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Review article

Biopsychosocial risk factors of persistent fatigue after acute infection: A systematic review to inform interventions

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ABSTRACT

Objectives: Fatigue is a prevalent and debilitating symptom, preceded by an acute infectious episode in some patients. This systematic review aimed to identify risk factors for the development of persistent fatigue after an acute infection, to develop an evidence-based working model of post-infectious fatigue.

Methods: Electronic databases (Medline, PsycINFO and EMBASE) were searched, from inception to March 2016, for studies which investigated biopsychosocial risk factors of on-going fatigue after an acute infection. Inclusion criteria were: prospective design; biological, psychological or social risk factors; standardised measure of post-infectious fatigue (self-report scales or clinical diagnosis). Studies were excluded if the sample had a pre-existing medical condition, infection was conceptualised as 'vaccination' or they were intervention trials. A narrative synthesis was performed.

Results: Eighty-one full texts were screened, of which seventeen were included in the review. Over half included glandular fever populations. Other infections included dengue fever, 'general'/'viral' and Q-fever. Risk factors were summarised under biological, social, behavioural, cognitive and emotional subthemes. Patients' cognitive and behavioural responses to the acute illness, and pre-infection or baseline distress and fatigue were the most consistent risk factors for post-infectious fatigue.

Conclusion: An empirical summary model is provided, highlighting the risk factors most consistently associated with persistent fatigue. The components of the model, the possible interaction of risk factors and implications for understanding the fatigue trajectory and informing preventative treatments are discussed.

1. Introduction

Fatigue is a commonly reported symptom. Every year 1.5% of the UK population present to the GP with tiredness or fatigue as a new symptom [1] and between 5 and 7% of people attending primary care present with a primary complaint of fatigue [2].

Around half of people with tiredness/fatigue as a major or concurrent symptom recover within one year [3,4]. However, for some, fatigue persists for over six months, which is then defined as chronic [5,6]. If more stringent criteria are met, including fatigue that is disabling in nature, a diagnosis of chronic fatigue syndrome (CFS) may be made [5,7,8]. A recent review suggests the prevalence of clinically assessed CFS is approximately 0.76% of the population [9].

A number of precipitants or triggers have been associated with chronic fatigue, but no clear cause has been found [10]. One common precipitant is moderate to severe, infectious viral illness, including infectious mononucleosis (IM)/glandular fever, Ross-River virus (RRV) and *Coxiella burnetii* (Q-fever) [11–13]. However, the majority of people experiencing these infections do recover, suggesting that acute infection may be a 'necessary but insufficient cause' ([14]; p4). Current guidelines advocate tiredness/fatigue management in primary care by identifying and addressing relatively broad 'modifiable psychological, social, and general health factors' [15]. However, it is currently not known which specific factors should be targeted. Summarising the current evidence of modifiable risk factors which interact with infection to maintain or perpetuate post-infectious fatigue may provide clearer guidance for treatment.

A review by Candy et al. [16] investigated clinical and

Abbreviations: CFS, chronic fatigue syndrome; IM, infectious mononucleosis; RRV, Ross-River virus; GP, general practitioner; N, number; CDC, Centre for Disease Control and Prevention

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psychological variables associated with recovery after IM and found that poor physical functioning predicted prolonged ill health, whilst evidence for symptom-related and psychological risk factors (mood disorder and personality) was mixed. The review, however, focused exclusively on IM and a number of prospective infectious studies have been published since this date. Additionally, the outcome was broadly defined as 'recovery' rather than persistent fatigue, for example, absence of persistent symptoms and psychological well-being. This could account for some of the inconsistent findings reported.

A more recent scoping review identified a large number of heterogeneous risk factors associated with the onset of CFS. These ranged from childhood trauma and mood disorder, to family members with CFS and recent ingestion of raw milk [17]. This review only included studies measuring clinically defined CFS, potentially missing risk factors of more general, persistent fatigue. Additionally, the studies included did not necessarily focus on post-infectious fatigue and 'did not appear to reveal risk factors that are evidently useful for clinicians' by being potentially modifiable ([17], p924). Although fatigue can be precipitated by a range of factors, post infectious chronic fatigue may provide a more homogenous group to study [18]. Therefore, the primary aim of this systematic review was to identify biopsychosocial risk factors associated with persistent fatigue post-infection across the fatigue trajectory, which are potentially modifiable. Unmodifiable demographic factors such as gender were beyond the scope of the review. The secondary aim was to summarise the empirical findings in a theoretical model to guide development of early interventions to treat post-infectious fatigue.

2. Methods

2.1. Search strategy

The databases Medline, PsycINFO and EMBASE were searched from inception to March 2016. The search strategy combined MeSH terms and key-words relating to fatigue, predictive design and infection (see Appendix A for full search strategies). Relevant grey literature was identified by contacting experts in the field and searching OpenGrey. The reference lists and citations of included studies were also hand-searched.

2.2. Study selection

Table 1 provides the overview of inclusion and exclusion criteria for studies. KH screened titles and abstracts and two authors (KH, PR) screened full-texts. Any uncertainties about study inclusion were resolved with the wider research team.

2.3. Data extraction

The following information was independently extracted by KH and PR; infection characteristics, sample demographic characteristics, study design, statistical methods, risk factors, fatigue measure and follow-up time-points, and the statistical outcomes. Where relevant analyses were missing authors were emailed to request statistical results but responses were not received (N = 3). Both univariate and multivariate results were extracted, but univariate findings were prioritised during synthesis to enable comparability across studies where possible.

2.4. Assessment of within study risk of bias and study quality

The methodological quality and risk of bias of included studies was assessed using The Effective Public Health Practice Project Quality Assessment Tool [19]. The tool rates studies on selection bias, study design, confounding variables, blinding, data collection and degree of withdrawal. The tool was modified to better assess observational studies, based on other tools [20,21] (see Appendix B). We explored whether quality assessment domains could account for heterogeneity in review findings, according to recommendations by Reeves et al. [22].

2.5. Methods of analysis

The wide range of risk factors and fatigue measurement methods ruled out a meta-analysis. Therefore, narrative synthesis was used, identifying themes among risk factors [23].

To provide meaningful comparison, risk factor data were extracted in categories according to fatigue time scales and definitions. Current guidelines suggest categorising fatigue according to three time periods following acute infection; ≤ 3 months, 4 + months, and 12 + months [15]. Accordingly, we classified fatigue as i) sub-acute, ii) chronic and iii) long-term, respectively. Within the 'chronic' grouping a distinction was made between studies using diagnostic criteria (e.g. Oxford [8] and/or CDC criteria) to define 'CFS' and those measuring the presence of 'chronic fatigue' using self-report.

The review was conducted in accordance with PRISMA guidelines [24].

3. Results

3.1. Study characteristics

The search returned 1850 citations, of which 78 full texts were retrieved after screening titles and abstracts. Three full texts were identified from other sources. Eighteen articles met inclusion criteria. Study characteristics, including fatigue measures/criteria used, are detailed in Appendix C. Acute infections included IM (N = 9), Q-fever, Ross-River virus (or a combination of the three), dengue fever, viral meningitis and shiga toxin-producing *Escherichia coli* 0104 (STEC) infection. Three studies investigated populations with 'general' or 'viral' infections. A range of follow-up time-points were used but six months (chronic) was the most common (N = 11). The number of participants ranged from 71 to 2327, and mean ages fell between 16.09 years and 48.50 years.

Significant risk factors were grouped under five component themes

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Prospective study design	Intervention trials.
Patients who had experienced an acute (short-term, non-chronic) infection confirmed by a doctor or laboratory test.	The patient sample had a pre-existing medical condition.
Assessed the presence of fatigue at a stated follow-up time-point following the infectious episode.	The patient sample was already chronically fatigued at baseline.
Reported quantitative and empirical data investigating risk factors of fatigue.	The infection was conceptualised as 'vaccination'.
Measured fatigue outcome using a valid and reliable self-report tool or diagnosis by a medical professional according to international diagnostic guidelines [8,18] or professional clinical opinion at follow-up.	
Measured biological, psychological, social or emotional risk factors, either before the onset or at the time of acute infection (not demographics).	