Psychological Medicine, Page 1 of 12. © 2007 Cambridge University Press
doi:10.1017/S0033291707001602 Printed in the United Kingdom

REVIEW ARTICLE

Risk factors for chronic fatigue syndrome/myalgic encephalomyelitis: a systematic scoping review of multiple predictor studies

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Background. The aetiology of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is still unknown. The identification of risk factors for CFS/ME is of great importance to practitioners.

Method. A systematic scoping review was conducted to locate studies that analysed risk factors for CFS/ME using multiple predictors. We searched for published and unpublished literature in 11 electronic databases, reference lists of retrieved articles and guideline stakeholder submissions in conjunction with the development of a forthcoming national UK guideline. Risk factors and findings were extracted in a concise tabular overview and studies synthesized narratively.

Results. Eleven studies were identified that met inclusion criteria: two case-control studies, four cohort studies, three studies combining a cohort with a case-control study design, one case-control and twin study and one cross-sectional survey. The studies looked at a variety of demographic, medical, psychological, social and environmental factors to predict the development of CFS/ME. The existing body of evidence is characterized by factors that were analysed in several studies but without replication of a significant association in more than two studies, and by studies demonstrating significant associations of specific factors that were not assessed in other studies. None of the identified factors appear suitable for the timely identification of patients at risk of developing CFS/ME within clinical practice.

Conclusions. Various potential risk factors for the development of CFS/ME have been assessed but definitive evidence that appears meaningful for clinicians is lacking.

Received 9 October 2006; Revised 11 July 2007; Accepted 18 July 2007

Key words: Chronic fatigue syndrome, myalgic encephalomyelitis, risk, review.

Introduction

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is characterized by a range of symptoms, namely fatigue (often triggered by minimal activity), malaise, headaches, sleep disturbances, difficulties with concentration and muscle pain. The symptoms can fluctuate in their intensity. The severity of the disease varies considerably and CFS/ME can be a disabling condition, placing a substantial burden on patients, their carers and health-care professionals. The population prevalence is estimated at about 0.4% for adults in the UK, making it a relatively common condition (Department of Health, 2002).

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The views expressed in this paper are those of the authors and not necessarily those of the NCC-PC, RCGP or National Institute for Health and Clinical Excellence.

Widely accepted criteria for case definitions are the Oxford criteria (Sharpe *et al*. 1991) and the Centre for Disease Control (CDC) definition (Fukuda *et al*. 1994). The condition has been the topic of much discussion over the past two decades (Prins *et al*. 2006). Research continues to investigate potential causes (Afari & Buchwald, 2003; White, 2004), how to diagnose the condition (Bagnall *et al*. 2005) and what its treatment and management (Chambers *et al*. 2006) should involve. Children and severely affected patients are of special interest to clinicians as not all treatments can be applied and very little is known about the effectiveness of treatment in these groups (Bagnall *et al*. 2005).

Given the potential impact of the condition on patients, their carers and health-care professionals, the ability to identify risk factors involved with the development of the condition would be a crucial breakthrough. Specifically, in people presenting with early suspected CFS/ME (e.g. before the 6 months' illness duration necessary for a formal diagnosis),

it would be useful to know what the risk factors or prognostic flags are that might be linked with progression to CFS/ME and possibly indicate early interventions. We therefore conducted a systematic scoping review, bringing together all available studies in the literature that use an appropriate research design in order to identify risk factors for the development of CFS/ME. This was part of a larger project to find evidence to support the development of guidelines on the diagnosis and management of CFS/ME in adults and children.

We systematically searched the literature for studies that met strict inclusion criteria. Studies were considered that explicitly had the syndrome CFS/ME according to recognized case definitions as the outcome and used multiple factors to predict the progression to the development of the syndrome. The review aims at documenting which potential risk factors have been assessed and which factors appear to be significantly associated with the development of the syndrome.

Method

Literature search

We searched the databases Medline (1966 to May 2005), EMBASE (1980 to May 2005), PsycINFO (1872 to April 2005), CENTRAL (May 2005), Social Science Citation Index (1945–2005), Science Citation Index (1945–2005), Index to Scientific and Technical Proceedings (1982–2005), PASCAL (May 2005), Inside Conferences (May 2005), AMED (1985–January 2005) and HEED (June 2005). For each database, individual search strategies were developed (these are available from the authors). The search was broad with the objective of identifying all studies of CFS/ME and possible synonyms. We applied no language restriction. Further references were sought by scanning the reference lists of retrieved articles and submissions of study references from stakeholders involved in the development of the UK CFS/ME guidelines for the National Institute for Health and Clinical Excellence (NICE). On peer review of this publication, referees identified three more papers that met inclusion criteria and had been published after the search dates.

Study selection

Two reviewers independently assessed all titles and abstracts identified from the literature searches for potential relevance to the review questions. Potentially relevant papers were retrieved in full and assessed by two independent reviewers, applying the specified inclusion criteria. Two reviewers are commonly used in systematic reviews to minimize the risk of introducing bias to the results of the review. If the two reviewers cannot agree, a third reviewer is consulted to resolve the differences.

Inclusion criteria

Study type. Any study aimed at identifying potential risk factors or prognostic flags for the development of CFS/ME. Studies focusing on fatigue rather than the defined syndromes CFS or ME were not eligible for inclusion in the review. Studies that only assessed factors affecting the progression of the disease severity in the course of the condition were also excluded.

Population. Adults and/or children aged 5 years or more.

Study design. Any study reporting a multivariate or regression analysis. Studies only reporting rates of occurrences of individual sample characteristics or only reporting correlations with single risk factors were not eligible for inclusion in the review because of the high potential for bias associated with these study types.

Study characteristics, data extraction and study quality

The study information regarding participants, setting, study design, statistical method, analysed predictor variables and findings was extracted into standardized forms. Studies were formally classified (e.g. case-control study, cohort study) and the data collection methods regarding the predictors of CFS/ME were classified as retrospective (the diagnosis was established first and characteristics were assessed later), concurrent (the diagnosis and the predictor variables were assessed at the same time) or prospective (the study was designed prospectively, the risk factors were assessed at baseline and the diagnosis was established at follow-up).

The data extraction and assessment were carried out by one reviewer and checked by a second reviewer. Discrepancies were resolved by reference to the original study. Where necessary, arbitration was by a third reviewer.

Data synthesis

The findings are synthesized in a narrative review and summarized in a concise table to facilitate the comparisons of individual study results (see Table 1). The replication of results and discrepancies were investigated. Data relating to the pre-specified

subgroups of children and patients severely affected by CFS/ME were considered separately.

Results

Search results

The literature search identified 10 768 publications. Their titles and abstracts were screened: 643 full paper copies were retrieved and assessed for inclusion in the review (see Fig. 1). Eleven studies met the inclusion criteria (Bell *et al*. 1991; Wessely *et al*. 1995; Cope *et al*. 1996; White *et al*. 2001; Chalder *et al*. 2003; Huibers *et al*. 2004*a*, *b*; Viner & Hotopf, 2004; Heim *et al*. 2006; Hickie *et al*. 2006; Kato *et al*. 2006).

Study characteristics and quality

One cross-sectional survey (Chalder *et al*. 2003), one nested case-control and twin study (Kato *et al*. 2006), two case-control studies (Bell *et al*. 1991; Heim *et al*. 2006), four cohort studies (White *et al*. 2001; Huibers *et al*. 2004*a*, *b*; Viner & Hotopf, 2004) and three studies that combined a cohort study with a case-control study design (Wessely *et al*. 1995; Cope *et al*. 1996; Hickie *et al*. 2006) were identified. The majority of studies used a prospective design (Wessely *et al*. 1995; Cope *et al*. 1996; White *et al*. 2001; Huibers *et al*. 2004*a*, *b*; Viner & Hotopf, 2004; Hickie *et al*. 2006; Kato *et al*. 2006), one prospective study (Huibers *et al*. 2004*b*) combined prospective and concurrent data (measurements at baseline and at follow-up) to predict CFS/ME, one study combined retrospective and concurrent data collection (Bell *et al*. 1991) and one cross-sectional study used a concurrent data collection (Chalder *et al*. 2003). In nine studies the focus of the publication was on predicting CFS/ME in adults, although the birth cohort study of Viner & Hotopf (2004) used the prediction of ever having had or currently suffering from CFS/ME. Two studies examined the development of CFS/ME in children (Bell *et al*. 1991; Chalder *et al*. 2003). The quality of the reporting varied; several publications failed to present detailed descriptions of their statistical methods and not all studies reported the goodness of fit of the final prediction model.

Cope et al. (*1996*). Sixty-four adult patients with chronic fatigue (3 months' duration and a score of 9 or more on a fatigue questionnaire) and 64 matching controls were identified from a cohort of primary-care patients recruited 6 months previously with a clinically diagnosed viral illness. Twenty-three of the cases fulfilled criteria for CFS.

Heim et al. (*2006*). This case-control study compared self-reported childhood trauma and psychopathology in participants with clinically confirmed CFS and a matched control group. Forty-three cases met the 1994 CDC criteria for CFS.

Hickie et al. (*2006*). Identified patients with Epstein–Barr virus, *Coxiella burnetii* or Ross River virus ($n = 253$) were followed from the time of acute infection. At 6 months, 28 patients met diagnostic criteria for CFS and these were followed for a further 6 months and compared to a matched control group.

Huibers et al. (*2004a*). Employees ($n = 151$) who were on sick leave because of fatigue were followed for 12 months. Of these, 66 were CFS-like cases (met research criteria for CFS without a formal diagnosis) at baseline. All persons with medical conditions that could explain fatigue were excluded. At follow-up, 28 participants met CFS criteria.

Huibers et al. (*2004b*). Employees ($n = 1143$) with unexplained fatigue (excluding somatic conditions that could explain fatigue) were followed prospectively for 44 months. At follow-up, 94 participants met research criteria for CFS without a formal diagnosis (CFS-like caseness), 457 were non-CFS fatigue cases and 592 were no longer fatigue cases.

Kato et al. (*2006*). This study linked data on personality traits and stress obtained previously in a large twin sample ($n = 19\,150$) and a diagnosis of CFS or CFS-like illnesses established in a telephone interview. In this sample, 447 participants met the 1994 CDC criteria, all participants who reported fatigue at the time of the personality and stress assessment were excluded.

Viner & Hotopf (*2004*). Data obtained from a national birth cohort (babies born in England, Scotland and Wales, 5–11 April 1970) followed up at 5, 10, 16 and 29–30 years were analysed. At the last follow-up, 93 of 11 261 participants (0.8%) reported ever having CFS/ME and 48 (0.4%) reported having the condition currently.

Wessely et al. (*1995*). Questionnaires to assess fatigue and psychiatric morbidity were sent to over 2000 adult patients in participating general practices. Prevalence of chronic fatigue and CFS was subsequently assessed in patients who attended the surgery with a symptomatic infection (exposed cohort) or for other reasons (non-exposed cohort). Most (84%) were followed up at 6 months.

Table 1. *Study characteristics and results*

Study	Participants	Setting	Design	Method and analysed variables	Findings
Bell *et al.* (1991)	$n=63$ children (21 cases, 42 controls), % female = 48 *Age*: mean 12.8 years (cases), 12.3 (controls); median 13; range 6–17	USA School	Case-control study Retrospective and concurrent data collection	*Method*: Linear/multiple regression *Predictor variables*: Raw milk (at any time, recently), raw eggs, raw shellfish, raw cheese, other family members with CFS symptoms, allergies/asthma, private well (at present, at any time), outdoor camping, proximity to orchards or farmland, exposure to animals in the house (dogs, cats, fish, mice, birds, hamsters, others), home heating source (oil, electricity, hot air, wood, kerosene, natural gas), exposure to animals on property (cattle, horses, sheep, swine, cats, dogs, ducks, goats, chickens, others), tick bite, blood transfusion, appendicitis	Twenty-one children met 1988 CDC criteria (physician-confirmed diagnosis). The best logistic regression model included the variables *other family members with symptoms of CFS* (RR 35.9, 95% CI 2.84–488.5, $p=0.007$), *recent ingestion of raw milk* (RR 44.3, 95% CI 3.21–606.5, $p=0.005$) and *history of allergies or asthma* (RR 23.3, 95% CI 1.67–327.3, $p=0.019$). RRs adjusted for the other variables
Chalder *et al.* (2003)	$n=4240$ children *Age*: range 11–15 years	UK Community	Cross-sectional survey Concurrent data collection	*Method*: Logistic regression *Predictor variables*: Age, sex, mother's score on GHQ, presence of any anxiety disorder and any depressive disorder	Eight children met 1994 CDC criteria. Risk factors for CFS (CDC, 1994) were older *age* (OR 1.9; 95% CI 1.0–3.7, $p=0.03$) and *presence of an anxiety disorder* (OR 8.8; 95% CI 1.8–43.5, $p=0.008$). Female sex was not a significant risk factor ($p=0.8$)
Cope *et al.* (1996)	$n=128$ (64 cases of chronic severe fatigue, 64 controls), % female = 78 *Age*: range 18–45 years; mean 30.5 (cases), 31.4 (controls); S.D. = 6.5 (cases), 7.3 (controls)	UK Primary care	Cohort and Case-control study Prospective data collection	*Method*: Logistic regression *Predictor variables*: Age, sex, GHQ-3 score (psychiatric morbidity), symptom attributional style (mainly psychological, equally psychological/physical, mainly physical), sick certification and the presence of fatigue (all recorded at the time of the viral illness), and past psychiatric history	Twenty-three patients met the Oxford criteria. CFS 6 months after viral illness was predicted by *sick certification* (OR 8.5, 95% CI 4.2–17.2, $p=0.002$), a *psychological symptom attribution* (OR 2.1, 95% CI 1.6–2.7, $p=0.007$) and presence of *fatigue at the time of viral illness* (OR 6.4, 95% CI 2.5–16.4, $p=0.05$)
Heim *et al.* (2006)	$n=103$ (43 cases, 60 controls), % female = 82 *Age*: mean 50.5 years	USA Community	Case-control study Retrospective data collection	*Method*: Logistic regression *Predictor variables*: Exposure to childhood trauma adjusted for: age, sex, race; sample split by low *versus* high psychopathology	Forty-three participants met 1994 CDC criteria. *Childhood trauma* was associated with an elevated CFS risk even in the presence of low levels of psychopathology; risk increased in the presence of high levels of psychopathology (ranging from OR 3.39 when predicting CFS and low level anxiety to OR 8.07 when predicting CFS and high level depression). Analyses adjusted for age, sex and race

Hickie *et al*. (2006)	$n=253$, % female = 43 *Age*: mean 34 years	Australia Primary care	Cohort and case-control study Prospective data collection	*Method*: Linear/multiple regression *Predictor variables*: Age, sex, education, acute sickness, irritability, musculoskeletal pain, mood disturbance, neurocognitive disturbance, fatigue, pre-morbid psychiatric disorder, intercurrent psychiatric disorder, neuroticism, locus of control, confirmed Epstein–Barr virus, confirmed Ross River virus, confirmed Q fever	Twenty-eight participants met 1994 CDC criteria. *Fatigue* at baseline predicted CFS post-infection at 6 ($p<0.001$) and 12 months ($p<0.05$), *musculoskeletal pain* at baseline predicted CFS at 6 months ($p<0.05$)
Huibers *et al*. (2004*a*)	$n=151$ (138 at follow-up), % female = 55 *Age*: mean 43 years	The Netherlands Workplace	Cohort study Prospective data collection	*Method*: Logistic regression *Predictor variables*: Age, sex, education, group allocation (therapy or control), fatigue (Checklist Individual Strength), duration of fatigue, physical functioning (SF-36), pain (SF-36), and self-reported health (SF-36), depression (SCL-90), cognitive difficulties (SCL-90), somatization (SCL-90), exhaustion (MBI-GS), professional efficacy (MBI-GS), self-efficacy (SES), somatic attribution (CAL), psychological attributions (CAL), absence from work at baseline	Sixty-six participants met 1994 CDC criteria. Lower baseline scores on *physical functioning* predicted CFS in the whole group (OR per S.D. = 0.27, 95% CI 0.15–0.46) and in those not CFS-like cases at baseline (OR per S.D. = 0.15, 95% CI 0.06–0.46) at 12 months' follow-up. In the CFS-like employees at baseline, CFS was predicted by higher fatigue (OR per S.D. = 2.25, 95% CI 1.06–5.31) and pain scores (OR per S.D. = 2.56, 95% CI 1.37–4.76)
Huibers *et al*. (2004*b*)	$n=1143$, % female = 35 (CFS-like cases at follow-up); 27 (non-CFS fatigue cases); 33 (non-fatigue cases) *Age*: mean 43.8 years (CFS-like cases); 41.2 (non-CFS fatigue cases); 41.3 (non-fatigue cases); S.D. = 7.5 (CFS-like cases); 7.9 (non-CFS fatigue cases); 7.9 (non-fatigue cases)	The Netherlands Community (Sample of the working population)	Cohort study Prospective and concurrent data collection	*Method*: Logistic regression *Predictor variables*: Age, sex, low/middle/high educational level, fatigue severity (Checklist Individual Strength), burnout, need for recovery, emotional exhaustion, psychological distress, anxious mood, depressed mood, physical attribution of fatigue, psychological attribution of fatigue, no specific attribution of fatigue, self-rated health, health complaints, absent from work, impairment in work, impartment in activities, pregnancy, shocking life events in past 12 months, visit to GP or occupational physician, sleep disturbances	Ninety-four participants met 1994 CDC criteria at follow-up. Baseline factors that predicted CFS-like caseness compared with non-CFS fatigue at 44 months follow-up were older *age* (OR per S.D. = 1.36, 95% CI 1.08–1.84), *exhaustion* (OR 1.33, 95% CI 1.04–1.67) female *sex* (OR 0.41, 95% CI 0.24–0.70), low *educational level* (*v*. high, OR 3.82, 95% CI 1.92–7.61), middle educational level (*v*. high, OR 2.48, 95% CI 1.35–4.51) and self-reported *visits to the GP* (OR 1.98, 95% CI 1.19–3.29). Factors that predicted CFS-like caseness compared with no fatigue were *fatigue severity* (OR 1.37, 95% CI 1.11–1.86), *exhaustion* (OR 1.66, 95% CI 1.28–2.18), low *educational level* (*v*. high, OR 2.61, 95% CI 1.29–5.24), middle educational level (*v*. high, OR 2.38, 95% CI 1.27–4.45) self-reported *visits to the GP* (OR 3.06, 95% CI 1.71–5.50) and *occupational physician* (OR 0.46, 95% CI 0.22–0.95) and poor self-rated *health* (OR 0.56, 95% CI 0.33–0.95)

Table 1. (*cont.*)

Study	Participants	Setting	Design	Method and analysed variables	Findings
Kato *et al*. (2006)	*n* = 19 150, % female = 53 *Age*: range 42–64 years	Sweden Community (twin registry)	Nested case-control study and twin study Prospective data collection	*Method*: Conditional logistic regression *Predictor variables*: Extraversion, emotional instability, stress, interaction between the variables	Four hundred and forty-seven participants met 1994 CDC criteria. There was a 72% CFS risk increase with each standard deviation increase in *emotional instability* and a 64% increase for *stress*. When genetic influences were controlled (by including only monozygotic twins), the association between emotional instability and chronic fatigue was no longer significant; however, the impact of stress became more pronounced suggesting some genes may serve as a buffer and others may increase susceptibility to stress
Viner & Hotopf (2004)	*n* = 11 261, % female = 51 *Age*: 29–30 years at follow-up	UK Community	Cohort study Prospective data collection	*Method*: Logistic regression *Predictor variables*: Sex, father in professional/managerial occupation, mother achieved A levels or equivalent/degree/diploma, ethnicity, birthweight, birth order, presence of long-standing medical condition significantly limiting home and school life at 10 years, history of atopy by 10 years; obesity at 10 years; sport played in spare time and at school at 10 years, days of school missed for health or emotional reasons in past year at 10 years, score on British ability scales at 10 years; significant illness in either parent before 10 years, child behaviour problems (Rutter scale) and maternal malaise at 5 years; self-esteem, Rutter score, conduct/impulsive/hyperactive score and maternal malaise at 10 years, score on adolescent GHQ and maternal malaise inventory score at 16 years, malaise and occupation at 30 years	Ninety-three participants reported ever having CFS/ME (with 48 having it currently). CFS/ME was associated with having a *long-standing limiting medical condition at 10 years* (OR 2.2, 95% CI 1.3–3.8), female *sex* (OR 2.4, 95% CI 1.4–4.3), *father in professional/managerial occupation* in childhood (OR 2.5, 95% CI 1.4–4.3), high scores on *malaise* inventory at 30 years (OR 2.6, 95% CI 1.6–4.3) and negatively with sometimes or often played *sport* in spare time rather than never at 10 years (OR 0.5, 95% CI 0.3–1.0). Mother's educational status and socio-economic status at 30 years were *a priori* included in the model

Wessely *et al*. (1995)	$n=2366$ (1199 patients with symptomatic infections, 1167 other patients), % female = 68 (exposed cohort), 70 (non-exposed cohort) *Age*: range 18–45 years; mean 32.7 (exposed), 33.5 (non-exposed); S.D. = 7.5 (exposed); 7.5 (non-exposed)	UK Primary care	Cohort and case-control study Prospective data collection	*Method*: Linear/multiple regression *Predictor variables*: Age, sex, social class, number of visits to GP, fatigue questionnaire, GHQ scores before presentation (from community screening) and at presentation; fatigue questionnaire and GHQ scores at 6-month follow-up; results of CFS checklist, psychological assessment, functional impairment (MOS-SF), psychiatric morbidity, somatic symptoms for fatigue, coping, life events, anxiety and depression (HADS)	Thirty-six participants met CDC 1994, 33 Oxford, 20 Australian and 16 CDC 1988 criteria. There were no significant differences between the exposed and non-exposed cohorts in the proportion of CFS cases (by Oxford, Australian or CDC criteria) at 6 months. Adjustment for number of visits to GP during the year before recruitment did not affect the OR for CFS. Multivariate analyses for the syndrome were not reported. The authors concluded that the study provides no evidence that common infections are related to the development of chronic fatigue or CFS
White *et al*. (2001)	$n=250$; % female = 51 *Age*: range 16–65 years; median = 22	UK Primary care	Cohort study Prospective data collection	*Method*: Logistic regression *Predictor variables*: Age, sex, sample (GP *v*. student), vocabulary IQ, socio-economic class, father's socio-economic class, infectious mononucleosis, positive Monospot at onset, Epstein–Barr virus IgM positive, cervical lymphadenopathy, atopy, biochemical markers, fatigue at onset, time in bed at onset, exercise power, fitness (1-min step test), GP attendances in years before onset, pre-morbid psychiatric disorder (various times and GP record), pre-morbid psychiatric treatment, pre-morbid mood disorder, anxiety and depression (HADS at 1 and 2 months), social adversity, extroversion, emotionality (self- and peer rating)	Thirty-eight participants met Oxford, 17 the 1994 CDC criteria (18 patients with 'idiopathic chronic fatigue' were added to this group). Significant predictors of CFS (Oxford) 6 months after an infection were belonging to a *general rather than student primary-care sample* (OR 3, 95% CI 1.63–5.49, $p<0.001$), *mood disorder at 2 months* (OR 2.32, 95% CI 1.22–4.42, $p<0.01$) and *fitness at 2 months* (OR 0.35, 95% CI 0.22–0.90, $p<0.05$). When predicting CDC defined CFS, a pre-morbid *mood disorder* (OR 1.82, 95% CI 1.15–2.89, $p<0.01$) rather than the mood disorder at 2 months was predictive, as was *days in bed* (OR 1.07, 95% CI 1.02–1.12, $p<0.01$). There was a positive interaction between emotional personality and bed rest

CFS, Chronic fatigue syndrome; ME, myalgic encephalomyelitis; S.D., standard deviation; OR, odds ratio; CI, confidence interval; RR, relative risk; GP, general practitioner; GHQ, General Health Questionnaire; SF-36, Short Form Health Survey; SCL-90, Symptom Checklist 90; MBI-GS, Maslach Burnout Inventory – General Survey; SES, Self-Efficacy Scale; CAL, Causal Attributions List; MOS-SF, Medical Outcome Study 20-item questionnaire; HADS, Hospital Anxiety and Depression Scale; IgM, immunoglobulin M.

A detailed data extraction table can be obtained from the authors.

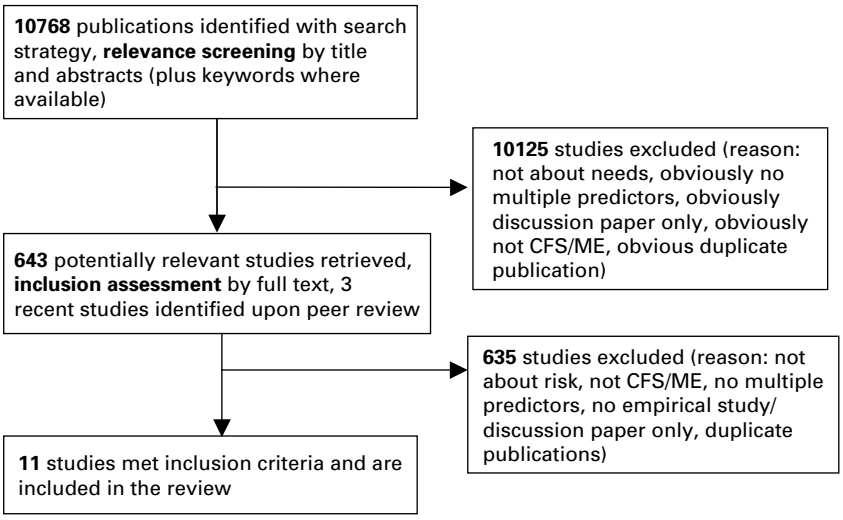

Fig. 1. Study flow.

White et al. (*2001*). Primary-care patients, including a cohort of students, with infectious mononucleosis or an upper respiratory tract infection were followed until 6 months after onset. The sample included patients meeting the Oxford criteria, the 1994 CDC criteria and patients with not otherwise specified fatigue or idiopathic chronic fatigue at follow-up.

Subgroups

Children and adolescents

Bell et al. (*1991*). All 914 students in a school district were sent a questionnaire regarding CFS symptoms. Thirty-three children with symptoms were interviewed, 21 had a physician-confirmed diagnosis of CFS. These were each matched with two randomly selected asymptomatic controls from the sample. Numerous risk factors and exposures were tested.

Chalder et al. (*2003*). Mothers ($n = 10\,438$) of children aged 5–15 in a survey of families living in private households in England, Scotland and Wales in 1999 were asked whether their child had ME or CFS. They were then asked to complete a General Health Questionnaire (GHQ). A sample ($n = 4240$) of children aged 11–15 was interviewed. The prevalence of CFS/ME was eight out of 4240 (0.19%).

Severely affected. No study was identified that predicted severe CFS/ME seperately.

Identified cases with CFS/ME and prevalences

The number of patients with CFS/ME who were identified in the individual studies and formed the basis for the outcome prediction varied from eight (Chalder *et al*. 2003) to 447 (Kato *et al*. 2006). The outcome CFS/ME was defined as meeting published criteria in three of the studies (Cope *et al*. 1996; Huibers *et al*. 2004*a*, *b*), in one study the self-report of having CFS or having had CFS was used (Viner & Hotopf, 2004), in four studies the participants seem to have been assessed in a diagnostic interview (Wessely *et al*. 1995; White *et al*. 2001; Chalder *et al*. 2003; Kato *et al*. 2006) and in three studies the participants had a diagnosis explicitly confirmed by a physician (Bell *et al*. 1991; Heim *et al*. 2006; Hickie *et al*. 2006).

The prevalence of CFS/ME was 0.19% in the social survey (Chalder *et al*. 2003), 0.43% (0.83% for lifetime prevalence) in the birth cohort study (Viner & Hotopf, 2004), 6.8% in the study of patients with infectious mononucleosis or upper respiratory infections (White *et al*. 2001), 8.2% in the sample of fatigued people within the working population of The Netherlands (Huibers *et al*. 2004*b*) and 18.5% in the group of fatigued employees (Huibers *et al*. 2004*a*).

Identified risk factors

The individual studies varied greatly in number and type of risk factors they analysed (see Table 1). These ranged from psychological characteristics (e.g. Huibers *et al*. 2004*a*) to very specific exposure incidences such as raw shellfish ingestion (Bell *et al*. 1991).

Factors that were found to be significantly associated with the development of CFS/ME in the final predictive models included: older *age* (Chalder *et al*. 2003; Huibers *et al*. 2004*b*), being *female* (Huibers *et al*. 2004*b*; Viner & Hotopf, 2004), low or middle

rather than high *educational level* (Huibers *et al*. 2004*b*), *father in professional/managerial occupation in childhood* (Viner & Hotopf, 2004), the presence of an *anxiety disorder* (Chalder *et al*. 2003), *mood disorder* (pre-morbid or 2 months post-infection, White *et al*. 2001), personality trait *emotional instability* (Kato *et al*. 2006), *stress* (Kato *et al*. 2006), *history of allergies or asthma* (Bell *et al*. 1991), a *long-standing limiting medical condition aged 10 years* (Viner & Hotopf, 2004), *musculoskeletal pain* (Hickie *et al*. 2006), *sick certification after viral illness* (Cope *et al*. 1996), *low fitness 2 months post-infection* (White *et al*. 2001), no *sport in spare time at 10 years old* (Viner & Hotopf, 2004), lower *physical functioning* at baseline assessment (Huibers *et al*. 2004*a*), *exhaustion* (Huibers *et al*. 2004*b*), the presence of *fatigue at time of viral illness* (Cope *et al*. 1996; Hickie *et al*. 2006), *fatigue severity* (Huibers *et al*. 2004*b*), *days spent in bed at the onset of an infection* (White *et al*. 2001), *visits to the general practitioner* (*GP*) *or occupational physician* (Huibers *et al*. 2004*b*), poor *self-rated health* (Huibers *et al*. 2004*b*), higher scores on *malaise* inventory at 30 years (Viner & Hotopf, 2004), *childhood trauma* (Heim *et al*. 2006), *psychological symptom attribution* (Cope *et al*. 1996), *other family members with symptoms of CFS* (Bell *et al*. 1991), *recent ingestion of raw milk* (Bell *et al*. 1991) and *belonging to a general rather than a student primary-care sample* (White *et al*. 2001).

All studies assessed the age of the participants and in most studies the association of age and the development of CFS/ME appeared to have been analysed. However, age was only found to be a significant predictor in two of the 11 studies: one a study predicting CFS/ME in children in England, Scotland and Wales (Chalder *et al*. 2003) and one a sample of the working population of The Netherlands (Huibers *et al*. 2004*b*). Gender was a predictor of CFS/ME in the final model in two out of the 11 studies, one following the working population sample (Huibers *et al*. 2004*b*) and the other the birth cohort study by Viner & Hotopf (2004). All included studies assessed the gender of the participants and several of the studies tested the association of gender and CFS/ME but in no other study was gender reported as a predictor in the final predictive model.

The educational level of the participant or the parents of the participating child was assessed in several studies. This variable was reported as significantly related to the development in CFS/ME in the final prediction model in two studies but conflicting effects were found; while a birth cohort study (Viner & Hotopf, 2004) found that growing up with a father in professional/managerial occupation increased the chances of developing CFS/ME slightly, Huibers *et al*. (2004*b*) reported that those employees with a higher educational level had lower odds of developing CFS/ME.

Several studies identified a medical or psychological vulnerability in the history of the participants who suffered from CFS/ME; that is, history of allergies or asthma in children (Bell *et al*. 1991), presence of an anxiety disorder in children (Chalder *et al*. 2003), sick certification related to a viral illness and presence of fatigue at the time of viral infection (Cope *et al*. 1996), a long-standing limiting medical condition at 10 years of age and scoring high on a malaise assessment inventory (Viner & Hotopf, 2004), high stress levels previous to diagnosis (Kato *et al*. 2006), musculoskeletal pain (Hickie *et al*. 2006) or a mood disorder (White *et al*. 2001). Childhood trauma was also associated with an elevated risk of CFS (Heim *et al*. 2006). Studies that followed up fatigued individuals seem to indicate that higher scores on defining or related CFS/ME criteria at the start of the study increases the likelihood of developing or continuing to suffer from CFS/ME (Huibers *et al*. 2004*a*, *b*).

In some studies a defining characteristic of CFS/ME was used, such as fatigue (e.g. Huibers *et al*. 2004*b*), to predict CFS/ME, or the differentiation between risk factor and defining characteristic or cause of CFS/ME was not made.

Discussion

For the presented systematic scoping review we searched the existing international literature thoroughly, applied strict inclusion and exclusion criteria, and took measures to reduce errors and bias to provide a comprehensive and clear overview of the existing multiple predictor studies on risk factors for the development of CFS/ME. This overview demonstrates clearly which potential risk factors have been assessed in the literature, which factors have shown a significant association with the development of CFS/ME, which results have been replicated and where there are inconsistencies in the existing literature.

The review identified 11 studies that met the specified inclusion criteria. These used a variety of methodological designs such as case-control study, cross-sectional survey, cohort studies including a study following a birth cohort, a combined cohort and case-control study design and a nested case-control study using data from a twin registry. Several studies used a prospective data collection design. In most studies the focus of the publication was on predicting CFS/ME in adults. No study was identified that predicted severe CFS/ME separately. The quality of the reporting varied but was poor overall, especially

with regard to the statistical methods, given the dependency of the results on the methods used.

The existing literature shows that a large number and a great variety of potential risk factors for CFS/ME have been assessed. However, the included studies did not appear to reveal risk factors that are evidently useful for clinicians in assisting them to establish a diagnosis for patients presenting with potential symptoms of CFS/ME. Significantly associated with the development of CFS/ME in the final predictive model were: older *age*, being *female*, low or middle rather than high *educational level*, *father in professional/managerial occupation in childhood*, presence of an *anxiety disorder*, *mood disorder* (pre-morbid or 2 months post-infection), *emotional instability*, *childhood trauma*, *history of allergies or asthma*, *long-standing limiting medical condition aged 10 years*, *sick certification after viral illness*, *low fitness 2 months post-infection*, no *sport in spare time at 10 years old*, lower *physical functioning* at baseline assessment, *exhaustion*, presence of *fatigue at time of viral illness*, *fatigue severity*, *days spent in bed at onset of an infection*, *visits to GP or occupational physician*, *musculoskeletal pain*, poor self-rated *health*, higher scores on *malaise* inventory at 30 years, *stress*, *psychological symptom attribution*, *other family members with symptoms of CFS*, *recent ingestion of raw milk* and *belonging to a general rather than a student primary-care sample*.

The included studies varied in the number and types of potential risk factors that they tested, ranging from psychological characteristics (e.g. Huibers *et al*. 2004*a*) to very specific exposure incidences such as raw shellfish ingestion (Bell *et al*. 1991). It stands to reason that only when potential factors have been assessed can an association be tested. Not all studies seem to have excluded CFS/ME-defining factors from the prediction of CFS/ME, which makes the studies difficult to compare.

The factors age and gender were kept in the final predictive model in two studies indicating that older age (in a sample of children and a working population sample of adults) and female sex increased the risk of developing CFS/ME. In other included studies these factors seem to have been assessed but the influence of the variable was negligible in the presence of other risk factors; for example, Chalder *et al*. (2003) explicitly reported that being female was not a significant risk factor. In the literature the prevalence of CFS/ME is reported to be approximately twice as common in women (e.g. Jason *et al*. 1999; Department of Health, 2002; Reyes *et al*. 2003). Educational level was also kept as a predictor in two of the included studies but the effects were in opposite directions. Even though CFS/ME was initially linked to a higher socio-economic status ('yuppie flu'), overall the studies included in the review do not suggest this, nor do other existing empirical studies (Department of Health, 2002).

Several predictors were clearly study specific (e.g. the sample affiliation the participant stemmed from; see White *et al*. 2001) or had not been assessed in other review eligible studies (e.g. raw milk ingestion; Bell *et al*. 1991). Some identified risk factors have been reported previously in studies predicting chronic ill health (e.g. being less fit or active after infectious mononucleosis has been replicated as a predictor of prolonged fatigue and state of illness; see Candy *et al*. 2002).

Several studies identified a medical or psychological vulnerability in the history of the person that will develop CFS/ME (e.g. the presence of an anxiety disorder in children or a history of allergies or asthma). However, the identified characteristics seem to be either common occurrences in people with or without CFS/ME or not sufficiently specific to CFS/ME, so it remains unclear whether health-care professionals could use these as a prognostic flag in clinical practice. Acute physical or psychological stress has been discussed in the literature as a precipitating factor that might trigger the onset of CFS/ME (see Prins *et al*. 2006). While it does appear that the identified factors cannot be used easily in clinical practice to specifically identify those people presenting with early suspected CFS/ME symptoms who will progress to develop CFS/ME, it is noteworthy that several characteristics could be addressed clinically and do not represent perpetuating or untreatable factors. Similarly, Candy *et al*. (2003) also concluded, regarding predictors of fatigue following the onset of infectious mononucleosis, that the individual identified psycho-behavioural predictors were characterized by being amenable to clinical interventions.

Our review was restricted to studies that used a specific type of analysis considered to be a suitable source of evidence to answer questions about the empirical evidence of risk factors for CFS/ME. Only studies that predicted the syndrome CFS/ME rather than fatigue or similar single characteristics of the syndrome were considered. Additionally, we set out to review studies that used a methodological design that allowed the simultaneous assessment of multiple potential risk factors, that is the syndrome had to be predicted in a multivariate analysis, a multiple regression or logistic regression. There are several other approaches to determine risk factors, one example being studies that count the prevalence of CFS/ME in a group that has been exposed to a discussed risk factor such as glandular fever (e.g. White *et al*. 1998), studies comparing the prevalence of CFS/ME in particular subgroups such as patients with or without

co-morbid psychological disorders (e.g. Wessely *et al*. 1997) or studies listing the prevalence of exposures or characteristics comparing a case and control group for CFS/ME (e.g. Reyes *et al*. 1996). The studies included in this review, by contrast, present a more focused, with regard to the outcome, and more advanced analysis with regard to the field of potential risk factors.

The studies varied greatly in the number of participants they identified that fulfilled agreed case definitions of the syndromes, with prevalences ranging from 8 to 447. From this, it follows that some of the studies had only a very small sample of patients with CFS/ME (e.g. Chalder *et al*. 2003), which provided the basis for finding characteristics that differentiate CFS/ME cases from non-cases that weaken the validity of the studies. The prevalences in the included cohort studies varied depending on the composition of the analysed sample of participants. Some studies were based on unselected samples such as a birth cohort study (Viner & Hotopf, 2004) and social survey data on children (Chalder *et al*. 2003) while others stemmed from selected populations such as a sample of fatigued employees absent from work (Huibers *et al*. 2004*a*, *b*) or a follow-up of patients diagnosed with viral illnesses (e.g. Cope *et al*. 1996). Large sample sizes are required in unselected samples, given that the prevalence of CFS/ME is an estimated 0.4% for adults in the UK for instance (Department of Health, 2002; replicated in the included birth cohort study by Viner & Hotopf, 2004).

The quality of the evidence depends on the quality of the study design and analysis and whether these allow correct inferences. However, the quality of the research depends also on the questions that are being asked, that is the selection of potential risk factors that are assessed and used as predictors for CFS/ME. The existing body of evidence is characterized by factors that were analysed in several studies but a significant association was not replicated in more than two studies, or by studies that showed significant associations of factors that no other study analysed. Further studies should answer the question of risk factors for CFS and ME with sufficiently large samples and by taking the existing body of evidence on risk factors into account.

Acknowledgements

We thank Vickie Orton for performing the literature searches, members of the NICE Guideline Development Group for the provision of additional literature, and Paul Wilson, Jeremy Miles and two anonymous reviewers for valuable comments on earlier drafts of the manuscript. The project was funded by the National Institute for Health and Clinical Excellence who commissioned the National Collaborating Centre for Primary Care (part of the Royal College of General Practitioners) to produce guidelines for 'The Diagnosis and Management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy) in Adults and Children'. The work forms part of the independent synthesis of research evidence to support the development of these guidelines.

Declaration of Interest

None.

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