup>14,17</sup> However, Buchwald's team found that there were no differences in their sample with regard to age or sex between those who participated and those who did not. White's group found that, in their cohort, females and younger individuals were more likely to participate.

Information biases may have affected the results of some studies. In retrospective studies, those in the high-risk group for worse outcome (IM) may recall events differently to those in the low-risk group (non-IM illness). Misclassification can occur when subjects are erroneously categorised by disease status. In the earlier studies,<sup>6-8,13,35,37</sup> the serological test for EBV was not available; their results are likely to be affected by including other conditions. Misclassification could also have occurred in identifying cases from past medical notes.<sup>7,13,36</sup> Only four studies widely used validated measurements and standardised assessments to explore potential risk factors and features of IM.<sup>14,17,34,35</sup> Some studies used subjective evaluation or indirect measurements for outcome parameters. For example, one study included, as a measurement of prolonged recovery, whether a patient returned to the clinic for counselling — which overlooks those who may have sought medical advice elsewhere.<sup>36</sup> Results may also differ because studies varied in follow-up length.

Finally, although we attempted to identify as many eligible studies as possible by using an extensive literature search, it is possible that unpublished work, or work published in journals not indexed on the electronic databases we used, were missed.

### *Work in related fields*

The results from the reviewed studies should be seen in the context of the general literature on recovery from other viral infections. Cohort studies of other viral infections have suggested several psychosocial factors associated with prolonged morbidity; they also provide some overlaps with the general IM literature, namely, consultation outcomes (lower patient satisfaction<sup>42</sup> or receiving a sick certificate and/or a less definite diagnosis<sup>43</sup>), changing or leaving employment,<sup>44</sup> denial of symptoms by the patient,<sup>45</sup> prolonged convalescence,<sup>43</sup> somatisation,<sup>43,44</sup> psychological morbidity,<sup>43,44,46</sup> a delay in consulting,<sup>42</sup> and reduced activity.<sup>44</sup> Likewise, the negative effect of limiting activity in recovery of a broad range of conditions is not disputed,<sup>47,48</sup> therefore there is no reason to think that EBV provides an exception. Finally, although we searched all other papers that were referenced by the searched articles, the single randomised controlled trial of which we are aware that explored exercise

following a severe acute infection (hepatitis) found it not to be associated with a worsening of symptoms.<sup>49</sup>

### Physical deconditioning

There is some indication from the consistent evidence in this review that the level of activity at onset and in recovery may prove an important risk factor for prolonged illness.

Reduced activity,<sup>6,17,35,44</sup> lower fitness,<sup>16</sup> and a lengthy convalescence<sup>7,43</sup> could be associated with prolonged illness because a person becomes physically deconditioned, which perpetuates fatigue and other symptoms. Likewise, a delay in consulting,<sup>42</sup> delayed diagnosis<sup>9</sup> or a less definite diagnosis,<sup>43</sup> greater family support,<sup>17</sup> and somatisation,<sup>17,43,44</sup> may all be associated with prolonged recovery because they allow a person to maintain a sick role longer and thereby lead to physical deconditioning. These factors are amenable to interventions that promote rehabilitation<sup>50-52</sup> and are currently being tested in a pilot study of primary care patients with IM.

### Limitations to our current knowledge

Current knowledge is limited because few prospective studies have attempted to gain an integrated understanding of recovery from IM using a bio-psychosocial model. Knowledge is also limited because of the methodological weaknesses in some of the studies reviewed here. The lack of consistent findings of clinical and psychological risk factors during acute IM may simply reflect the wide variety of measures used. Further work is needed to assess how generalisable their findings are. We are now conducting a pilot of a prospective cohort study that tests the association of these factors in maintaining symptoms post acute IM.

### Conclusion

There is certainly room for more information, but we can already conclude that delayed recovery is not uncommon and that poor physical functioning during the acute phase and in recovery is associated with a poorer outcome.

Pending definitive evidence from randomised controlled trials, health workers can already use the information on the length of recovery and factors influencing it to advise patients, particularly those who fear longer incapacity. Likewise, because physical deconditioning is predictive, associated with side effects, yet amenable to simple remedies, doctors should be very cautious indeed before advising rest, as has been concluded in the case of low back pain.<sup>53</sup>

#### Key points

Fatigue is the most commonly noted symptom that can persist after the resolution of other acute symptoms in IM. Best evidence concludes that a fatigue syndrome exists in 9% to 22% of cases at six months after illness onset. The risk factor most consistently reported as predictive of chronic illness is reduced physical activity during the acute stage and in recovery from IM. Certain behavioural risk factors, such as reduced activity, may be amenable to interventions in primary care. The advice given by GPs to people with acute back pain has undergone a major shift in the last decade; perhaps a similar shift is needed for IM.

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