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Case definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) - A systematic review

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Abstract

Objective To identify case definitions for Chronic Fatigue Syndrome/Myalgic Encephalitis (CFS/ME) and explore how one can evaluate the validity of case definitions in the absence of a reference standard.

Design Systematic review.

Data sources and eligibility criteria The Cochrane Library, Ovid AMED, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, CINAHL, Ovid PsycINFO, and PEDRO databases, and reference lists were searched for studies presenting or validating case definitions for CFS/ME for adult populations.

Review methods We searched for relevant case definitions and validation studies. Potential validation studies were assessed for risk of bias and categorised according to three validation models: independent application of several case definitions on the same population, sequential application of different sets of diagnostic criteria, or comparison of prevalence estimates from different case definitions applied on different populations.

Results We identified 20 case definitions. A total of 36 studies contributed data of sufficient quality and consistency for evaluation of validity, with CDC-1994/Fukuda as the most frequently applied definition. No study rigorously assessed reproducibility or feasibility of case definitions. Validation studies were small with methodological weaknesses and inconsistent results. No empirical data indicated that certain case definitions specifically identified patients with a neuroimmunological condition.

Conclusions Classification of patients according to severity and symptom patterns, aiming to predict prognosis or therapy effect, seems useful. Development of further case definitions of CFS/ME should be given low priority. One can achieve consistency in research by applying diagnostic criteria that have been subjected to systematic evaluation.

Article summary

Article focus

- Several case definitions for CFS/ME exist, but there is no general agreement on a reference standard for diagnosis.
- This study aims to identify and describe differences between case definitions for Chronic Fatigue Syndrome/Myalgic Encephalitis (CFS/ME).
- Second, we explore how accuracy and validity of the case definitions can be evaluated in the absence of a reference standard.

Key messages

- None of the included studies rigorously assesses the reproducibility or feasibility of existing case definitions.
- Only one included study reports data in a way that facilitates robust and direct comparisons of different case definitions.
- We found no empirical evidence supporting the hypothesis that some case definitions more specifically identify patients with a neuroimmunological condition.

Strengths and limitations of this study

- The main strength of our study is the systematic methods used to identify and appraise articles presenting and evaluating case definitions of CFS/ME.
- We have used systematic and transparent approaches to extract data, categorise the studies according to pre-specified models, and to analyse and compare the data.
- The included validation studies show considerable methodological weaknesses and inconsistent results, and it is therefore difficult to draw firm conclusions.

Introduction

Chronic fatigue syndrome (CFS) is a serious disorder characterised by persistent post-exertional fatigue and substantial symptoms related to cognitive, immune and autonomous dysfunction [1;2]. Disease mechanisms are complex [3], with no single causal factor identified. Yet there are indications that infections [4-8] and autoimmune dysfunction [9] contribute to development and maintenance of symptoms, probably interacting with genetic [10] and psychosocial [11-13] factors.

Studies have identified pathological patterns and structures of the central nervous system [14;15], dysregulation of body temperature and blood pressure [16;17], and dysfunctional stress hormonal systems [18;19] in CFS patients compared to normal controls. None of these appears sufficiently consistent to constitute a diagnostic test. Case definitions (diagnostic criteria) are used in research and clinical practice to define the CFS diagnosis. Since the first case definition - the CDC-1988/Holmes Criteria - was presented in 1988 [20], numerous revisions have been developed, aiming for distinctive and reliable identification of individuals who represent a homogenous and consistent phenotype of the hypothesized disease entity, consistent with pathophysiological and psychosocial findings.

Holmes et al [20] coined the term "Chronic Fatigue Syndrome" in 1988, as an alternative to "The chronic Epstein-Barr virus syndrome". Today the term "Myalgic Encephalomyelitis" (ME) is commonly used to conceptualize a specific neuroimmunological condition, assumed to be more severe and less psychologically attributed than CFS. In 2003, Carruthers et al presented the Canadian-2003 Criteria, for diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome [21]. A revised version was presented as International Consensus Criteria (the ICC- 2011 Criteria) for Myalgic Encephalomyelitis [22], claiming to be a selective case definition for identification of patients with neuroimmune exhaustion with a pathologically low threshold of fatigability and symptom flare after exertion. The assertion that CFS and ME are different clinical entities is disputed. Below, we will pragmatically apply the term CFS/ME.

Johnston et al conducted a systematic review of the adoption of CFS/ME case definitions to assess prevalence and identified eight different case definitions [23]. There is no general

agreement on a reference standard for diagnosis, and no diagnostic test is available. No studies exist where diagnostic accuracy is assessed by comparing case definitions with a reference standard in consecutive patients suspected of having CFS/ME [24]. Bossuyt et al. include case definitions in their understanding of the term "test", emphasizing that diagnostic tests are highly dynamic and need rigorous evaluation before they are introduced into clinical practice [25].

The objectives of our study were to explore strategies for evaluation of accuracy and concept validity of different case definitions for CFS/ME in the absence of a reference standard. First, we wanted to conduct a systematic review to identify and describe different case definitions (sets of diagnostic criteria) for CFS/ME. Second, we wanted to explore differences between various case definitions by identifying and reviewing validation studies.

Method and material

Protocol and registration

We developed a protocol for our study, but we did not publish or register it.

Eligibility criteria

We included studies presenting or validating case definitions for CFS/ME for adult populations (>18 years). No language restrictions were employed.

Information sources and search

We searched The Cochrane Library, Ovid AMED, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, CINAHL, Ovid PsycINFO, and PEDRO databases January 2012 using subject headings and text words (Appendix 1). We checked the reference lists of all included articles and searched for unpublished and on-going studies by correspondence with authors and field experts.

Study selection

To select publications eligible for this review, two authors independently read all titles and abstracts in the records retrieved by the searches. We obtained publications in full text if the abstract was deemed eligible by at least one review author. At least two authors independently read the full text papers and selected studies according to the inclusion criteria.

Data collection process

First, we listed all the identified *case definitions for CFS/ME*. We gathered information about citation from ISI and Google Scholar to indicate the impact or widespread of use, but we made no attempts to assess or rank the quality of the case definitions at this stage.

Then we organized and reviewed those of the identified studies which held a potential to compare and evaluate different case definitions – the *validation studies*. We developed three different models in which the validation studies could be categorised for comparison and evaluation:

Model A includes studies with *independent application of different case definitions on the same population* (Figure 1). This model presents the interrelationship between subpopulations identified by the different case definitions.

<Insert Figure 1 about here>

Model B includes studies where patients diagnosed with CFS/ME with *one set of diagnostic criteria are diagnosed sequentially with other case definitions* assumed to have increasing specificity (Figure 2).

<Insert Figure 2 about here>

Model C includes surveys or cross-sectional studies aimed at estimating the *prevalence* of CFS/ME obtained by applying different case definitions on different populations (Figure 3). These studies do not directly compare different case definitions, but may be used for proxy evaluation, similar to the strategy applied by Johnston et al [23;26].

<Insert figure 3 about here>

Risk of bias in individual studies

To differentiate between studies with higher and lower risk of bias, we critically appraised all included validation studies according to check lists: Studies comparing two or more case definitions directly (i.e. Model A or B) were appraised according to the QUADAS-criteria [27] (patient selection, index test, reference standard, flow, and timing). For evaluation of prevalence studies (i.e. Model C) we used an outline for assessment of external and internal validity (11 items) of prevalence studies [28].

Analysis

Participation in prevalence studies, surveys, and questionnaires vary across the included studies. Non-response is known to introduce bias, and methods to adjust for low response rates are available [29]. In studies affected by non-response, we have reported adjusted estimates whenever applicable. If adjusted estimates were unavailable, we have defined the proportion as the number of cases divided by the number of responders. We estimated 95 % confidence intervals for all proportions by using the Clopper-Pearson exact binomial method. We used R software version 3.0.0 and the rmeta package for statistical computations and plotting [30;31].

Results

Study selection

Our systematic literature search identified 1036 unique references, of which 56 articles fulfilled our inclusion criteria (Figure 4). Among these, 20 articles present different *case definitions* of CFS/ME for research or clinical practice [20-22;32-48] (Table 1). The remaining 36 studies were classified as *validation studies*, contributing data of sufficient quality and consistency for evaluation of different case definitions according to our inclusion criteria.

< Insert Table 1 and Figure 4 about here>

The degree to which the different case definitions had been applied in research and clinical guidelines varied widely, with CDC-1994/Fukuda [38] as the most frequently cited case definition of CFS/ME.

12 of the 20 identified case definitions had been assessed in one or more validation study [20;21;32;33;35;36;38-40;42;43;46]. For eight case definitions, no foundation for validation could be identified. We did not identify any study which rigorously assessed the reproducibility or feasibility of the different case definitions.

Independent application of several case definitions on the same population (Model A)

Five studies (Table 2) applied several case definitions on the same population, but only one of these reported data in a way that facilitated sufficiently robust comparisons of case definitions [49;50]. Nacul et al.[49] used GP databases and questionnaires and identified 278 patients with unexplained chronic fatigue conforming to one or more of the case definition applied, i.e. CDC-1994/Fukuda [38], Canadian-2003 [21] or ECD-2008 [33]. Most of the patients who were positive according to the Canada-criteria [C+] were also positive using the Fukuda criteria [F+]. 47% of the Fukuda positive patients were also positive according to the Canada criteria. Patients who were positive to both the Canada and Fukuda [C+/ F+] reported a higher level of symptoms than those who were [F+/ C-]. The authors did not identify differences in the distribution of triggering factors [49].

< Insert Table 2 about here>

None of the other four studies in this group reported data on the correlation between case definitions, patient profile, and symptom burden. Application of CDC-1988/Holmes case definition was consistently associated with lower prevalence estimates than CDC-1994/Fukuda, Oxford-1991, and Australian-1990 criteria across these four studies. There was no consistent trend for the other case definitions, but the studies were heterogeneous regarding application of the different case definitions and data collection (Table 2). This observation suggests that prevalence numbers obtained by different case definitions should be controlled according to diagnostic procedure, cut-off points and reasons for exclusions before concluding upon differences.

Different case definitions with assumed increasing specificity applied sequentially on the same population (Model B)

Eleven studies (Table 3) had sequentially applied different case definitions on the same population. In these studies, patients were screened by the use of an evaluation standard. Subsequently, test-positive individuals were screened with one or more comparators. Eight of the eleven studies applied CDC-1994/Fukuda as the evaluation standard, and then tested Fukuda-positive patients with CDC-1988/Holmes, Canadian-2003, ME-2011, Empirical-2006/Reeves, London-1990/Dowsett or Neurasthenia case definitions.

< Insert Table 3 about here>

We have taken the actual evaluation standard as a point of departure, and calculated the proportion of these patients still positive when applying other case definitions. Since there are no test negatives for the case definition used as point of departure, true sensitivities or specificities cannot be calculated. Results from two of the studies by Jason et al. [32;51] suggest that 40-70% of the Fukuda positive patients are also Canada positives [F+/C+]. One study [51] concluded that there was less psychiatric co-morbidity and more physical functional impairment in the sub-sample which was positive on both case definitions [F+/C+] than those who were negative according to the Canada criteria [F+/C-]. However, the other study [32] suggested a higher incidence of mental and cognitive problems among Fukuda positive patients who were also Canada positive [F+/C+] as compared to the remaining Fukuda positive but Canada negative patients [F+/C-].

The comparisons presented in table 3 are associated with high risk of bias as well as random errors, and the results should be interpreted with great caution. For example, two of the included studies reported similar point prevalence according to CDC-1994/Fukuda (2.1% and 2.6%) but reported very different estimates using the Australian-1990 criteria (7.6% and 1.4%) [52;53]. Sometimes diagnoses were based on questionnaire responses only, sometimes following detailed clinical interviews and laboratory testing. There are differences in the way similar case definitions had been practiced in the various studies, e.g. some studies applied a low threshold for exclusion of cases with psychiatric co-morbidity, while others did not.

Indirect comparisons of prevalence estimates from several case definitions applied on different populations (Model C)

We identified 17 studies (Table 4) presenting prevalence estimates for CFS/ME (Figure 3), in addition to the five studies presenting prevalence estimates following the application of multiple case definitions (Table 2). Based on these studies, we extracted 13 independent estimates of the prevalence following application of the CDC-1994/Fukuda criteria (Figure 5).

< Insert Table 4 about here>

Our analysis suggests that the population prevalence of CFS/ME according to the CDC-1994/Fukuda case definition probably is less than 1% (range 0.2 to 6.4%; median 1.2%), with higher prevalence among consecutive GP-attendants than from population studies. Prevalence estimates seemed higher when patients were diagnosed without a preceding medical examination. Prevalence estimates of CFS/ME according to CDC-1988/Holmes case definition seemed lower, with all the studies reporting prevalence estimates ranging from 0.0 to 0.3% (median 0.05%).

Five studies [52-56] reported CFS/ME prevalence estimates according to the Oxford-1991 case definition. These estimates ranged from 0.4% - 3.7% (median 1.5%). Four studies [43;52-54] reported prevalence estimates according to the Australian-1990 case definition ranging from 0.04% - 7.6% (median 1.2%).

Discussion

We identified 20 studies presenting different CFS/ME case definitions, and 36 studies with data providing access to comparison and evaluation of some of these. Only a minority of existing case definitions had been submitted to comparative evaluations. The validation studies were methodologically weak and heterogeneous, making it difficult to compare case definitions. The most cited case definition (CDC-1994/Fukuda[38]) is also the most extensively validated one, whereas validation studies are few (Canadian-2003[21]) or missing (NICE-2007[45], ICC-2011[22]) for more recently presented and debated case

definitions. We found no empirical evidence supporting the hypothesis that some case definitions more specifically identify patients with a neuroimmunological condition, excluding patients with psychiatric co-morbidity.

Strengths and weaknesses of our study

The main strength of our study is the systematic methods used to identify and appraise articles presenting case definitions of CFS/ME and studies potentially useful to evaluate the case definitions. Furthermore, we have used systematic and transparent approaches to extract data from the validation studies, categorise the studies according to three different models, and to analyse and compare the data.

The STARD initiative aims to improve the reporting on studies of diagnostic accuracy, considering any method for obtaining additional information on a patient's health status as a test [25]. Due to the lack of a reference standard, we found this guideline less suitable for review of articles evaluating case definitions for CFS/ME. Still, issues such as study populations, test methods and rationale, technical specifications for application of the test, statistical methods for comparing measures of accuracy and uncertainty, estimates of diagnostic accuracy, variability, and clinical applicability [25] are relevant also for our analysis.

The validation studies we identified were small with considerable methodological weaknesses and inconsistent results. Only one study held a level of rigor where independent application of several case definitions was conducted on the same population (Model A) [49]. Such a study should ideally be based on a population sample rather than a GP practice database, and should compare a selection of currently applied and debated case definitions, such as CDC-1994/Fukuda, Oxford-1991, Canadian-2003 and NICE-2007.

The QUADAS-criteria [27] demonstrate that Model B is an evaluation strategy prone to several sources of bias. First, the spectrum of patients subjected to the comparator is selected and not representative of the population receiving the test if it is used alone.

Second, as comparators were mostly applied subsequently to the evaluation standard, the clinical evaluations were not independent. The estimates from two of the Jason studies [32;51] suggest a comparable correspondence (40-70% of the F+ are also C+) with the results presented by Nacul and co-workers [49]. Yet, Model B gives no or limited information regarding those who screened negative in the first place. We do not know if some of those might have had a positive diagnosis if screened with one of the other case definitions.

Compared to Model B, we are even more prone to bias when exploring the consistency of different case definitions through indirect comparisons of prevalence estimates obtained from different populations (Model C), and great caution is needed when such indirect comparisons are undertaken. For example, two of the included studies reported similar point prevalence according to CDC-1994/Fukuda (2.1% and 2.6%) but reported very different estimates following the application of the Australian-1990 criteria (7.6% and 1.4%) [52;53]. This inconsistency is likely to be explained by the major methodological differences seen across the included studies; heterogeneity of study power and quality (such as recruitment strategy, response rate and strategies for non-response adjustment) and heterogeneity of how the diagnostic process was implemented. Some authors made diagnoses based on questionnaire responses, other conducted clinical interviews and laboratory testing. In their meta-analysis of 14 studies applying the CDC-1994/Fukuda case definition, Johnston et al found that the pooled prevalence for self-reporting assessment was 3.28% (95% CI: 2.24–4.33) and 0.76% (95% CI: 0.23–1.29) for clinical assessment [26]. Prevalence was lower in community samples (0.87%; 0.32–1.42) than in primary care samples (1.72%; 1.40–2.04). The prevalence estimates based on self-reports showed high variability, while clinically assessed estimates were more consistent, especially in the community samples.

The utility of case definitions and diagnoses

The utility of a diagnosis is linked to the potential effects of being diagnosed (e.g. benefits and harms of the patient role, access to treatment and insurance). More importantly, a diagnosis is useful if it is linked to valid information regarding outcomes

of therapy or prognosis. Reitsma et al suggest clinical test validation as an alternative paradigm for evaluation of a diagnostic test when an acceptable reference standard is missing [24]. Hence, primary studies and systematic reviews on prognosis and therapy are alternative sources to evaluate the usefulness of different case definitions of CFS/ME. We have identified only one such publication, the PACE trial [57]. Here, participants were diagnosed according to the Oxford-1991 criteria, Empirical criteria-2007/ Reeves and London ME-1994/ National Task Force criteria, and then randomised to either standard medical treatment, graded exercise therapy, cognitive behaviour therapy or pacing. The results showed that the effectiveness of the treatments was similar across groups, irrespective of which case definition that was used. Fluge et al applied the CDC-1994/Fukuda and retrospectively added the Canada criteria in their study on the effects of rituximab in CFS [9] with comparable results.

A study comparing the prognosis of different diagnostic labels of fatigue found that patients with ME had the worst prognosis; while patients with post-viral fatigue syndrome had the best [58]. This could mean that the patients destined to the worst prognosis were labelled with the ME diagnosis, or it might be explained as an adverse effect of being labelled with ME. The authors found no significant difference in recorded fatigue before the diagnosis of CFS and ME, and the data in this retrospective study supported the hypothesis of the labeling effect. Another study found that the prognosis of patients who attributed their fatigue to ME was worse than of patients who attributed their fatigue to psychological or social factors [59].

Broad or narrow case definitions?

Ideally, correspondence validity between test and target should be 100% for *sensitivity* (the capacity to identify patients in the target group) and *specificity* (the capacity to rule out patients that do not belong to the target group). More often, there is a trade-off between these measures, depending on the purpose of diagnosis. Emphasizing sensitivity implies a risk of over-diagnosis, which dilutes the actual diagnostic concept, while emphasizing specificity implies a risk of under-diagnosis, dismissing patients who might benefit from treatment. Development of more exclusive case definitions for CFS/ME

have been proposed, claiming that existing case definitions do not select homogenous sets of patients [22]. More specifically, Oxford-1991, Fukuda-1994 and NICE-2007 have been criticized, especially by patient organizations, for undue overlap with psychopathology. Proponents of recent case definitions such as Canada-2003 and ICC-2011 aim for a narrow selection of patients with myalgic encephalomyelitis conforming to a hypothesized specific pathophysiology. Our review demonstrates, however, that these case definitions do not necessarily exclude patients with psychopathology.

A lesson could be learnt from Reeves, who tried to elaborate the CDC1994/Fukuda definition and bring methodological rigor into the diagnostic criteria by scores from standardized and validated instruments [60]. The Empirical-2006/Reeves case definition led to a tenfold prevalence estimate as compared with the CDC1994/Fukuda definition [61], probably due to misclassification and inclusion of patients with major depressive disorder [62]. The purpose of rigor had not been achieved, and the Empirical-2006/Reeves case definition was never broadly implemented. According to our review, it is uncertain whether a more homogenous subset of patients can be achieved with the Canada-2003 and ICC-2011 case definitions. The authors of the latter paper write: "Collectively, members have approximately 400 years of both clinical and teaching experience, authored hundreds of peer-reviewed publications, diagnosed or treated approximately 50 000 patients with ME, and several members co-authored previous criteria." [22]. This declaration is no validity criterion and provides no guarantee that the case definition works according to the intentions.

Case definitions for research or clinical practice?

Research requires uniform and reproducible criteria, suitable for unambiguous definitions of the target population. Another concern is to compare studies across time and nations. These are arguments for an inclusive case definition, preferably one which has been in use for a while, and for which validation studies are available. In CFS/ME research, the Oxford-1991 and CDC-1994/Fukuda are the most frequently used case definitions. Our review indicates that the former might be more inclusive, with lower specificity than the latter, although the impact of this is unclear. Proponents for more restrictive case

definitions dismiss findings from treatment studies documenting effects of cognitive behavioural treatment or graded exercise therapy for patients diagnosed with the Oxford-1991 or CDC-1994/Fukuda case definitions [63]. Their claim is that for a more exclusive selection of patients with ME, defined according to specific hypothesized pathophysiology, the side effects of these treatment modalities are hazardous. So far, however, treatment studies of side effects based on the Canada-2003 or ICC-2011 case definitions are not available.

Case definitions for *clinical practice* should be research based, validated and manageable to provide a tool which can relieve patient uncertainty, prevent adverse effects of unnecessary treatment and diagnostic procedures, conserve limited healthcare resources and initiate the most appropriate treatment [64]. They should be founded on available knowledge regarding the mechanisms of the actual condition, validated through credible and transparent processes, and presented in a format which can be implemented in everyday practice. An argument for more inclusive case definitions for CFS/ME would be the issue of treatment, since based on existing evidence side effects of cognitive behavioural treatment or graded exercise therapy are negligible. For this context, the CDC-1994/Fukuda case definition appears suitable, with the NICE-2007 as a good candidate for validation studies.

Implications for research and clinical practice

Based on our review, we argue that development of further case definitions of CFS/ME should be given low priority, as long as causal explanations for the disease are limited. It might still be useful to classify patients according to severity and symptom patterns, aiming to identify characteristics of patients that might predict differences in prognosis or expected effects of therapy.

It is likely that all CFS/ME case definitions capture conditions with different or multifactorial pathogenesis and varying prognosis. The futile dichotomy of "organic" versus "psychic" disorder should be abandoned. Most medical disorders have a complex etiology. Psychological treatments are often helpful also for clear-cut somatic disorders. Unfortunately patient groups and researchers with vested interests in the belief that ME is

a distinct somatic disease, seem unwilling to leave the position that ME is an organic disease only. This position has damaged the research and practice for patients suffering of CFS/ME.

Conclusions

Our review provided no evidence that any of the case definitions identify patients with specific or "organic only" disease etiology. Priority should be given to further development and testing of promising treatment options for patients with CFS/ME. Classification of patients according to severity and symptom patterns, aiming to identify characteristics of patients that might predict differences in prognosis or expected effects of therapy, might be useful. Development of further case definitions of CFS/ME should on the other hand be given low priority. Consistency in research can be achieved by application of diagnostic criteria which have been systematically evaluated and compared to other case definitions.

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Contributors: KM had the original idea, and all five authors worked together to develop an appropriate theoretical framework and design. MSF developed the search, and all authors were involved in the selection process. LL and KGB extracted relevant data, KGB performed the statistical analysis, and all authors were involved in the data interpretation. KM wrote the manuscript draft and revised the draft based on input from the other authors. All authors revised it critically for content and approved the final version.

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Table 1
Case definitions for CFS/ME

CASE DEFINITIONS (chronologically)	Developed from other criteria or definitions?	INSTITUTION AND COUNTRY OF FIRST AUTHOR	CITATIONS[A] ISI/Google Scholar
CDC-1988/Holmes [20]		Centers for Disease Control, Atlanta, USA	1106/1542
Myalgic encephalomyelitis 1988/Ramsey [41]		Royal Free Hospital, London, UK	6/51
London-1990/Dowsett [36]		Royal Free Hospital, London, UK	55/88
Australian-1990 [43]		The Prince Henry Hospital, Little Bay, Australia	230/343
Post-viral fatigue syndrome-1990 [42]		Raigmore Hospital, Inverness, UK	14/28
Oxford-1991 [39]		University of Oxford, Oxford, UK	476/667
London ME-1994/National Task Force Guidelines [47]		National Task Force, Bristol, UK	no records
CDC-1994/Fukuda [38]	CDC-1988	Centers for Disease Control, Atlanta, USA	1860/3006
Working Case Definition-1996 [37]	CDC-1988	Brigham and Women's Hospital Massachusetts, USA	78/138
Chronic Fatigue Syndrome-1998 [48]	CDC-1994	Medical College of Wisconsin, USA	8/23
Canadian-2003 [21]		Royal College of Physicians and Surgeons of Canada, Canada	69/233
Empirical CDC-2005/Reeves [60]	CDC-1994	Centers for Disease Control and Prevention, Atlanta, USA	73/154
Empirical-2007 [40]		DePaul University, Chicago, USA	5/14
Brighton Collaboration-2007 [34]		Centers for Disease Control and Prevention, Atlanta, USA	1/5
NICE-2007 Guidelines [45]		National Institute for Health and Clinical Excellence, London, UK	no records/23[B]
The Nightingale Definition of ME/Hyde-2007 [44]		The Nightingale Research Foundation, Canada	no records/5
Epidemiological CFS/ME Definition-2008 [33]		Southampton, Hampshire, UK	2/4
Revised Canadian-2010 [46]	CDC-1994, Empirical CDC-2005, Canadian-2003	DePaul University, Illinois, USA	8/18
ICC-2011 [22]	Canadian-2003	Independent, Canada	4/16
ME-2011 [32]	Dowsett, Ramsey, Hyde	DePaul University, Illinois, USA	1/1

[A]Searched 23. May 2012 [B] Summary of the NICE Guidelines in: Diagnosis and management of chronic fatigue syndrome or myalgic encephalomyelitis (or encephalopathy): summary of NICE guidance BMJ 2007; 335:446

Table 2

Studies presenting prevalence estimates* by independent application of several case definitions on the same population (Model A)

First author, year, country	Data collection	Prevalence (95 % CI)
Nacul [49] 2011, UK	609 possible cases electronically identified in databases of 29 GP practices. 70 excluded after clinical revision (explained fatigue), 135 refusals and 126 non-cases.	ECD: 0.03 % (0.02-0.04) Canada: 0.10 % (0.09-0.12) Fukuda: 0.19 % (0.17-0.21)
Bates [54] 1993, US	995 consecutive GP visitors invited - 94 % screened by a questionnaire to detect major fatigue. Selected patients further evaluated by questionnaires, physical examinations and interviews.	Holmes: 0.3 % (0.1-0.9) Oxford: 0.4 % (0.1 -1.1) Australia: 1.1 % (0.5-2.0)
Kawakami [55] 1998, Japan	All adults (n=508) in Town A, Kofu-city, were invited to participate in this structured psychiatric diagnostic interview survey. 137 (27%) completed the study	Holmes: 0.0 % (0.0-2.7) Fukuda: 1.5 % (0.2-5.2) Oxford: 1.5 % (0.2-5.2)
Lindal [53] 2002, Iceland	Survey sent to 4000 randomly selected adult participants – 63% responded. Questionnaire included questions on all items in the four case definitions. Diagnosis were set electronically based on received responses. No medical tests or examinations were undertaken.	Holmes 0.0 % (0.0-1.5) Fukuda: 2.1 % (1.6-2.8) Oxford: 3.7 % (3.2-4.6) Australia: 7.6 % (6.6-8.7)
Wessely [52;65] 1997, UK	2363 patients followed in a cohort study – 84% completed. Fatigued participant subjected to detailed questionnaires, interviews, and laboratory testing. Separate estimates reported for inclusion/exclusion of psychiatric co-morbidity.	Holmes: 1.2 % (0.5-1.8) Australia: 1.4 % (0.8-2.0) Oxford: 2.2 % (1.4-3.0) Fukuda: 2.6 % (1.7-3.4)

*Prevalence estimates were calculated with the number of responders in the denominator. The choice of denominator may have large implications with regard to the subsequent prevalence estimate, particularly in studies with low response rate. Hence, depending on the actual response rate, estimates presented for each study may be biased.

Table 3

Conformity of prevalence estimates in studies where patients diagnosed with CFS/ME with one set of diagnostic criteria are diagnosed sequentially with other case definitions (Model B)

Study Recruitment	Case definitions	Conformity[#] (95% CI)	Symptom and burden profile
Brimacombe [66], US Fukuda-positive from register	Fukuda* (n=200) Holmes (n=171)	1 0.85 (0.80-0.90)	[F+/H-] patients do not endorse infectious-type symptoms as often or to the same degree of severity as [F+/H+] patients
Jason [67], US Fukuda-positive from register	Fukuda* (n=32) Holmes (n=14)	1 0.44 (0.26-0.62)	[F+/H+] patients with more symptoms and functional impairment than [F+/H-]. No difference in psychological co-morbidity
Jason [51], US Fukuda-positive from register	Fukuda* (n=32) Canada (n=23)[§]	1 0.63 (0.44-0.79)	C+ patients have less psychiatric co-morbidity, more physical function impairment, are more fatigued with more neurological symptoms than [F+/C-] patients
Jason [32], US Fukuda-positive recruited from many sources	Fukuda* (n=114) Canada (n=57) ME-2011 (n=27)	1 0.50 (0.41-0.60) 0.24 (0.16-0.33)	[F+/C+] patients had more functional impairments, and physical, mental, and cognitive problems than [F+/C-] patients. [F+/ME+] patients had more functional impairments, and more severe physical and cognitive symptoms than [F+/ME-] patients.
Fluge [9], Norway Fukuda-positive patients recruited to trial	Fukuda* (n=30) Canada (n=28)	1 0.93 (0.78-0.99)	Not reported
Jason [68], US Register	Fukuda* (n=24) Reeves empirical Canada	Of 24 F+ and 84 F- patients empirical criteria and Canada identified 79 and 87% correctly	Canadia-2003 case definition appear to select more cardinal and central features of the illness than Empirical CDC-2005/Reeves case definition
Jason [62], US Register	Fukuda* (n=27) Reeves emp. (n=41)[§§]	1 1.00 (0.87-1.00)	Empirical CDC-2005/Reeves case definition led to mis-classification of major depressive disorder as CFS

Jason [69], US Fukuda-positive from register	Fukuda* (n=32) Dowsett (n=17) §§§	1 0.44 (0.26-0.62)	D+ patients appear to be more symptomatic than [F+/D-] patients, especially in the neurological and neuropsychiatric areas.
White [57], UK Oxford-positive patients recruited to trial	Oxford* (n=641) Fukuda (n=427) London ME (n=329)	1 0.67 (0.63-0.70) 0.51 (0.47-0.55)	Effect of CBT and GET similar regardless of diagnostic group affiliation
Wearden [70], UK Oxford-positive patients recruited to trial	Oxford* (n=296) London ME (n=92)	1 0.31 (0.26-0.37)	Not reported
Stubhaug [71], Norway Neurasthenia-positive patients recruited to trial	Neurasthenia* (n=72) Oxford (n=65) Fukuda (n=29)	1 0.90 (0.81-0.96) 0.40 (0.29-0.53)	Not reported

#The proportion of cases relative to the evaluation standard; *Evaluation standard;
§ 3/23 participants testing positive according to Canada were negative according to Fukuda
§§14/37 depressed patients tested positive according to Reeves and negative on Fukuda
§§§ 3/17 participants testing positive according to Dowsett were negative according to Fukuda

Table 4

Studies presenting prevalence estimates for CFS/ME from several case definitions applied on different populations (Model C)

First author, year COUNTRY	CASE DEFINITION	RECRUITMENT STRATEGY
Bazelmans 1999 [72] The Netherlands	As recognized by GP	Questionnaire to all GPs, Prevalence estimated to 0.11 %
Lloyd 1990 [43] Australia	Australian	Recruited through GP's covering 76206 patients
Buchwald 1995 [73] US	CDC-1988/ Holmes	Postal survey to 4000 randomly selected participants
Gunn 1993 [74] US	CDC-1988/ Holmes	Recruited by contact with primary health care providers; prevalence in the range 0.002-0.007%
Price 1992 [75] USA	CDC-1988/ Holmes	Interview survey with 13538 participants
Versluis 1997 [76] The Netherlands	CDC-1988/ Holmes	23000 patients in GP database
Bierl 2004 US	CDC-1994/ Fukuda	Random digit-dialing survey with 7317 respondent
Cho 2009 [77] UK	CDC-1994/ Fukuda	2530 consecutive GP visitors
Cho 2009 [77] Brazil	CDC-1994/ Fukuda	3921 consecutive GP visitors
Evengård 2005 [78] Sweden	CDC-1994/ Fukuda	Phone survey of 41499 participants in a twin register
Hamagucchi 2011 [79] Japan	CDC-1994/ Fukuda	3000 random participants in a health check program
Jason 1999 [80] US	CDC-1994/ Fukuda	Phone survey with 18675 respondents
Kim 2005 [81] South Korea	CDC-1994/ Fukuda	1962 consecutive GP visitors
Njoku 2007 [82] Nigeria	CDC-1994/ Fukuda	Interview survey with 1500 participants
Reeves 2007 [61] US	CDC-1994/ empirical	Phone survey with 10837 responding households
Reyes 2003 [83] US	CDC-1994/ Fukuda	Phone survey with 33997 responding households
Steele 1998 [84] US	CDC-1994/ Fukuda	Phone survey with 8004 responding households
van't Leven 2009 [85] The Netherlands	CDC-1994/ Fukuda	Postal survey to 22500 randomly selected participants
Yiu 2005 [86] China	CDC-1994/ Fukuda	Unknown
Lawrie 1995 [56] UK	Oxford	Postal survey to 1039 randomly selected participants
Ho-Yen 1991 [87] UK	Post viral exhaustion syndrome	Postal survey to 195 GPs; prevalence 0.13 % (0.12-0.15)

Figure legends

Figure 1

Model A: Evaluation design with independent application of several case definitions on the same background population

Figure 2

Model B: Evaluation design where different case definitions with assumed increasing specificity are applied sequentially on the same population

Figure 3

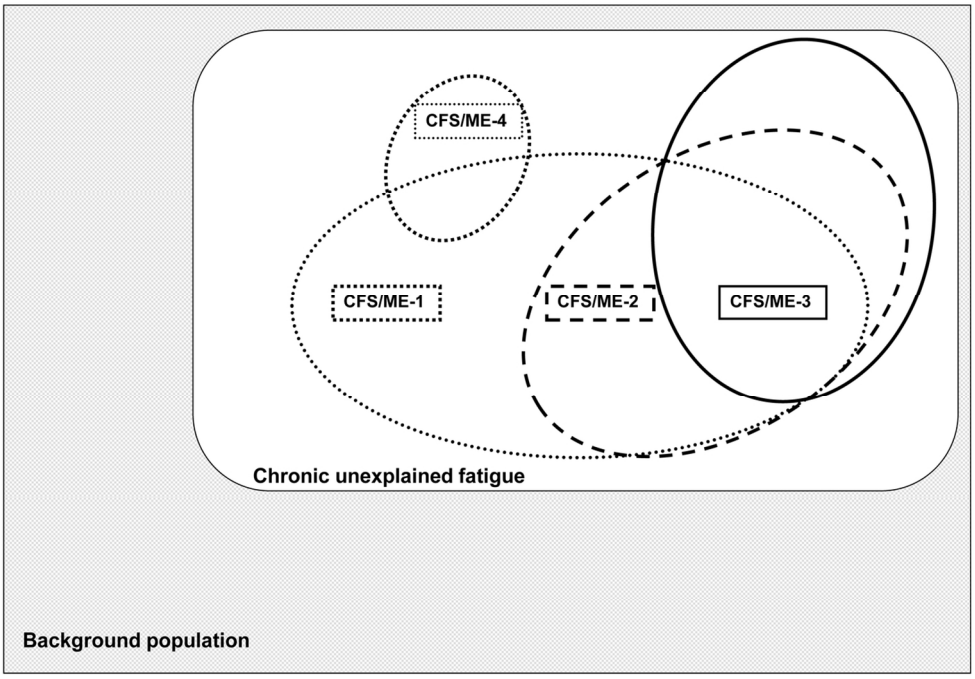
Model C: Evaluation design with indirect comparisons of prevalence estimates from several case definitions applied on different populations

Figure 4

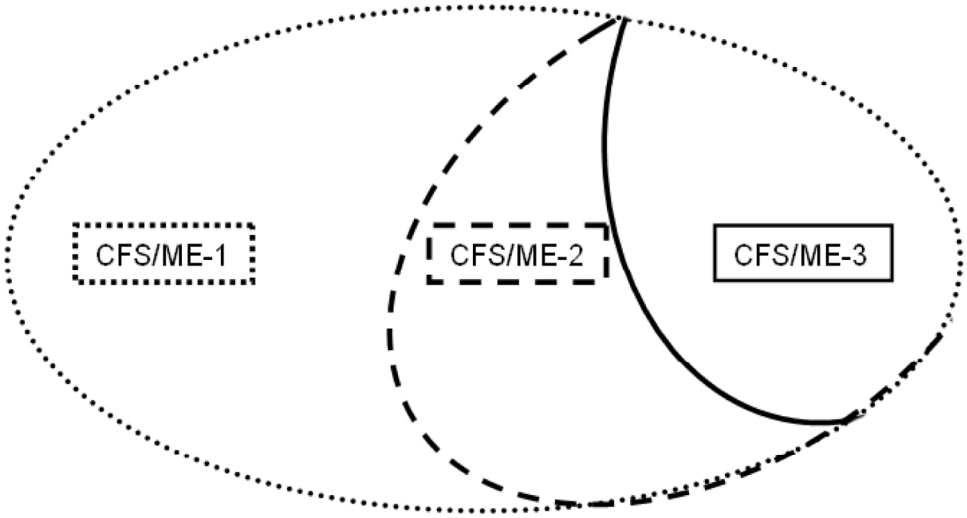
Flow chart summarising the selection process

Figure 5

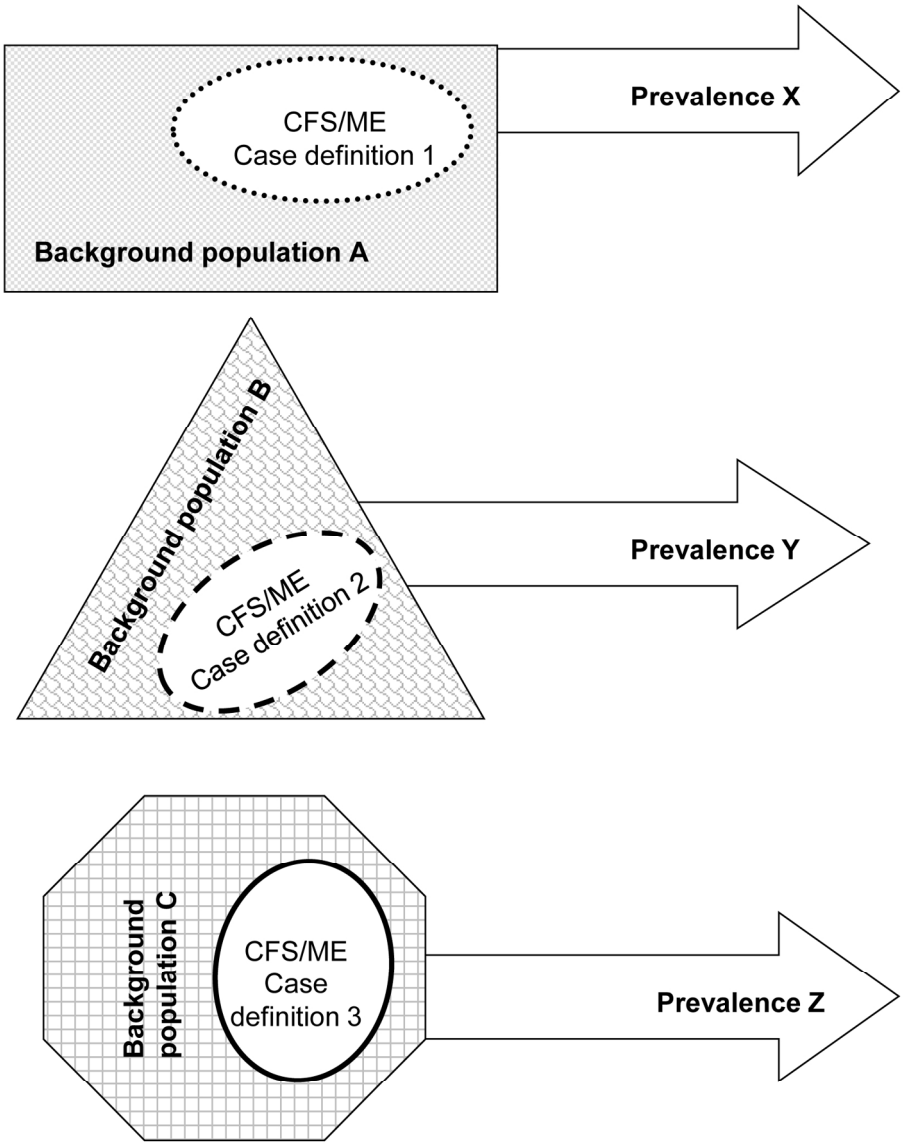
Forest plot summarising indirect comparisons of prevalence estimates from different case definitions with the CDC-1994/Fukuda criteria (Model C). Studies presenting point prevalence weighted for non-response are asterisked (*)



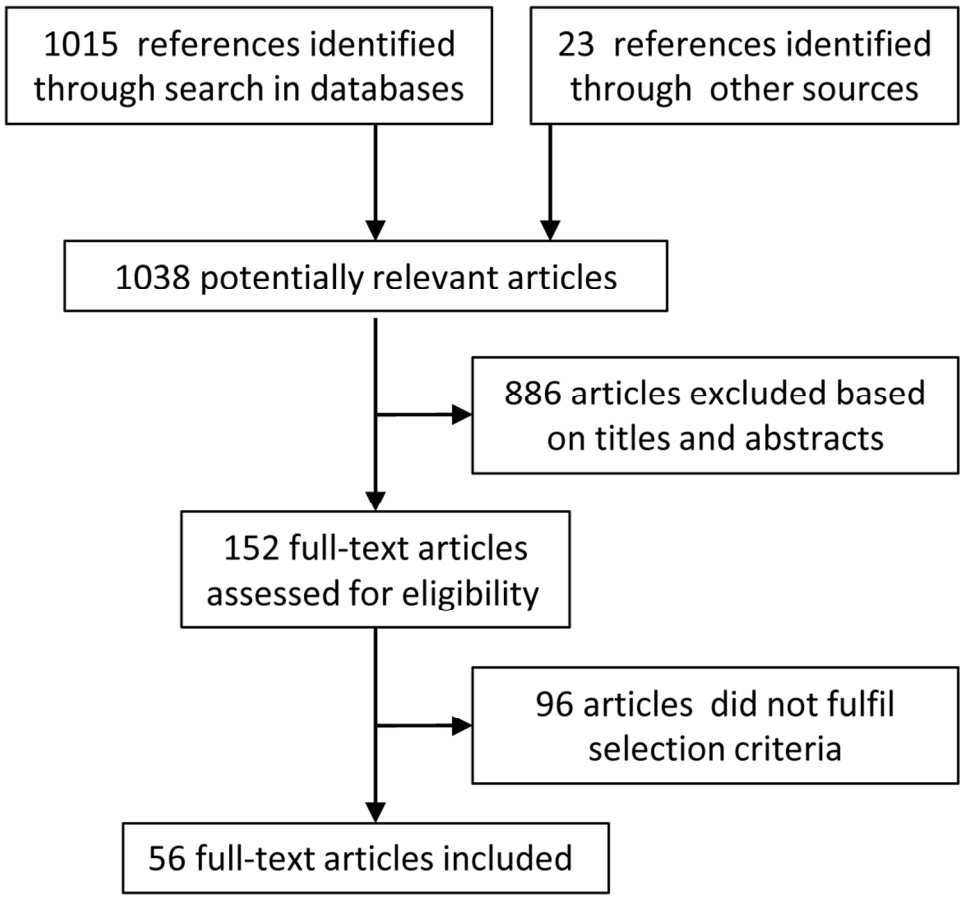
Model A: Evaluation design with independent application of several case definitions on the same background population
123x87mm (300 x 300 DPI)



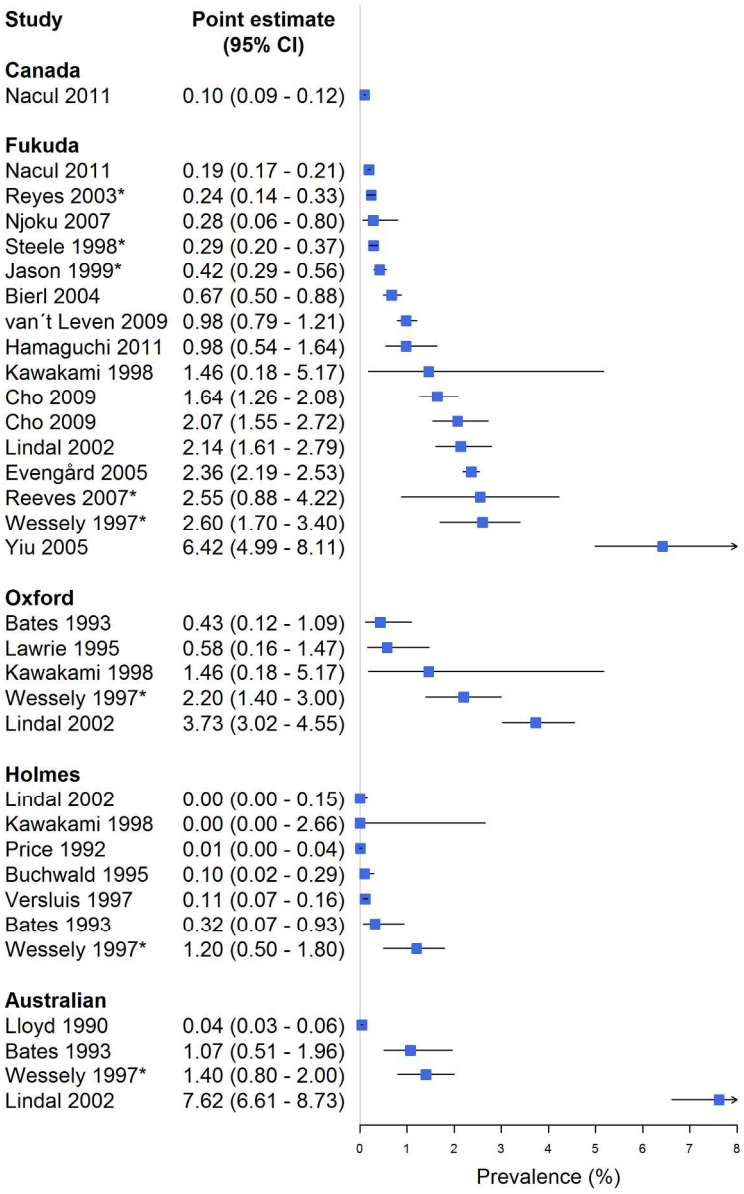
Model B: Evaluation design where different case definitions with assumed increasing specificity are applied sequentially on the same population
139x77mm (300 x 300 DPI)



Model C: Evaluation design with indirect comparisons of prevalence estimates from several case definitions applied on different populations
145x185mm (300 x 300 DPI)



Flow chart summarising the selection process
103x99mm (300 x 300 DPI)



Forest plot summarising indirect comparisons of prevalence estimates from different case definitions with the CDC-1994/Fukuda criteria (Model C). Studies presenting point prevalence weighted for non-response are asterisked (*)
155x242mm (300 x 300 DPI)

Appendix 1

Search strategy CFS/ME Case Definitions

Total search hits: 1559
Search hits after duplet removal: 1015

AMED, EMBASE, MEDLINE, PsycINFO
Date: 24.1.2012
Total search hits: 1517

All the sources were search in Ovid simultaneously

Ovid AMED (Allied and Complementary Medicine) 1985 to January 2012 Search hits: 163
Ovid EMBASE 1980 to 2012 Week 03 Search hits: 776
Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present Search hits: 341
Ovid PsycINFO 1887 to January Week 3 2012 Search hits: 237

1. Fatigue Syndrome, Chronic/

2. (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or (chronic adj4 mononucleos*) or post infectious encephalo* or PVFS).tw.

3. 1 or 2

4. "diagnostic techniques and procedures"/

5. guideline/ or practice guideline/

6. (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics).tw.

7. 4 or 5 or 6

8. 3 and 7

9. 8 use prmz

10. chronic fatigue syndrome/

11. (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or (chronic adj4 mononucleos*) or post infectious encephalo* or PVFS).tw.

12. 10 or 11

13. diagnostic procedure/ or diagnostic test/ or physical examination/

14. (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics).tw.

15. 13 or 14

16. 12 and 15

17. 16 use emez

18. fatigue syndrome chronic/

19. (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or (chronic adj4 mononucleos*) or post infectious encephalo* or PVFS).tw.

20. 18 or 19

21. "diagnostic techniques and procedures"/ or patient assessment/ or physical examination/

22. (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics).tw.

23. 21 or 22

24. 20 and 23

25. 24 use amed

26. exp Chronic Fatigue Syndrome/

27. (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or (chronic adj4 mononucleos*) or post infectious encephalo* or PVFS).tw.

28. 26 or 27

29. medical diagnosis/ or diagnosis/ or physical examination/

30. (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics).tw.

31. 29 or 30

32. 28 and 31

33. 32 use psyf

34. 9 or 17 or 25 or 33

35. remove duplicates from 34

CINAHL
Date: 24.1.2012
Total search hits: 22

S6 S3 and S4 Limiters - Exclude MEDLINE records

S5 S3 and S4

S4 S1 or S2

S3 TI (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics) OR AB (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics)

S2 TI (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or post infectious encephalo* or PVFS) OR AB (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or post infectious encephalo* or PVFS)

S1 (MH "Fatigue Syndrome, Chronic")

PEDro

Date: 20.1.2012
Total search hits: 20

Search phrases and words: chronic fatigue syndrome and diagnos*

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1,2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2, 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5, 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8,9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2-4, Fig 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9,10,11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11,12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16,17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

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Case definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) - A systematic review

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Case definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) - A systematic review

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Keywords: Chronic fatigue syndrome, diagnosis, criteria, case definition

Abstract

Objective: To identify case definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), and explore how the validity of case definitions can be evaluated in the absence of a reference standard.

Design: Systematic review.

Setting: International.

Participants: A literature search, updated as of November 2013, led to identification of 20 case definitions and inclusion of 38 validation studies.

Primary and secondary outcome measure: Validation studies were assessed for risk of bias and categorised according to three validation models: A) independent application of several case definitions on the same population, B) sequential application of different case definitions on patients diagnosed with CFS/ME with one set of diagnostic criteria, or C) comparison of prevalence estimates from different case definitions applied on different populations.

Results: A total of 38 studies contributed data of sufficient quality and consistency for evaluation of validity, with CDC-1994/Fukuda as the most frequently applied case definition. No study rigorously assessed reproducibility or feasibility of case definitions. Validation studies were small with methodological weaknesses and inconsistent results. No empirical data indicated that any case definition specifically identified patients with a neuroimmunological condition.

Conclusions: Classification of patients according to severity and symptom patterns, aiming to predict prognosis or effectiveness of therapy, seems useful. Development of further case definitions of CFS/ME should be given low priority. Consistency in research can be achieved by applying diagnostic criteria that have been subjected to systematic evaluation.

Article summary

Article focus

- Several case definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) exist, but there is no general agreement on a reference standard for diagnosis.
- This study aims to identify and compare case definitions for CFS/ME.
- We also explore how accuracy and validity of the case definitions can be evaluated in the absence of a reference standard.

Key messages

- None of the included studies rigorously assessed the reproducibility or feasibility of existing case definitions.
- Only one included study reported data in a way that made it possible to compare different case definitions rigorously and directly.
- We found no empirical evidence supporting the hypothesis that some case definitions more specifically identify patients with a neuroimmunological condition.

Strengths and limitations of this study

- The main strength of our study is the systematic methods used to identify and appraise articles presenting and evaluating case definitions of CFS/ME.
- We used systematic and transparent approaches to extract data, categorise the studies according to pre-specified models, and to analyse and compare the data.
- The included validation studies showed considerable methodological weaknesses and inconsistent results, and it is therefore difficult to draw firm conclusions.

Introduction

Chronic fatigue syndrome (CFS) is a serious disorder characterised by persistent post-exertional fatigue and substantial symptoms related to cognitive, immune and autonomous dysfunction [1;2]. Disease mechanisms are complex [3], with no single causal factor identified. Yet there are indications that infections [4-8] and immunologic dysfunction [9] contribute to development and maintenance of symptoms, probably interacting with genetic [10] and psychosocial [11-13] factors.

Studies have identified pathological patterns and structures of the central nervous system [14;15], dysregulation of body temperature and blood pressure [16;17], and dysfunctional stress hormonal systems [18;19] in CFS patients compared to normal controls. None of these appears sufficiently consistent to constitute a diagnostic test, and case definitions (diagnostic criteria) are therefore used to define the CFS diagnosis. When case definitions are developed, the context of application must be considered, since different properties are needed for case definition intended for research purposes compared to case definitions used to diagnose individual patients. It is also necessary to consider whether a broad (i.e. sensitive criteria ensuring that we do not miss relevant cases) or narrow (i.e. specific criteria ensuring that all positive cases are definite) approach is most appropriate.

Holmes et al [20] coined the term "Chronic Fatigue Syndrome" in 1988, as an alternative to "The chronic Epstein-Barr virus syndrome". Since this case definition - the CDC-1988/Holmes Criteria - was presented in 1988 [20], numerous revisions have been developed, aiming for distinctive and reliable identification of individuals who represent a homogenous and consistent phenotype of the hypothesized disease entity, consistent with pathophysiological and psychosocial findings. Today the term "Myalgic Encephalomyelitis" (ME) is commonly used to conceptualize a specific neuroimmunological condition, assumed to be more severe and less psychologically attributed than CFS [21]. In 2003, Carruthers et al presented the Canadian-2003 Criteria for diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome [22]. A revised version was presented as International Consensus Criteria (the ICC-2011 Criteria) for Myalgic Encephalomyelitis [23], claiming to be a selective case definition for identification of patients with neuroimmune exhaustion with a pathologically low threshold of fatigability

and symptom flare after exertion. The assertion that CFS and ME are different clinical entities is disputed. Below, we will pragmatically apply the term CFS/ME.

Johnston et al conducted a systematic review of the adoption of CFS/ME case definitions to assess prevalence and identified eight different case definitions [24]. There is no general agreement on a reference standard for diagnosis, and no diagnostic test is available. Bossuyt et al. include case definitions in their understanding of the term "test", emphasizing that diagnostic tests are highly dynamic and need rigorous evaluation before they are introduced into clinical practice [25;26].

The objectives of our study were to explore strategies for evaluation of accuracy and concept validity of different case definitions for CFS/ME in the absence of a reference standard. First, we wanted to conduct a systematic review to identify and describe different case definitions (sets of diagnostic criteria) for CFS/ME. Second, we wanted to explore differences between various case definitions by identifying and reviewing validation studies.

Method and material

Protocol and registration

We developed a protocol for our study. However, we did not publish or register it.

Eligibility criteria

We included studies presenting or validating case definitions for CFS/ME for adult populations (>18 years). No language restrictions were employed.

Information sources and search

We searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from 1946, Ovid EMBASE from 1980, Ovid PsycINFO from 1806, Ovid AMED from 1985, The Cochrane Library from 1898, CINAHL from 1981, and PEDRO from 1929 using subject headings and text words (Appendix 1). All searches were up to

date as of 25. November 2013. We checked the reference lists of all included articles and searched for unpublished and on-going studies by correspondence with authors and field experts.

Study selection

To select publications eligible for this review, two authors independently read all titles and abstracts in the records retrieved by the searches. We obtained publications in full text if the abstract was deemed eligible by at least one review author. At least two authors independently read the full text papers and selected studies according to the inclusion criteria. Any disagreement between review authors was resolved by discussion between the two review authors or, if necessary, by involving all authors.

Data collection process

First, we listed all the identified *case definitions for CFS/ME*. One author gathered information about citation from ISI and Google Scholar to indicate the impact or widespread of use, but we made no attempt to assess or rank the quality of the case definitions at this stage.

To facilitate the validity assessment, we developed a framework consisting of three different models:

Model A includes studies with *independent application of different case definitions on the same population* (Figure 1). This model presents the interrelationship between subpopulations identified by the different case definitions.

<Insert Figure 1 about here>

Model B includes studies where patients diagnosed with CFS/ME with *one set of diagnostic criteria are diagnosed sequentially with other case definitions* assumed to have increasing specificity (Figure 2).

<Insert Figure 2 about here>

Model C includes surveys or cross-sectional studies estimating the *prevalence* of CFS/ME by applying different case definitions on different populations (Figure 3). These studies do not directly compare different case definitions, but may be used for proxy evaluation, similar to the strategy applied by Johnston et al [24;27].

<Insert figure 3 about here>

Two authors reviewed all potentially relevant *validations studies*, and categorised them according to Model A, B or C. Any disagreement between review authors at this stage was resolved by reaching consensus in the author group.

Risk of bias in individual studies

To differentiate between studies with higher and lower risk of bias, we critically appraised all included validation studies according to check lists: Studies comparing two or more case definitions directly (i.e. Model A or B) were appraised according to the QUADAS-criteria [28] (patient selection, index test, reference standard, flow, and timing). For evaluation of prevalence studies (i.e. Model C) we used an outline for assessment of external and internal validity (11 items) of prevalence studies [29].

Analysis

Participation in prevalence studies, surveys, and questionnaires vary across the included studies. Non-response is known to introduce bias, and methods to adjust for low response rates are available [30]. In studies affected by non-response, we have reported adjusted estimates whenever applicable. If adjusted estimates were unavailable, we have defined the proportion as the number of cases divided by the number of responders. We estimated 95% confidence intervals for all proportions by using the Clopper-Pearson exact binomial method. We used R software version 3.0.0 and the rmeta package for statistical computations and plotting [31;32].

Results

Study selection

Our systematic literature search identified 1660 unique references, of which 56 articles fulfilled our inclusion criteria (Figure 4). Twenty articles present different *case definitions* of CFS/ME for research or clinical practice [20;22;23;33-49] (Table 1). Furthermore, 38 studies were classified as *validation studies*, contributing data of sufficient quality and consistency for evaluation of different case definitions according to our inclusion criteria.

< Insert Table 1 and Figure 4 about here>

The degree to which the different case definitions had been applied in research and clinical guidelines varied widely, with CDC-1994/Fukuda [39] as the most frequently cited case definition of CFS/ME.

Thirteen of the 20 identified case definitions had been assessed in one or more validation study [20;22;23;33;34;36;37;39-41;43;44;47]. For seven case definitions, no foundation for validation could be identified. We did not identify any study which rigorously assessed the reproducibility or feasibility of the different case definitions.

Independent application of several case definitions on the same population (Model A)

Five studies (Table 2) applied several case definitions on the same population, but only one of these reported data in a way that made it possible to compare the case definitions [50;51]. Nacul et al[50] used GP databases and questionnaires and identified 278 patients with unexplained chronic fatigue conforming to one or more of the case definition applied, i.e. CDC-1994/Fukuda [39], Canadian-2003 [22] or ECD-2008 [34]. Most of the patients who were positive according to the Canada-criteria [C+] were also positive using the Fukuda criteria [F+]. 47% of the Fukuda positive patients were also positive according to the Canada criteria. Patients who were positive to both the Canada and Fukuda [C+/F+] reported a higher level of symptoms than those who were [F+/C-]. The authors did not identify differences in the distribution of triggering factors [50].

< Insert Table 2 about here>

None of the other four studies in this group reported data on the correlation between case definitions, patient profile, and symptom burden. Application of CDC-1988/Holmes case definition was consistently associated with lower prevalence estimates than CDC-1994/Fukuda, Oxford-1991, and Australian-1990 criteria across these four studies. There was no consistent trend for the other case definitions, but the studies were heterogeneous regarding the application of different case definitions and data collection (Table 2). This observation suggests that prevalence numbers obtained by different case definitions should be controlled according to diagnostic procedure, cut-off points and reasons for exclusions before concluding upon differences.

Different case definitions with assumed increasing specificity applied sequentially on the same population (Model B)

Twelve studies (Table 3) sequentially applied different case definitions on the same population. In these studies, patients were screened by the use of an evaluation standard. Subsequently, test-positive individuals were screened with one or more comparators. Nine of the twelve studies applied CDC-1994/Fukuda as the evaluation standard, and then tested Fukuda-positive patients with CDC-1988/Holmes, Canadian-2003, ICC-2011, ME-2011, Empirical-2006/Reeves, London-1990/Dowsett, or Neurasthenia case definitions.

< Insert Table 3 about here>

We have taken the actual evaluation standard as a point of departure, and calculated the proportion of these patients still positive when applying other case definitions. Since there are no test negatives for the case definition used as point of departure, true sensitivities or specificities cannot be calculated. Results from two of the studies by Jason et al. [33;52] suggest that 40-70% of the Fukuda positive patients are also Canada positives [F+/C+]. One study [52] concluded that there was less psychiatric co-morbidity and more physical functional impairment in the sub-sample which was positive on both case definitions [F+/C+] than those who were negative according to the Canada criteria [F+/C-]. However, the other study [33] suggested a higher incidence of mental and cognitive problems among Fukuda positive patients who were also Canada positive [F+/C+] as

compared to the remaining Fukuda positive but Canada negative patients [F+/C-]. In a separate publication [53], the same Fukuda positive patients as referred in Jason 2012 [33] were used to contrast ICC-2011. About 34% (95% CI 26%-44%) of the Fukuda positive patients were also ICC positives [F+/ICC+]. Similar to the [F+/C+] subset, it was found that [F+/ICC+] patients experienced more functional impairments as well as more mental and cognitive problems and higher psychiatric comorbidity than [F+/ICC-] patient.

The comparisons presented in table 3 are associated with high risk of bias as well as random errors, and the results should be interpreted with great caution. For example, two of the included studies reported similar point prevalence according to CDC-1994/Fukuda (2.1% and 2.6%) but reported very different estimates using the Australian-1990 criteria (7.6% and 1.4%) [54;55]. Sometimes diagnoses were based on questionnaire responses only, sometimes following detailed clinical interviews and laboratory testing. There were also differences in the way similar case definitions were practiced in the various studies, e.g. some studies applied a low threshold for exclusion of cases with psychiatric comorbidity, while others did not.

Indirect comparisons of prevalence estimates from several case definitions applied on different populations (Model C)

We identified 21 studies (Table 4) presenting prevalence estimates for CFS/ME (Figure 3), in addition to the five studies presenting prevalence estimates following the application of multiple case definitions (Table 2). Based on these studies, we extracted 17 independent estimates of the prevalence following application of the CDC-1994/Fukuda criteria (Figure 5).

< Insert Table 4 about here>

Our analysis suggests that the population prevalence of CFS/ME according to the CDC-1994/Fukuda case definition probably is less than 1% (range 0.1 to 6.4%; median 1.0%), with higher prevalence among consecutive GP-attendants than from population studies. Prevalence estimates seemed higher when patients were diagnosed without a preceding medical examination. Prevalence estimates of CFS/ME according to CDC-1988/Holmes

case definition seemed lower, with all the studies reporting prevalence estimates ranging from 0.0 to 0.3% (median 0.05%).

Five studies [54-58] reported CFS/ME prevalence estimates according to the Oxford-1991 case definition. These estimates ranged from 0.4% - 3.7% (median 1.5%). Four studies [44;54-56] reported prevalence estimates according to the Australian-1990 case definition ranging from 0.04% - 7.6% (median 1.2%).

Discussion

We identified 20 studies presenting different CFS/ME case definitions, and 38 studies with data providing access to comparison and evaluation of some of these. Only a minority of existing case definitions had been submitted to comparative evaluations. The validation studies were methodologically weak and heterogeneous, making it questionable to compare the case definitions. The most cited case definition (CDC-1994/Fukuda[39]) is also the most extensively validated one, whereas validation studies are few (Canadian-2003[22], ICC-2011[23]) or missing (NICE-2007[46]) for more recently presented and debated case definitions. We found no empirical evidence supporting the hypothesis that some case definitions more specifically identify patients with a neuroimmunological condition.

Strengths and weaknesses of our study

The main strength of our study is the systematic methods used to identify and appraise articles presenting case definitions of CFS/ME and studies potentially useful to evaluate the case definitions. Furthermore, we have used systematic and transparent approaches to extract data from the validation studies, categorise the studies according to three different models, and to analyse and compare the data.

The STARD initiative aims to improve the reporting on studies of diagnostic accuracy, considering any method for obtaining additional information on a patient's health status as a test [25]. Due to the lack of a reference standard, we found this guideline less suitable for review of articles evaluating case definitions for CFS/ME. Still, issues such as study

populations, test methods and rationale, technical specifications for application of the test, statistical methods for comparing measures of accuracy and uncertainty, estimates of diagnostic accuracy, variability, and clinical applicability [25] are relevant also for our analysis.

The validation studies we identified were small with considerable methodological weaknesses and inconsistent results. Only one study held a level of rigor where independent application of several case definitions was conducted on the same population (Model A) [50]. Such a study should ideally be based on a population sample rather than a GP practice database, and should compare a selection of currently applied and debated case definitions, such as CDC-1994/Fukuda, Oxford-1991, Canadian-2003 and NICE-2007.

The QUADAS-criteria [28] demonstrate that Model B is an evaluation strategy prone to several sources of bias. First, the spectrum of patients subjected to the comparator is selected and not representative of the population receiving the test if it is used alone. Second, as comparators were mostly applied subsequently to the evaluation standard, the clinical evaluations were not independent. The estimates from two of the Jason studies [33;52] suggest a comparable correspondence (40-70% of the F+ are also C+) with the results presented by Nacul and co-workers [50]. Yet, Model B gives no or limited information regarding those who screened negative in the first place. We do not know if some of those might have had a positive diagnosis if screened with one of the other case definitions.

We are even more prone to bias when exploring the consistency of different case definitions through indirect comparisons of prevalence estimates obtained from different populations (Model C), and great caution is needed when such proxy comparisons are undertaken. For example, two of the included studies reported similar point prevalence according to CDC-1994/Fukuda (2.1% and 2.6%), but reported very different estimates following the application of the Australian-1990 criteria (7.6% and 1.4%) [54;55]. This inconsistency can be explained by major methodological differences seen across the included studies. Our sample includes studies in which a diagnosis of CFS/ME is made on the basis on either questionnaire responses or clinical interview. Previous studies

suggest that patients who receive a standardised questionnaire report considerable more symptoms than when asked to report their symptoms spontaneously [59]. There are several other sources to this between study heterogeneity, such as recruitment strategy, response rate and strategies for non-response adjustment. We were not able to identify the most important one. However, Johnston et al performed interesting subgroup analysis in their meta-analysis of 14 studies applying the CDC-1994/Fukuda case definition, and found that the pooled prevalence for self-reporting assessment was 3.28% (95% CI: 2.24–4.33) compared to 0.76% (95% CI: 0.23–1.29) for clinical assessment [27]. Prevalence was lower in community samples (0.87%; 0.32–1.42) than in primary care samples (1.72%; 1.40–2.04). The prevalence estimates based on self-reports showed high variability, while clinically assessed estimates were more consistent, especially in the community samples.

The utility of case definitions and diagnoses

The utility of a diagnosis is linked to the potential effects of being diagnosed (e.g. benefits and harms of the patient role, access to treatment and insurance). More important, a diagnosis is useful if it is linked to valid information regarding prognosis or outcomes of therapy. Reitsma et al suggest clinical test validation as an alternative paradigm for evaluation of a diagnostic test when an acceptable reference standard is missing [26]. Hence, primary studies and systematic reviews on prognosis and therapy are alternative sources to evaluate the usefulness of different case definitions of CFS/ME. We have identified only one such publication, the PACE trial [60]. Here, participants were diagnosed according to the Oxford-1991 criteria, Empirical criteria-2007/Reeves and London ME-1994/National Task Force criteria, and then randomised to either standard medical treatment, graded exercise therapy, cognitive behaviour therapy or pacing. The results showed that the effectiveness of the treatments was similar across groups, irrespective of the case definition which had been used. Fluge et al applied the CDC-1994/Fukuda and retrospectively added the Canada criteria in their study on the effects of rituximab in CFS with comparable results [9]. In a recent publication, Maes et al measured symptom severity, selected biomarkers and post-exertional malaise in 144 patients with chronic fatigue (CF), of whom 107 fulfilled the CDC-1994/Fukuda criteria of CFS/ME [21].

They claimed that CF, CFS and ME are distinct categories, although stating that patients group together in one continuum with no clear boundaries between them [21]. Such studies would be even more useful if outcomes of specific treatment modes had also been tested.

A study comparing the prognosis of different diagnostic labels of fatigue found that patients with ME had the worst prognosis while patients with post-viral fatigue syndrome had the best [61]. This could mean that the patients destined to the worst prognosis were labelled with the ME diagnosis, or it might be explained as an adverse effect of being labelled with ME. The authors found no significant difference in recorded fatigue before the diagnosis of CFS and ME, and the data in this retrospective study supported the hypothesis of the labeling effect. Another study found that patients who attributed their fatigue to ME were more fatigued and more handicapped in relation to home, work, social and private leisure activities than patients who attributed their fatigue to psychological or social factors [62].

Broad or narrow case definitions?

Ideally, correspondence validity between test and target should be 100% for *sensitivity* (the capacity to identify patients in the target group) and *specificity* (the capacity to rule out patients that do not belong to the target group). More often, there is a trade-off between these measures, depending on the purpose of diagnosis. Emphasizing sensitivity implies a risk of over-diagnosis, which dilutes the actual diagnostic concept, while emphasizing specificity implies a risk of under-diagnosis, dismissing patients who might benefit from treatment. Development of more exclusive case definitions for CFS/ME has been proposed, claiming that existing case definitions do not select homogenous sets of patients [23]. More specifically, Oxford-1991, Fukuda-1994 and NICE-2007 have been criticised, especially by patient organizations, for undue overlap with psychopathology. Proponents of recent case definitions such as Canada-2003 and ICC-2011, claim to achieve a narrow selection of patients with ME conforming to a hypothesized specific pathophysiology. Our review demonstrates, however, that these case definitions do not necessarily exclude patients with psychopathology.

A lesson could be learnt from Reeves, who tried to elaborate the CDC1994/Fukuda definition and bring methodological rigor into the diagnostic criteria by scores from standardized and validated instruments [63]. The Empirical-2006/Reeves case definition led to a tenfold prevalence estimate as compared with the CDC1994/Fukuda definition [64], probably due to misclassification and inclusion of patients with major depressive disorder [65]. The purpose of rigor had not been achieved, and the Empirical-2006/Reeves case definition was never broadly implemented. According to our review, it is uncertain whether a more homogenous subset of patients can be achieved with the Canada-2003 and ICC-2011 case definitions. The authors of the latter paper write: "Collectively, members have approximately 400 years of both clinical and teaching experience, authored hundreds of peer-reviewed publications, diagnosed or treated approximately 50 000 patients with ME, and several members co-authored previous criteria." [23]. This declaration is no validity criterion and provides no guarantee that the case definition works according to the intentions.

Case definitions for research or clinical practice?

Research requires uniform and reproducible criteria, suitable for unambiguous definitions of the target population. Another concern is to compare studies across time and nations. These are arguments for an inclusive case definition, preferably one which has been in use for a while, and for which validation studies are available. In CFS/ME research, the Oxford-1991 and CDC-1994/Fukuda are the most frequently used case definitions. Our review indicates that the former might be more inclusive, with lower specificity than the latter, although the impact of this is unclear. Proponents for more restrictive case definitions dismiss findings from treatment studies documenting effects of cognitive behavioural treatment or graded exercise therapy for patients diagnosed with the Oxford-1991 or CDC-1994/Fukuda case definitions [66]. Their claim is that for a more exclusive selection of patients with ME, defined according to specific hypothesized pathophysiology, the side effects of these treatment modalities are hazardous. So far, however, treatment studies based on the Canada-2003 or ICC-2011 case definitions are not available.

Case definitions for *clinical practice* should be research based, validated and manageable to provide a tool which can relieve patient uncertainty, indicate the most appropriate treatment, and prevent adverse effects and waste of health care resources of unnecessary treatment and diagnostic procedures[67]. They should be founded on available knowledge regarding the mechanisms of the actual condition, validated through credible and transparent processes, and presented in a format which can be implemented in everyday practice. An argument for more inclusive case definitions for CFS/ME would be the issue of treatment, since existing evidence indicates that side effects of cognitive behavioural treatment or graded exercise therapy are negligible. For this context, the CDC-1994/Fukuda case definition appears suitable, with the NICE-2007 as a good candidate for validation studies.

Implications for research and clinical practice

Based on our review, we argue that development of further case definitions of CFS/ME should be given low priority, as long as causal explanations for the disease are limited. It might still be useful to classify patients according to severity and symptom patterns, aiming to identify characteristics of patients that might predict differences in prognosis or expected effects of therapy.

It is likely that all CFS/ME case definitions capture conditions with different or multifactorial pathogenesis and varying prognosis. The futile dichotomy of "organic" versus "psychic" disorder should be abandoned. Most medical disorders have a complex etiology. Psychological treatments are often helpful also for clear-cut somatic disorders. Unfortunately patient groups and researchers with vested interests in the belief that ME is a distinct somatic disease, seem unwilling to leave the position that ME is an organic disease only. This position has damaged the research and practice for patients suffering of CFS/ME.

Conclusions

Our review provided no evidence that any of the case definitions identify patients with specific or "organic only" disease etiology. Priority should be given to further development and testing of promising treatment options for patients with CFS/ME. Classification of patients according to severity and symptom patterns, aiming to identify characteristics of patients that might predict differences in prognosis or expected effects of therapy, might be useful. Development of further case definitions of CFS/ME should be given low priority. Consistency in research can be achieved by application of diagnostic criteria which have been systematically evaluated and compared to other case definitions.

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Contributors: KM had the original idea, and all five authors worked together to develop an appropriate theoretical framework and design. MSF developed the search, and all authors were involved in the selection process. LL and KGB extracted relevant data, KGB performed the statistical analysis, and all authors were involved in the data interpretation. KM wrote the manuscript draft and revised the draft based on input from the other authors. All authors revised it critically for content and approved the final version.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that: (1) no support from any organisation for the submitted work; (2) no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; (4) no other non-financial interests that may be relevant to the submitted work.

Ethical approval: Not required.

Data sharing statement: All data are extracted from the cited primary studies.

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Table 1
Case definitions for CFS/ME

CASE DEFINITIONS (chronologically)	Developed from other criteria or definitions?	INSTITUTION AND COUNTRY OF FIRST AUTHOR	CITATIONS[A] ISI/Google Scholar
CDC-1988/Holmes [20]		Centers for Disease Control, Atlanta, USA	1106/1542
Myalgic encephalomyelitis 1988/Ramsey [42]		Royal Free Hospital, London, UK	6/51
London-1990/Dowsett [37]		Royal Free Hospital, London, UK	55/88
Australian-1990 [44]		The Prince Henry Hospital, Little Bay, Australia	230/343
Post-viral fatigue syndrome-1990 [43]		Raigmore Hospital, Inverness, UK	14/28
Oxford-1991 [40]		University of Oxford, Oxford, UK	476/667
London ME-1994/National Task Force Guidelines [48]		National Task Force, Bristol, UK	no records
CDC-1994/Fukuda [39]	CDC-1988	Centers for Disease Control, Atlanta, USA	1860/3006
Working Case Definition-1996 [38]	CDC-1988	Brigham and Women's Hospital Massachusetts, USA	78/138
Chronic Fatigue Syndrome-1998 [49]	CDC-1994	Medical College of Wisconsin, USA	8/23
Canadian-2003 [22]		Royal College of Physicians and Surgeons of Canada, Canada	69/233
Empirical CDC-2005/Reeves [63]	CDC-1994	Centers for Disease Control and Prevention, Atlanta, USA	73/154
Empirical-2007 [41]		DePaul University, Chicago, USA	5/14
Brighton Collaboration-2007 [35]		Centers for Disease Control and Prevention, Atlanta, USA	1/5
NICE-2007 Guidelines [46]		National Institute for Health and Clinical Excellence, London, UK	no records/23[B]
The Nightingale Definition of ME/Hyde-2007 [45]		The Nightingale Research Foundation, Canada	no records/5
Epidemiological CFS/ME Definition-2008 [34]		Southampton, Hampshire, UK	2/4
Revised Canadian-2010 [47]	CDC-1994, Empirical CDC-2005, Canadian-2003	DePaul University, Illinois, USA	8/18
ICC-2011 [23]	Canadian-2003	Independent, Canada	4/16
ME-2011 [33]	Dowsett, Ramsey, Hyde	DePaul University, Illinois, USA	1/1

[A]Searched 23. May 2012 [B] Summary of the NICE Guidelines in: Diagnosis and management of chronic fatigue syndrome or myalgic encephalomyelitis (or encephalopathy): summary of NICE guidance BMJ 2007; 335:446

Table 2

Studies presenting prevalence estimates* by independent application of several case definitions on the same population (Model A)

First author, year, country	Data collection	Prevalence (95 % CI)
Nacul [50] 2011, UK	609 possible cases electronically identified in databases of 29 GP practices. 70 excluded after clinical revision (explained fatigue), 135 refusals and 126 non-cases.	ECD: 0.03 % (0.02-0.04) Canada: 0.10 % (0.09-0.12) Fukuda: 0.19 % (0.17-0.21)
Bates [56] 1993, US	995 consecutive GP visitors invited - 94 % screened by a questionnaire to detect major fatigue. Selected patients further evaluated by questionnaires, physical examinations and interviews.	Holmes: 0.3 % (0.1-0.9) Oxford: 0.4 % (0.1 -1.1) Australia: 1.1 % (0.5-2.0)
Kawakami [57] 1998, Japan	All adults (n=508) in Town A, Kofu-city, were invited to participate in this structured psychiatric diagnostic interview survey. 137 (27%) completed the study	Holmes: 0.0 % (0.0-2.7) Fukuda: 1.5 % (0.2-5.2) Oxford: 1.5 % (0.2-5.2)
Lindal [55] 2002, Iceland	Survey sent to 4000 randomly selected adult participants – 63% responded. Questionnaire included questions on all items in the four case definitions. Diagnosis were set electronically based on received responses. No medical tests or examinations were undertaken.	Holmes 0.0 % (0.0-1.5) Fukuda: 2.1 % (1.6-2.8) Oxford: 3.7 % (3.2-4.6) Australia: 7.6 % (6.6-8.7)
Wessely [54;68] 1997, UK	2363 patients followed in a cohort study – 84% completed. Fatigued participant subjected to detailed questionnaires, interviews, and laboratory testing. Separate estimates reported for inclusion/exclusion of psychiatric co-morbidity.	Holmes: 1.2 % (0.5-1.8) Australia: 1.4 % (0.8-2.0) Oxford: 2.2 % (1.4-3.0) Fukuda: 2.6 % (1.7-3.4)

*Prevalence estimates were calculated with the number of responders in the denominator. The choice of denominator may have large implications with regard to the subsequent prevalence estimate, particularly in studies with low response rate. Hence, depending on the actual response rate, estimates presented for each study may be biased.

Table 3

Conformity of prevalence estimates in studies where patients diagnosed with CFS/ME with one set of diagnostic criteria are diagnosed sequentially with other case definitions (Model B)

Study Recruitment	Case definitions	Conformity[#] (95% CI)	Symptom and burden profile
Brimacombe [69], US Fukuda-positive from register	Fukuda* (n=200) Holmes (n=171)	1 0.85 (0.80-0.90)	[F+/H-] patients do not endorse infectious-type symptoms as often or to the same degree of severity as [F+/H+] patients
Jason [70], US Fukuda-positive from register	Fukuda* (n=32) Holmes (n=14)	1 0.44 (0.26-0.62)	[F+/H+] patients with more symptoms and functional impairment than [F+/H-]. No difference in psychological co-morbidity
Jason [52], US Fukuda-positive from register	Fukuda* (n=32) Canada (n=23)[§]	1 0.63 (0.44-0.79)	C+ patients have less psychiatric co-morbidity, more physical function impairment, are more fatigued with more neurological symptoms than [F+/C-] patients
Jason [33], US Fukuda-positive recruited from many sources	Fukuda* (n=113) Canada (n=57) ME-2011 (n=27)	1 0.50 (0.41-0.60) 0.24 (0.16-0.33)	[F+/C+] patients had more functional impairments, and physical, mental, and cognitive problems than [F+/C-] patients. [F+/ME+] patients had more functional impairments, and more severe physical and cognitive symptoms than [F+/ME-] patients.
Fluge [9], Norway Fukuda-positive patients recruited to trial	Fukuda* (n=30) Canada (n=28)	1 0.93 (0.78-0.99)	Not reported
Jason [71], US Register	Fukuda* (n=24) Reeves empirical Canada	Of 24 F+ and 84 F- patients empirical criteria and Canada identified 79 and 87% correctly	Canadia-2003 case definition appear to select more cardinal and central features of the illness than Empirical CDC-2005/Reeves case definition
Jason [65], US Register	Fukuda* (n=27) Reeves emp. (n=41)[§§]	1 1.00 (0.87-1.00)	Empirical CDC-2005/Reeves case definition led to mis-classification of major depressive disorder as CFS

Brown [53], US Fukuda-positive recruited from many sources	Fukuda* (n=113) ICC (n=39)	1 0.35 (0.26-0.44)	ICC+ patients with more functional impairments and physical, mental and cognitive problems than [F+/ICC-] patients. The ICC+ patients also had greater rates of psychiatric comorbidity
Jason [72], US Fukuda-positive from register	Fukuda* (n=32) Dowsett (n=17) §§§	1 0.44 (0.26-0.62)	D+ patients appear to be more symptomatic than [F+/D-] patients, especially in the neurological and neuropsychiatric areas.
White [60], UK Oxford-positive patients recruited to trial	Oxford* (n=641) Fukuda (n=427) London ME (n=329)	1 0.67 (0.63-0.70) 0.51 (0.47-0.55)	Effect of CBT and GET similar regardless of diagnostic group affiliation
Wearden [73], UK Oxford-positive patients recruited to trial	Oxford* (n=296) London ME (n=92)	1 0.31 (0.26-0.37)	Not reported
Stubhaug [74], Norway Neurasthenia-positive patients recruited to trial	Neurasthenia* (n=72) Oxford (n=65) Fukuda (n=29)	1 0.90 (0.81-0.96) 0.40 (0.29-0.53)	Not reported

#The proportion of cases relative to the evaluation standard; *Evaluation standard;
§ 3/23 participants testing positive according to Canada were negative according to Fukuda
§§14/37 depressed patients tested positive according to Reeves and negative on Fukuda
§§§ 3/17 participants testing positive according to Dowsett were negative according to Fukuda

Table 4

Studies presenting prevalence estimates for CFS/ME from several case definitions applied on different populations (Model C)

First author, year COUNTRY	CASE DEFINITION	RECRUITMENT STRATEGY
Bazelmans 1999 [75] The Netherlands	As recognized by GP	Questionnaire to all GPs, Prevalence estimated to 0.11 %
Lloyd 1990 [44] Australia	Australian	Recruited through GP's covering 76206 patients
Buchwald 1995 [76] US	CDC-1988/ Holmes	Postal survey to 4000 randomly selected participants
Gunn 1993 [77] US	CDC-1988/ Holmes	Recruited by contact with primary health care providers; prevalence in the range 0.002-0.007%
Price 1992 [78] USA	CDC-1988/ Holmes	Interview survey with 13538 participants
Versluis 1997 [79] The Netherlands	CDC-1988/ Holmes	23000 patients in GP database
Bierl 2004 [80] US	CDC-1994/ Fukuda	Random digit-dialing survey with 7317 respondent
Cho 2009 [81] UK	CDC-1994/ Fukuda	2530 consecutive GP visitors
Cho 2009 [81] Brazil	CDC-1994/ Fukuda	3921 consecutive GP visitors
Evengård 2005 [82] Sweden	CDC-1994/ Fukuda	Phone survey of 41499 participants in a twin register
Hamagucchi 2011 [83] Japan	CDC-1994/ Fukuda	3000 random participants in a health check program
Jason 1999 [84] US	CDC-1994/ Fukuda	Phone survey with 18675 respondents
Kim 2005 [85] South Korea	CDC-1994/ Fukuda	1962 consecutive GP visitors
Njoku 2007 [86] Nigeria	CDC-1994/ Fukuda	Interview survey with 1500 participants
Reeves 2007 [64] US	CDC-1994/ empirical	Phone survey with 10837 responding households
Reyes 2003 [87] US	CDC-1994/ Fukuda	Phone survey with 33997 responding households
Steele 1998 [88] US	CDC-1994/ Fukuda	Phone survey with 8004 responding households
van't Leven 2009 [89] The Netherlands	CDC-1994/ Fukuda	Postal survey to 22500 randomly selected participants
Vincent 2012 [90] US	CDC-1994/ Fukuda	Retrospective medical record review in Olmsted County; 183841 residents
Yiu 2005 [91] China	CDC-1994/ Fukuda	Unknown
Lawrie 1995 [58] UK	Oxford	Postal survey to 1039 randomly selected participants
Ho-Yen 1991 [92] UK	Post viral exhaustion syndrome	Postal survey to 195 GPs; prevalence 0.13 % (0.12-0.15)

Case definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) - A systematic review

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Abstract

Objective: To identify case definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), and explore how the validity of case definitions can be evaluated in the absence of a reference standard.

Design: Systematic review.

Setting: International.

Participants: A literature search, updated as of November 2013, led to identification of 20 case definitions and inclusion of 38 validation studies.

Primary and secondary outcome measure: Validation studies were assessed for risk of bias and categorised according to three validation models: A) independent application of several case definitions on the same population, B) sequential application of different case definitions on patients diagnosed with CFS/ME with one set of diagnostic criteria, or C) comparison of prevalence estimates from different case definitions applied on different populations.

Results: A total of 38 studies contributed data of sufficient quality and consistency for evaluation of validity, with CDC-1994/Fukuda as the most frequently applied case definition. No study rigorously assessed reproducibility or feasibility of case definitions. Validation studies were small with methodological weaknesses and inconsistent results. No empirical data indicated that any case definition specifically identified patients with a neuroimmunological condition.

Conclusions: Classification of patients according to severity and symptom patterns, aiming to predict prognosis or effectiveness of therapy, seems useful. Development of further case definitions of CFS/ME should be given low priority. Consistency in research can be achieved by applying diagnostic criteria that have been subjected to systematic evaluation.

Abstract

Objective To identify case definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), and explore how one can evaluate the validity of case definitions in the absence of a reference standard.

Design Systematic review.

Data sources and eligibility criteria The Cochrane Library, Ovid AMED, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, CINAHL, Ovid PsycINFO, PEDRO databases, and reference lists were searched for studies presenting or validating case definitions for CFS/ME for adult populations November 2013.

Review methods We searched for relevant case definitions and validation studies. Potential validation studies were assessed for risk of bias and categorised according to three validation models: independent application of several case definitions on the same population, sequential application of different sets of diagnostic criteria, or comparison of prevalence estimates from different case definitions applied on different populations.

Results We identified 20 case definitions. A total of 38 studies contributed data of sufficient quality and consistency for evaluation of validity, with CDC-1994/Fukuda as the most frequently applied case definition. No study rigorously assessed reproducibility or feasibility of case definitions. Validation studies were small with methodological weaknesses and inconsistent results. No empirical data indicated that any case definition specifically identified patients with a neuroimmunological condition.

Conclusions Classification of patients according to severity and symptom patterns, aiming to predict prognosis or effectiveness of therapy, seems useful. Development of further case definitions of CFS/ME should be given low priority. One can achieve consistency in research by applying diagnostic criteria that have been subjected to systematic evaluation.

Article summary

Article focus

- Several case definitions for ~~CFS/ME~~Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) exist, but there is no general agreement on a reference standard for diagnosis.
- This study aims to identify and ~~describe differences between~~compare case definitions for ~~Chronic Fatigue Syndrome/Myalgic Encephalitis (~~CFS/ME~~).~~.
- ~~Second, we~~We also explore how accuracy and validity of the case definitions can be evaluated in the absence of a reference standard.

Key messages

- None of the included studies rigorously assessed the reproducibility or feasibility of existing case definitions.
- Only one included study reported data in a way that ~~facilitates robust and direct comparisons of~~made it possible to compare different case definitions rigorously and directly.
- We found no empirical evidence supporting the hypothesis that some case definitions more specifically identify patients with a neuroimmunological condition.

Strengths and limitations of this study

- The main strength of our study is the systematic methods used to identify and appraise articles presenting and evaluating case definitions of CFS/ME.
- We ~~have~~ used systematic and transparent approaches to extract data, categorise the studies according to pre-specified models, and to analyse and compare the data.
- The included validation studies showed considerable methodological weaknesses and inconsistent results, and it is therefore difficult to draw firm conclusions.

Introduction

Chronic fatigue syndrome (CFS) is a serious disorder characterised by persistent post-exertional fatigue and substantial symptoms related to cognitive, immune and autonomous dysfunction [1;2]. Disease mechanisms are complex [3], with no single causal factor identified. Yet there are indications that infections [4-8] and ~~autoimmune~~immunologic dysfunction [9] contribute to development and maintenance of symptoms, probably interacting with genetic ~~[10] and~~[10] and psychosocial [11-13] factors.

Studies have identified pathological patterns and structures of the central nervous system [14;15], dysregulation of body temperature and blood pressure [16;17], and dysfunctional stress hormonal systems [18;19] in CFS patients compared to normal controls. None of these appears sufficiently consistent to constitute a diagnostic test, and case definitions (diagnostic criteria) are therefore used to define the CFS diagnosis. When case definitions are developed, the context of application must be considered, since different properties are needed for case definition intended for research purposes compared to case definitions used to diagnose individual patients. It is also necessary to consider whether a broad (i.e. sensitive criteria ensuring that we do not miss relevant cases) or narrow (i.e. specific criteria ensuring that all positive cases are definite) approach is most appropriate.

Holmes et al [20] coined the term "Chronic Fatigue Syndrome" in 1988, as an alternative to "The chronic Epstein-Barr virus syndrome". ~~. Case definitions (diagnostic criteria) are used in research and clinical practice to define the CFS diagnosis. Since the first~~Since this case definition - the CDC-1988/Holmes Criteria - was presented in 1988 [20], numerous revisions have been developed, aiming for distinctive and reliable identification of individuals who represent a homogenous and consistent phenotype of the hypothesized disease entity, consistent with pathophysiological and psychosocial findings.

~~Holmes et al [20] coined the term "Chronic Fatigue Syndrome" in 1988, as an alternative to "The chronic Epstein-Barr virus syndrome".~~Today the term "Myalgic Encephalomyelitis" (ME) is commonly used to conceptualize a specific neuroimmunological condition, assumed to be more severe and less psychologically attributed than CFS[21]. In 2003, Carruthers et al presented the Canadian-2003 Criteria~~,~~ for diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome ~~[21]~~[21;22]. A revised

version was presented as International Consensus Criteria (the ICC--2011 Criteria) for Myalgic Encephalomyelitis [22~~22~~23], claiming to be a selective case definition for identification of patients with neuroimmune exhaustion with a pathologically low threshold of fatigability and symptom flare after exertion. The assertion that CFS and ME are different clinical entities is disputed. Below, we will pragmatically apply the term CFS/ME.

Johnston et al conducted a systematic review of the adoption of CFS/ME case definitions to assess prevalence and identified eight different case definitions [~~23~~ 24]. There is no general agreement on a reference standard for diagnosis, and no diagnostic test is available. ~~No studies exist where diagnostic accuracy is assessed by comparing case definitions with a reference standard in consecutive patients suspected of having CFS/ME [24].~~ Bossuyt et al. include case definitions in their understanding of the term "test", emphasizing that diagnostic tests are highly dynamic and need rigorous evaluation before they are introduced into clinical ~~practice~~[25] practice [25;26].

The objectives of our study were to explore strategies for evaluation of accuracy and concept validity of different case definitions for CFS/ME in the absence of a reference standard. First, we wanted to conduct a systematic review to identify and describe different case definitions *(*sets of diagnostic criteria) for CFS/ME. Second, we wanted to explore differences between various case definitions by identifying and reviewing validation studies**.**

Method and material

Protocol and registration

We developed a protocol for our study~~, but~~**.** However, we did not publish or register it.

Eligibility criteria

We included studies presenting or validating case definitions for CFS/ME for adult populations (>18 years). No language restrictions were employed.

Information sources and search

We searched ~~The Cochrane Library,~~ Ovid ~~AMED,~~MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations~~,~~ from 1946, Ovid EMBASE~~, CINAHL~~ from 1980, Ovid PsycINFO from 1806, Ovid AMED from 1985, The Cochrane Library from 1898, CINAHL from 1981, and PEDRO ~~databases January 2012, with an updated search in November 2013~~from 1929 using subject headings and text words (Appendix 1). All searches were up to date as of 25. November 2013. We checked the reference lists of all included articles and searched for unpublished and on-going studies by correspondence with authors and field experts.

Study selection

To select publications eligible for this review, two authors independently read all titles and abstracts in the records retrieved by the searches. We obtained publications in full text if the abstract was deemed eligible by at least one review author. At least two authors independently read the full text papers and selected studies according to the inclusion criteria. Any disagreement between review authors was resolved by discussion between the two review authors or, if necessary, by involving all authors.

Data collection process

First, we listed all the identified *case definitions for CFS/ME*. ~~We~~One author gathered information about citation from ISI and Google Scholar to indicate the impact or widespread of use, but we made no attempt to assess or rank the quality of the case definitions at this stage.

~~Then we organized and reviewed those of the identified studies which held a potential to compare and evaluate different case definitions – the *validation studies*. We developed three different models in which the validation studies could be categorised for comparison and evaluation:~~

To facilitate the validity assessment, we developed a framework consisting of three different models:

Model A includes studies with *independent application of different case definitions on the same population* (Figure 1). This model presents the interrelationship between subpopulations identified by the different case definitions.

<Insert Figure 1 about here>

Model B includes studies where patients diagnosed with CFS/ME with *one set of diagnostic criteria are diagnosed sequentially with other case definitions* assumed to have increasing specificity (Figure 2).

<Insert Figure 2 about here>

Model C includes surveys or cross-sectional studies ~~aimed at~~ estimating the *prevalence* of CFS/ME ~~obtained~~ by applying different case definitions on different populations (Figure 3). These studies do not directly compare different case definitions, but may be used for proxy evaluation, similar to the strategy applied by Johnston et al [~~23,26~~24,27].

<Insert figure 3 about here>

Two authors reviewed all potentially relevant *validations studies*, and categorised them according to Model A, B or C. Any disagreement between review authors at this stage was resolved by reaching consensus in the author group.

Risk of bias in individual studies

To differentiate between studies with higher and lower risk of bias, we critically appraised all included validation studies according to check lists: Studies comparing two or more case definitions directly (i.e. Model A or B) were appraised according to the QUADAS-criteria [~~27~~28] (patient selection, index test, reference standard, flow, and timing). For evaluation of prevalence studies (i.e. Model C) we used an outline for assessment of external and internal validity (11 items) of prevalence studies [~~28~~29].

Analysis

Participation in prevalence studies, surveys, and questionnaires vary across the included studies. Non-response is known to introduce bias, and methods to adjust for low response rates are available [~~29~~30]. In studies affected by non-response, we have reported adjusted estimates whenever applicable. If adjusted estimates were unavailable, we have defined the proportion as the number of cases divided by the number of responders. We estimated 95-% confidence intervals for all proportions by using the Clopper-Pearson exact binomial method. We used R software version 3.0.0 and the rmeta package for statistical computations and plotting [~~30;~~31;32].

Results

Study selection

Our systematic literature search identified ~~1036~~1660 unique references, of which 56 articles fulfilled our inclusion criteria (Figure 4). ~~Among these, 20~~Twenty articles present different *case definitions* of CFS/ME for research or clinical practice [20;22;~~32-48~~23;33-49] (Table 1). ~~The remaining 36~~Furthermore, 38 studies were classified as *validation studies*, contributing data of ~~sufficientquality~~sufficient quality and consistency for evaluation of different case definitions according to our inclusion criteria.

< Insert Table 1 and Figure 4 about here>

The degree to which the different case definitions had been applied in research and clinical guidelines varied widely, with CDC-1994/Fukuda [39] as the most frequently cited case definition of CFS/ME.

~~12~~Thirteen of the 20 identified case definitions had been assessed in one or more validation study [20;~~21;32~~22;23;33;~~35~~34;36;~~38-40;42~~37;39-41;43;~~46~~44;47]. For ~~eight~~seven case definitions, no foundation for validation could be identified. We did not identify any study which rigorously assessed the reproducibility or feasibility of the different case definitions.

Independent application of several case definitions on the same population (Model A)

Five studies (Table 2) applied several case definitions on the same population, but only one of these reported data in a way that ~~facilitatedsufficiently robust comparisons of~~made it possible to compare the case definitions [49;50;51]. Nacul et ~~al.~~ [49]al [50] used GP databases and questionnaires and identified 278 patients with unexplained chronic fatigue conforming to one or more of the case definition applied, i.e. CDC-1994/Fukuda [38]39, Canadian-2003 [21]22 or ECD-~~2008~~[33]2008 [34]. Most of the patients who were positive according to the Canada-criteria [C+] were also positive using the Fukuda criteria [F+]. 47-% of the Fukuda positive patients were also positive according to the Canada criteria. Patients who were positive to both the Canada and Fukuda [C+/-F+] reported a higher level of symptoms than those who were [F+/-C-]. The authors did not identify differences in the distribution of triggering factors [49]50.

< Insert Table 2 about here>

None of the other four studies in this group reported data on the correlation between case definitions, patient profile, and symptom burden. Application of CDC-1988/Holmes case definition was consistently associated with lower prevalence estimates than CDC-1994/Fukuda, Oxford-1991, and Australian-1990 criteria across these four studies. There was no consistent trend for the other case definitions, but the studies were heterogeneous regarding the application of ~~the~~ different case definitions and data collection (Table 2). This observation suggests that prevalence numbers obtained by different case definitions should be controlled according to diagnostic procedure, cut-off points and reasons for exclusions before concluding upon differences.

Different case definitions with assumed increasing specificity applied sequentially on the same population (Model B)

~~Eleven~~Twelve studies (Table 3) ~~had~~ sequentially applied different case definitions on the same population. In these studies, patients were screened by the use of an evaluation standard. Subsequently, test-positive individuals were screened with one or more comparators. ~~Eight~~Nine of the ~~eleven~~twelve studies applied CDC-1994/Fukuda as the evaluation standard, and then tested Fukuda-positive patients with CDC-1988/Holmes,

Canadian-2003, ICC- 2011, ME-2011, Empirical-2006/Reeves, London-1990/Dowsett, or Neurasthenia case definitions.

< Insert Table 3 about here>

We have taken the actual evaluation standard as a point of departure, and calculated the proportion of these patients still positive when applying other case definitions. Since there are no test negatives for the case definition used as point of departure, true sensitivities or specificities cannot be calculated. Results from two of the studies by Jason et al.[32;51] [33;52] suggest that 40-70% of the Fukuda positive patients are also Canada positives [F+/C+]. One study [51][52] concluded that there was less psychiatric co-morbidity and more physical functional impairment in the sub-sample which was positive on both case definitions [F+/C+] than those who were negative according to the Canada criteria [F+/C-]. However, the other study [33] suggested a higher incidence of mental and cognitive problems among Fukuda positive patients who were also Canada positive [F+/C+] as compared to the remaining Fukuda positive but Canada negative patients [F+/C-]. In a separate publication [53], the same Fukuda positive patients as referred in Jason 2012 [33] were used to contrast ICC-2011. About 34% (95% CI 26%-44%) of the Fukuda positive patients were also ICC positives [F+/ICC+]. Similar to the [F+/C+] subset, it was found that [F+/ICC+] patients experienced more functional impairments as well as more mental and cognitive problems and higher psychiatric comorbidity than [F+/ICC-] patient.

The comparisons presented in table 3 are associated with high risk of bias as well as random errors, and the results should be interpreted with great caution. For example, two of the included studies reported similar point prevalence according to CDC-1994/Fukuda (2.1% and 2.6%) but reported very different estimates using the Australian-1990 criteria (7.6% and 1.4%)[52;53] [54;55]. Sometimes diagnoses were based on questionnaire responses only, sometimes following detailed clinical interviews and laboratory testing. There ~~are~~were also differences in the way similar case definitions ~~had been~~were practiced in the various studies, e.g. some studies applied a low threshold for exclusion of cases with psychiatric ~~co-morbidity~~comorbidity, while others did not.

Indirect comparisons of prevalence estimates from several case definitions applied on different populations (Model C)

We identified ~~17~~21 studies (Table 4) presenting prevalence estimates for CFS/ME (Figure 3), in addition to the five studies presenting prevalence estimates following the application of multiple case definitions (Table 2). Based on these studies, we extracted ~~13~~17 independent estimates of the prevalence following application of the CDC-1994/Fukuda criteria (Figure 5).

< Insert Table 4 about here>

Our analysis suggests that the population prevalence of CFS/ME according to the CDC-1994/Fukuda case definition probably is less than 1% (range 0.~~2~~1 to 6.4%; median 1.~~2~~0%), with higher prevalence among consecutive GP-attendants than from population studies. Prevalence estimates seemed higher when patients were diagnosed without a preceding medical examination. Prevalence estimates of CFS/ME according to CDC-1988/Holmes case definition seemed lower, with all the studies reporting prevalence estimates ranging from 0.0 to 0.3% (median 0.05%).

Five studies [54-58] reported CFS/ME prevalence estimates according to the Oxford-1991 case definition. These estimates ranged from 0.4% - 3.7% (median 1.5%). Four studies [44;54-56] reported prevalence estimates according to the Australian-1990 case definition ranging from 0.04% - 7.6% (median 1.2%).

Discussion

We identified 20 studies presenting different CFS/ME case definitions, and ~~36studies~~38 studies with data providing access to comparison and evaluation of some of these. Only a minority of existing case definitions had been submitted to comparative evaluations. The validation studies were methodologically weak and heterogeneous, making it ~~difficult~~questionable to compare the case definitions. The most cited case definition (CDC-1994/Fukuda[39]) is also the most extensively validated one, whereas validation studies are few (Canadian-2003[22], ICC-2011[23]) or missing (NICE-2007[46]) for more recently presented and debated case definitions. We found no empirical evidence

supporting the hypothesis that some case definitions more specifically identify patients with a neuroimmunological condition~~, excluding patients with psychiatric co-morbidity~~.

Strengths and weaknesses of our study

The main strength of our study is the systematic methods used to identify and appraise articles presenting case definitions of CFS/ME and studies potentially useful to evaluate the case definitions. Furthermore, we have used systematic and transparent approaches to extract data from the validation studies, categorise the studies according to three different models, and to analyse and compare the data.

The STARD initiative aims to improve the reporting on studies of diagnostic accuracy, considering any method for obtaining additional information on a patient's health status as a test [25]. Due to the lack of a reference standard, we found this guideline less suitable for review of articles evaluating case definitions for CFS/ME. Still, issues such as study populations, test methods and rationale, technical specifications for application of the test, statistical methods for comparing measures of accuracy and uncertainty, estimates of diagnostic accuracy, variability, and clinical applicability [25] are relevant also for our analysis.

The validation studies we identified were small with considerable methodological weaknesses and inconsistent results. Only one study held a level of rigor where independent application of several case definitions was conducted on the same population (Model A) [~~49~~50]. Such a study should ideally be based on a population sample rather than a GP practice database, and should compare a selection of currently applied and debated case definitions, such as CDC-1994/Fukuda, Oxford-1991, Canadian-2003 and NICE-2007.

The QUADAS-criteria [28] demonstrate that Model B is an evaluation strategy prone to several sources of bias. First, the spectrum of patients subjected to the comparator is selected and not representative of the population receiving the test if it is used alone. Second, as comparators were mostly applied subsequently to the evaluation standard, the

clinical evaluations were not independent. The estimates from two of the Jason studies [32;51]33;52 suggest a comparable correspondence (40-70% of the F+ are also C+) with the results presented by Nacul and co-workers [50]. Yet, Model B gives no or limited information regarding those who screened negative in the first place. We do not know if some of those might have had a positive diagnosis if screened with one of the other case definitions.

Compared to Model B, weWe are even more prone to bias when exploring the consistency of different case definitions through indirect comparisons of prevalence estimates obtained from different populations (Model C), and great caution is needed when such indirectproxy comparisons are undertaken. For example, two of the included studies reported similar point prevalence according to CDC-1994/Fukuda (2.1% and 2.6%), but reported very different estimates following the application of the Australian-1990 criteria (7.6% and 1.4%)[52;53] [54;55]. This inconsistency is likely tocan be explained by the major methodological differences seen across the included studies;. Our sample includes studies in which a diagnosis of CFS/ME is made on the basis on either questionnaire responses or clinical interview. Previous studies suggest that patients who receive a standardised questionnaire report considerable more symptoms than when asked to report their symptoms spontaneously [59]. There are several other sources to this between study heterogeneity of study power and quality (, such as recruitment strategy, response rate and strategies for non-response adjustment) and heterogeneity of how. We were not able to identify the diagnostic process was implemented. Some authors made diagnoses based on questionnaire responses, other conducted clinical interviews and laboratory testing. Inmost important one. However, Johnston et al performed interesting subgroup analysis in their meta-analysis of 14 studies applying the CDC-1994/Fukuda case definition, Johnston et al and found that the pooled prevalence for self-reporting assessment was 3.28% (95% CI: 2.24–4.33) andcompared to 0.76% (95% CI: 0.23–1.29) for clinical assessment [27]. Prevalence was lower in community samples (0.87%; 0.32–1.42) than in primary care samples (1.72%; 1.40–2.04). The prevalence estimates based on self-reports showed high variability, while clinically assessed estimates were more consistent, especially in the community samples.

The utility of case definitions and diagnoses

The utility of a diagnosis is linked to the potential effects of being diagnosed (e.g. benefits and harms of the patient role, access to treatment and insurance). More ~~importantly~~important, a diagnosis is useful if it is linked to valid information regarding prognosis or outcomes of therapy ~~or prognosis~~. Reitsma et al suggest clinical test validation as an alternative paradigm for evaluation of a diagnostic test when an acceptable reference standard is missing [~~24~~26]. Hence, primary studies and systematic reviews on prognosis and therapy are alternative sources to evaluate the usefulness of different case definitions of CFS/ME. We have identified only one such publication, the PACE trial [~~57~~60]. Here, participants were diagnosed according to the Oxford-1991 criteria, Empirical criteria-2007/~~-~~Reeves and London ME-1994/~~-~~National Task Force criteria, and then randomised to either standard medical treatment, graded exercise therapy, cognitive behaviour therapy or pacing. The results showed that the effectiveness of the treatments was similar across groups, irrespective of ~~which~~the case definition ~~that was~~which had been used. Fluge et al applied the CDC-1994/Fukuda and retrospectively added the Canada criteria in their study on the effects of rituximab in CFS [9] ~~with comparable results.~~with comparable results [9]. In a recent publication, Maes et al measured symptom severity, selected biomarkers and post-exertional malaise in 144 patients with chronic fatigue (CF), of whom 107 fulfilled the CDC-1994/Fukuda criteria of CFS/ME [21]. They claimed that CF, CFS and ME are distinct categories, although stating that patients group together in one continuum with no clear boundaries between them [21]. Such studies would be even more useful if outcomes of specific treatment modes had also been tested.

A study comparing the prognosis of different diagnostic labels of fatigue found that patients with ME had the worst prognosis~~;~~ while patients with post-viral fatigue syndrome had the best [~~58~~61]. This could mean that the patients destined to the worst prognosis were labelled with the ME diagnosis, or it might be explained as an adverse effect of being labelled with ME. The authors found no significant difference in recorded fatigue before the diagnosis of CFS and ME, and the data in this retrospective study supported the hypothesis of the labeling effect. Another study found that ~~the prognosis of~~ patients who attributed their fatigue to ME ~~was worse than of~~were more fatigued and

more handicapped in relation to home, work, social and private leisure activities than patients who attributed their fatigue to psychological or social factors [62].

Broad or narrow case definitions?

Ideally, correspondence validity between test and target should be 100% for *sensitivity* (the capacity to identify patients in the target group) and *specificity* (the capacity to rule out patients that do not belong to the target group). More often, there is a trade-off between these measures, depending on the purpose of diagnosis. Emphasizing sensitivity implies a risk of over-diagnosis, which dilutes the actual diagnostic concept, while emphasizing specificity implies a risk of under-diagnosis, dismissing patients who might benefit from treatment. Development of more exclusive case definitions for CFS/ME ~~have~~has been proposed, claiming that existing case definitions do not select homogenous sets of patients [23]. More specifically, Oxford-1991, Fukuda-1994 and NICE-2007 have been criticised, especially by patient organizations, for undue overlap with psychopathology. Proponents of recent case definitions such as Canada-2003 and ICC-2011 ~~aim for~~, claim to achieve a narrow selection of patients with ~~myalgic encephalomyelitis~~ME conforming to a hypothesized specific pathophysiology. Our review demonstrates, however, that these case definitions do not necessarily exclude patients with psychopathology.

A lesson could be learnt from Reeves, who tried to elaborate the CDC1994/Fukuda definition and bring methodological rigor into the diagnostic criteria by scores from standardized and validated instruments [63]. The Empirical-2006/Reeves case definition led to a tenfold prevalence estimate as compared with the CDC1994/Fukuda definition [~~61~~64], probably due to misclassification and inclusion of patients with major depressive disorder [~~62~~65]. The purpose of rigor had not been achieved, and the Empirical-2006/Reeves case definition was never broadly implemented. According to our review, it is uncertain whether a more homogenous subset of patients can be achieved with the Canada-2003 and ICC-2011 case definitions. The authors of the latter paper write: “Collectively, members have approximately 400 years of both clinical and teaching experience, authored hundreds of peer-reviewed publications, diagnosed or treated approximately

50 000 patients with ME, and several members co-authored previous criteria." [22~~23~~]. This declaration is no validity criterion and provides no guarantee that the case definition works according to the intentions.

Case definitions for research or clinical practice?

Research requires uniform and reproducible criteria, suitable for unambiguous definitions of the target population. Another concern is to compare studies across time and nations. These are arguments for an inclusive case definition, preferably one which has been in use for a while, and for which validation studies are available. In CFS/ME research, the Oxford-1991 and CDC-1994/Fukuda are the most frequently used case definitions. Our review indicates that the former might be more inclusive, with lower specificity than the latter, although the impact of this is unclear. Proponents for more restrictive case definitions dismiss findings from treatment studies documenting effects of cognitive behavioural treatment or graded exercise therapy for patients diagnosed with the Oxford-1991 or CDC-1994/Fukuda case definitions [~~63~~66]. Their claim is that for a more exclusive selection of patients with ME, defined according to specific hypothesized pathophysiology, the side effects of these treatment modalities are hazardous. So far, however, treatment studies ~~of side effects~~ based on the Canada-2003 or ICC-2011 case definitions are not available.

Case definitions for *clinical practice* should be research based, validated and manageable to provide a tool which can relieve patient uncertainty, indicate the most appropriate treatment, and prevent adverse effects and waste of health care resources of unnecessary treatment and diagnostic ~~procedures, conserve limited healthcare resources and initiate the most appropriate treatment~~ [64]procedures[67]. They should be founded on available knowledge regarding the mechanisms of the actual condition, validated through credible and transparent processes, and presented in a format which can be implemented in everyday practice. An argument for more inclusive case definitions for CFS/ME would be the issue of treatment, since ~~based on~~ existing evidence indicates that side effects of cognitive behavioural treatment or graded exercise therapy are negligible. For this

context, the CDC-1994/Fukuda case definition appears suitable, with the NICE-2007 as a good candidate for validation studies.

Implications for research and clinical practice

Based on our review, we argue that development of further case definitions of CFS/ME should be given low priority, as long as causal explanations for the disease are limited. It might still be useful to classify patients according to severity and symptom patterns, aiming to identify characteristics of patients that might predict differences in prognosis or expected effects of therapy.

It is likely that all CFS/ME case definitions capture conditions with different or multifactorial pathogenesis and varying prognosis. The futile dichotomy of "organic" versus "psychic" disorder should be abandoned. Most medical disorders have a complex etiology. Psychological treatments are often helpful also for clear-cut somatic disorders. Unfortunately patient groups and researchers with vested interests in the belief that ME is a distinct somatic disease, seem unwilling to leave the position that ME is an organic disease only. This position has damaged the research and practice for patients suffering of CFS/ME.

Conclusions

Our review provided no evidence that any of the case definitions identify patients with specific or "organic only" disease etiology. Priority should be given to further development and testing of promising treatment options for patients with CFS/ME. Classification of patients according to severity and symptom patterns, aiming to identify characteristics of patients that might predict differences in prognosis or expected effects of therapy, might be useful. Development of further case definitions of CFS/ME should ~~on the other hand~~ be given low priority. Consistency in research can be achieved by application of diagnostic criteria which have been systematically evaluated and compared to other case definitions.

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Contributors: KM had the original idea, and all five authors worked together to develop an appropriate theoretical framework and design. MSF developed the search, and all authors were involved in the selection process. LL and KGB extracted relevant data, KGB performed the statistical analysis, and all authors were involved in the data interpretation. KM wrote the manuscript draft and revised the draft based on input from the other authors. All authors revised it critically for content and approved the final version.

Ethical approval: Not required.

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Table 1
Case definitions for CFS/ME

CASE DEFINITIONS (chronologically)	Developed from other criteria or definitions?	INSTITUTION AND COUNTRY OF FIRST AUTHOR	CITATIONS[A] ISI/Google Scholar
CDC-1988/Holmes [20]		Centers for Disease Control, Atlanta, USA	1106/1542
Myalgic encephalomyelitis 1988/Ramsey [42]		Royal Free Hospital, London, UK	6/51
London-1990/Dowsett [36,37]		Royal Free Hospital, London, UK	55/88
Australian-1990 [43,44]		The Prince Henry Hospital, Little Bay, Australia	230/343
Post-viral fatigue syndrome-1990 [42,43]		~~Raigmore Hospital~~Raigmore Hospital, Inverness, UK	14/28
Oxford-1991 [39,40]		University of Oxford, Oxford, UK	476/667
London ME-1994/National Task Force Guidelines [47,48]		National Task Force, Bristol, UK	no records
CDC-1994/Fukuda [38,39]	CDC-1988	Centers for Disease Control, Atlanta, USA	1860/3006
Working Case Definition-1996 [37,38]	CDC-1988	Brigham and Women's ~~Hospital Massachusetts~~Hospital Massachusetts, USA	78/138
Chronic Fatigue Syndrome-1998 [48,49]	CDC-1994	Medical College of Wisconsin, USA	8/23
Canadian-2003 [21,22]		~~Royal College~~Royal College of Physicians and Surgeons of Canada, Canada	69/233
Empirical CDC-2005/Reeves [60,63]	CDC-1994	Centers for Disease Control and Prevention, Atlanta, USA	73/154
Empirical-2007 [40,41]		~~DePaul University~~DePaul University, Chicago, USA	5/14
Brighton Collaboration-2007 [34,35]		Centers for Disease Control and Prevention, Atlanta, USA	1/5
NICE-2007 Guidelines [45,46]		National Institute for Health and Clinical Excellence, London, UK	no records/23[B]
The Nightingale Definition of ME/Hyde-2007 [44,45]		The Nightingale Research Foundation, Canada	no records/5
Epidemiological CFS/ME Definition-2008 [33,34]		Southampton, Hampshire, UK	2/4
Revised Canadian-2010 [46,47]	CDC-1994, Empirical CDC-2005, Canadian-2003	DePaul University, Illinois, USA	8/18
ICC-2011 [22,23]	Canadian-2003	Independent, Canada	4/16
ME-2011 [32,33]	Dowsett, Ramsey, Hyde	DePaul University, Illinois, USA	1/1

[A]Searched 23. May 2012 [B] Summary of the NICE Guidelines in: Diagnosis and management of chronic fatigue syndrome or myalgic encephalomyelitis (or encephalopathy):

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CASE DEFINITIONS (chronologically)	Developed from other criteria or definitions?	INSTITUTION AND COUNTRY OF FIRST AUTHOR	CITATIONS[A] ISI/Google Scholar
summary of NICE guidance BMJ 2007; 335:446			

Table 2

Studies presenting prevalence estimates* by independent application of several case definitions on the same population (Model A)

First author, year, country	Data collection	Prevalence (95 % CI)
Nacul [49,50] 2011, UK	609 possible cases electronically identified in databases of 29 GP practices. 70 excluded after clinical revision (explained fatigue), 135 refusals and 126 non-cases.	ECD: 0.03 % (0.02-0.04) Canada: 0.10 % (0.09-0.12) Fukuda: 0.19 % (0.17-0.21)
Bates [54,56] 1993, US	995 consecutive GP visitors invited - 94 % screened by a questionnaire to detect major fatigue. Selected patients further evaluated by questionnaires, physical examinations and interviews.	Holmes: 0.3 % (0.1-0.9) Oxford: 0.4 % (0.1 -1.1) Australia: 1.1 % (0.5-2.0)
Kawakami [55,57] 1998, Japan	All adults (n=508) in Town A, Kofu-city, were invited to participate in this structured psychiatric diagnostic interview survey. 137 (27%) completed the study	Holmes: 0.0 % (0.0-2.7) Fukuda: 1.5 % (0.2-5.2) Oxford: 1.5 % (0.2-5.2)
Lindal [53,55] 2002, Iceland	Survey sent to 4000 randomly selected adult participants – 63% responded. Questionnaire included questions on all items in the four case definitions. Diagnosis were set electronically based on received responses. No medical tests or examinations were undertaken.	Holmes 0.0 % (0.0-1.5) Fukuda: 2.1 % (1.6-2.8) Oxford: 3.7 % (3.2-4.6) Australia: 7.6 % (6.6-8.7)
Wessely [52;65,54;68] 1997, UK	2363 patients followed in a cohort study – 84% completed. Fatigued participant subjected to detailed questionnaires, interviews, and laboratory testing. Separate estimates reported for inclusion/exclusion of psychiatric co-morbidity.	Holmes: 1.2 % (0.5-1.8) Australia: 1.4 % (0.8-2.0) Oxford: 2.2 % (1.4-3.0) Fukuda: 2.6 % (1.7-3.4)

*Prevalence estimates were calculated with the number of responders in the denominator. The choice of denominator may have large implications with regard to the subsequent prevalence estimate, particularly in studies with low response rate. Hence, depending on the actual response rate, estimates presented for each study may be biased.

Table 3

Conformity of prevalence estimates in studies where patients diagnosed with CFS/ME with one set of diagnostic criteria are diagnosed sequentially with other case definitions (Model B)

Study Recruitment	Case definitions	Conformity[#] (95% CI)	Symptom and burden profile
Brimacombe [69], US Fukuda-positive from register	Fukuda* (n=200) Holmes (n=171)	1 0.85 (0.80-0.90)	[F+/H-] patients do not endorse infectious-type symptoms as often or to the same degree of severity as [F+/H+] patients
Jason [70], US Fukuda-positive from register	Fukuda* (n=32) Holmes (n=14)	1 0.44 (0.26-0.62)	[F+/H+] patients with more symptoms and functional impairment than [F+/H-]. No difference in psychological co-morbidity
Jason [52], US Fukuda-positive from register	Fukuda* (n=32) Canada (n=23)[§]	1 0.63 (0.44-0.79)	C+ patients have less psychiatric co-morbidity, more physical function impairment, are more fatigued with more neurological symptoms than [F+/C-] patients
Jason [33], US Fukuda-positive recruited from many sources	Fukuda* (n=~~114~~113) Canada (n=57) ME-2011 (n=27)	1 0.50 (0.41-0.60) 0.24 (0.16-0.33)	[F+/C+] patients had more functional impairments, and physical, mental, and cognitive problems than [F+/C-] patients. [F+/ME+] patients had more functional impairments, and more severe physical and cognitive symptoms than [F+/ME-] patients.
Fluge [9], Norway Fukuda-positive patients recruited to trial	Fukuda* (n=30) Canada (n=28)	1 0.93 (0.78-0.99)	Not reported
Jason [71], US Register	Fukuda* (n=24) Reeves empirical Canada	Of 24 F+ and 84 F- patients empirical criteria and Canada identified 79 and 87% correctly	Canadia-2003 case definition appear to select more cardinal and central features of the illness than Empirical CDC-2005/Reeves case definition
Jason [65], US Register	Fukuda* (n=27) Reeves emp. (n=41)[§§]	1 1.00 (0.87-1.00)	Empirical CDC-2005/Reeves case ~~definitionled~~definition led to mis-classification of major depressive disorder as CFS

Brown [53], US Fukuda-positive recruited from many sources	Fukuda* (n=113) ICC (n=39)	1 0.35 (0.26-0.44)	ICC+ patients with more functional impairments and physical, mental and cognitive problems than [F+/ICC-] patients. The ICC+ patients also had greater rates of psychiatric comorbidity
Jason [72], US Fukuda-positive from register	Fukuda* (n=32) Dowsett (n=17) §§§	1 0.44 (0.26-0.62)	D+ patients appear to be more symptomatic than [F+/D-] patients, especially in the neurological and neuropsychiatric areas.
White [60], UK Oxford-positive patients recruited to trial	Oxford* (n=641) Fukuda (n=427) ~~London~~ME London ME (n=329)	1 0.67 (0.63-0.70) 0.51 (0.47-0.55)	Effect of CBT and GET similar regardless of diagnostic group affiliation
Wearden [73], UK Oxford-positive patients recruited to trial	Oxford* (n=296) ~~London~~ME London ME (n=92)	1 0.31 (0.26-0.37)	Not reported
Stubhaug [74], Norway Neurasthenia-positive patients recruited to trial	Neurasthenia* (n=72) Oxford (n=65) Fukuda (n=29)	1 0.90 (0.81-0.96) 0.40 (0.29-0.53)	Not reported

#The proportion of cases relative to the evaluation standard; *Evaluation standard;
§ 3/23 participants testing positive according to Canada were negative according to Fukuda
§§14/37 depressed patients tested positive according to Reeves and negative on Fukuda
§§§ 3/17 participants testing positive according to Dowsett were negative according to Fukuda

Table 4

Studies presenting prevalence estimates for CFS/ME from several case definitions applied on different populations (Model C)

First author, year COUNTRY	CASE DEFINITION	RECRUITMENT STRATEGY
Bazelmans 1999 [72][75] The Netherlands	As recognized by GP	Questionnaire to all GPs, Prevalence estimated to 0.11 %
Lloyd 1990 [43][44] Australia	Australian	Recruited through GP's covering 76206 patients
Buchwald 1995 [73][76] US	CDC-1988/ Holmes	Postal survey to 4000 randomly selected participants
Gunn 1993 [74][77] US	CDC-1988/ Holmes	Recruited by contact with primary health care providers; prevalence in the range 0.002-0.007%
Price 1992 [75][78] USA	CDC-1988/ Holmes	Interview survey with 13538 participants
Versluis 1997 [79] The Netherlands	CDC-1988/ Holmes	23000 patients in GP database
Bierl 2004 [80] US	CDC-1994/ Fukuda	Random digit-dialing survey with 7317 respondent
Cho 2009 [77][81] UK	CDC-1994/ Fukuda	2530 consecutive GP visitors
Cho 2009 [77][81] Brazil	CDC-1994/ Fukuda	3921 consecutive GP visitors
Evengård 2005 [78][82] Sweden	CDC-1994/ Fukuda	Phone survey of 41499 participants in a twin register
Hamagucchi 2011 [79][83] Japan	CDC-1994/ Fukuda	3000 random participants in a health check program
Jason 1999 [80][84] US	CDC-1994/ Fukuda	Phone survey with 18675 respondents
Kim 2005 [85] South Korea	CDC-1994/ Fukuda	1962 consecutive GP visitors
Njoku 2007 [82][86] Nigeria	CDC-1994/ Fukuda	Interview survey with 1500 participants
Reeves 2007 [61][64] US	CDC-1994/ empirical	Phone survey with 10837 responding households
Reyes 2003 [83][87] US	CDC-1994/ Fukuda	Phone survey with 33997 responding households
Steele 1998 [84][88] US	CDC-1994/ Fukuda	Phone survey with 8004 responding households
van't Leven 2009 [85][89] The Netherlands	CDC-1994/ Fukuda	Postal survey to 22500 randomly selected participants
Vincent 2012 [90] US	CDC-1994/ Fukuda	Retrospective medical record review in Olmsted County; 183841 residents
Yiu 2005 [86][91] China	CDC-1994/ Fukuda	Unknown
Lawrie 1995 [56][58] UK	Oxford	Postal survey to 1039 randomly selected participants

	Ho-Yen ~~1991~~[87] 1991 [92] UK	Post viral exhaustion syndrome	Postal survey to 195 GPs; prevalence 0.13 % (0.12-0.15)

Figure legends

Figure 1

Model A: Evaluation design with independent application of several case definitions on the same background population

Figure 2

Model B: Evaluation design where different case definitions with assumed increasing specificity are applied sequentially on the same population

Figure 3

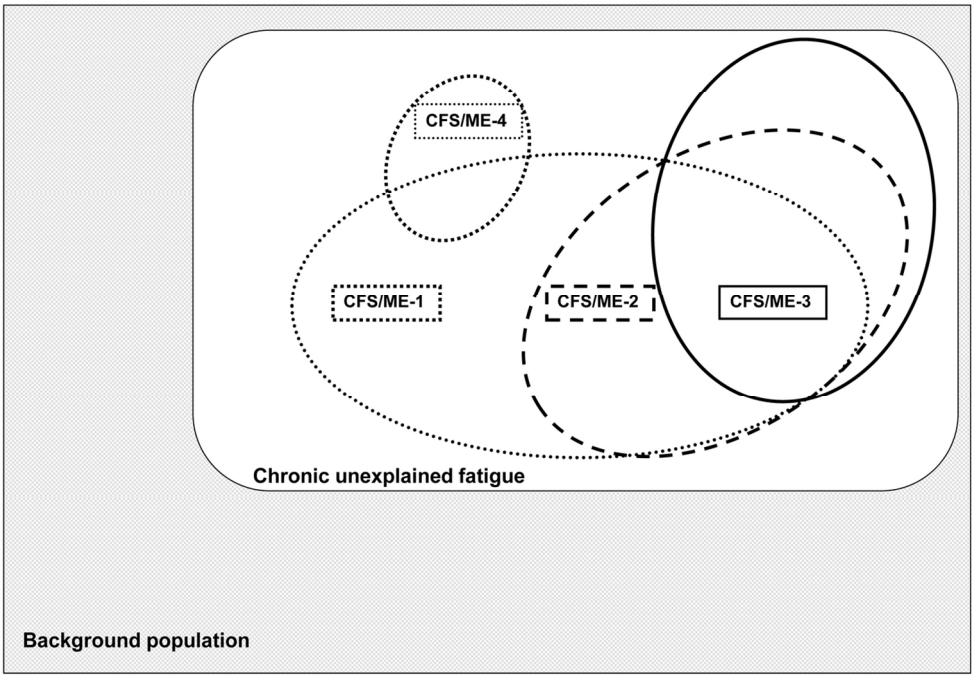
Model C: Evaluation design with indirect comparisons of prevalence estimates from several case definitions applied on different populations

Figure 4

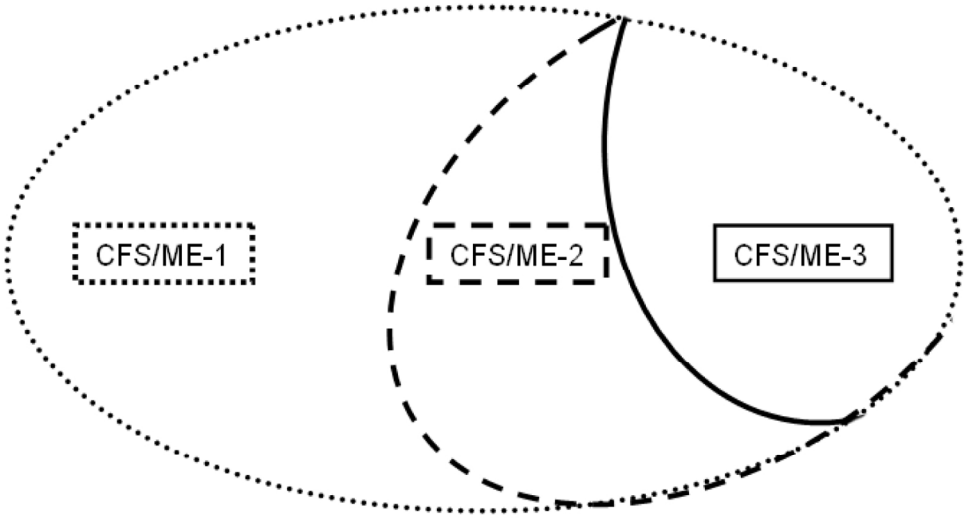
Flow chart summarising the selection process

Figure 5

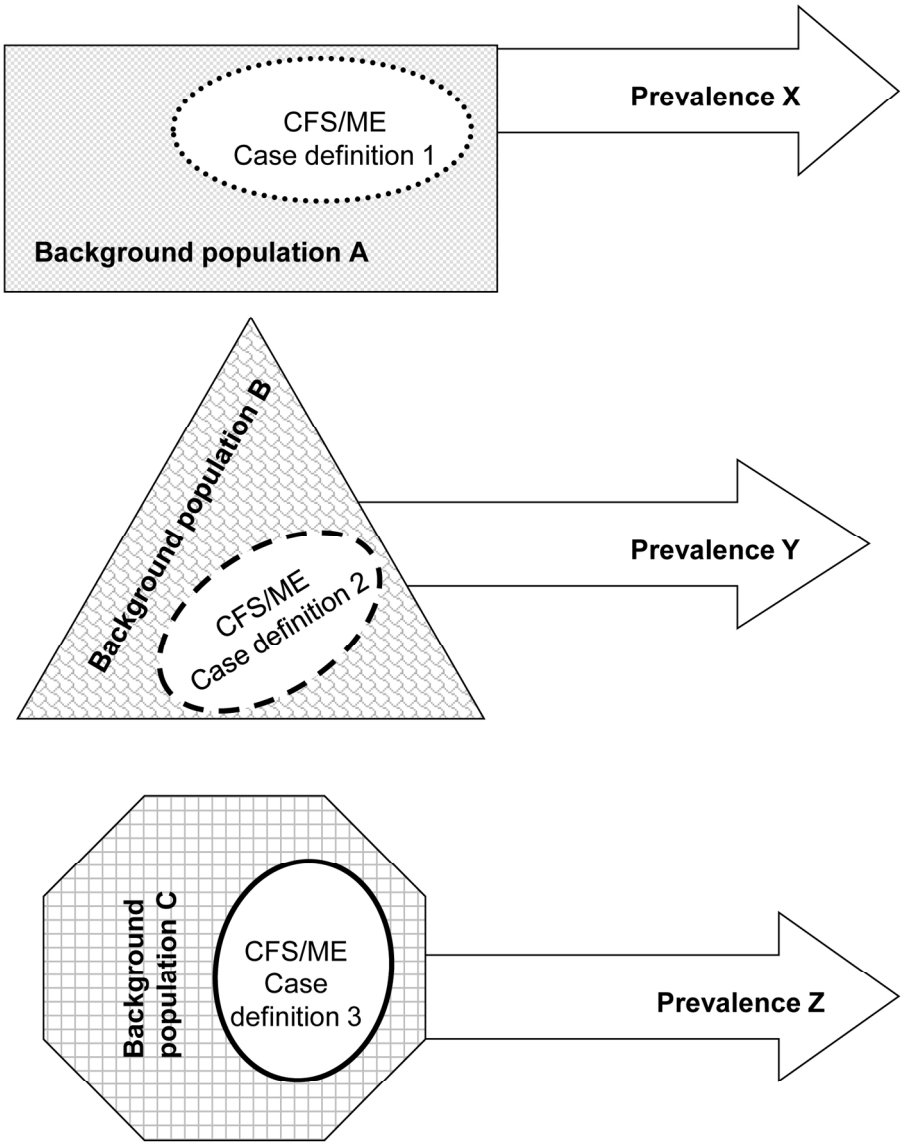
Forest plot summarising indirect comparisons of prevalence estimates from different case definitions with the CDC 1994/Fukuda criteria (Model C). Studies presenting point prevalence weighted for non-response are asterisked (*)



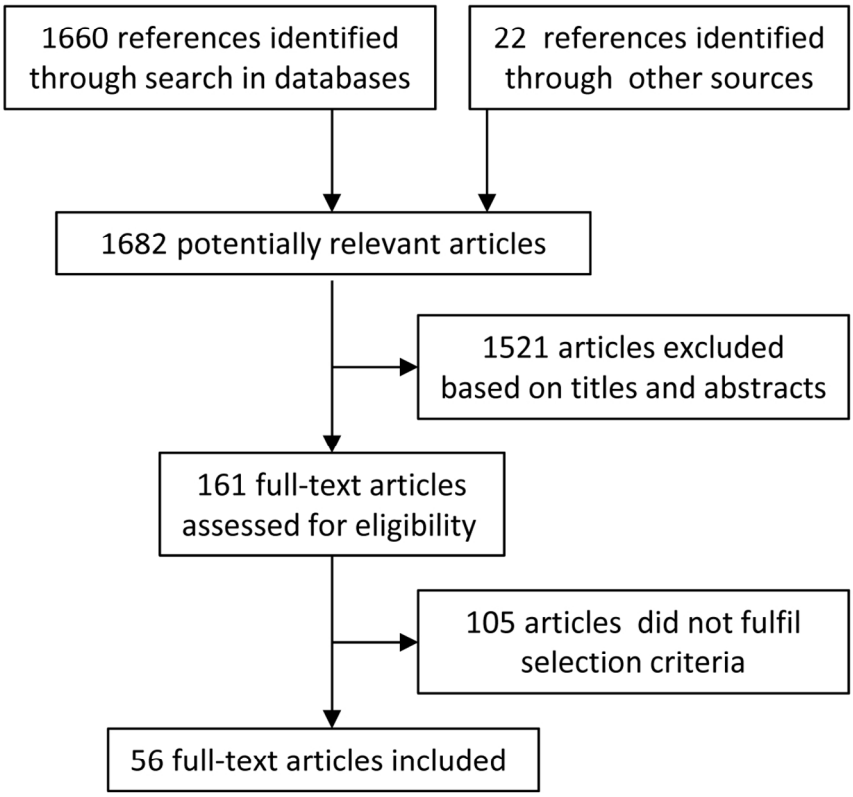
Model A: Evaluation design with independent application of several case definitions on the same background population
123x87mm (300 x 300 DPI)



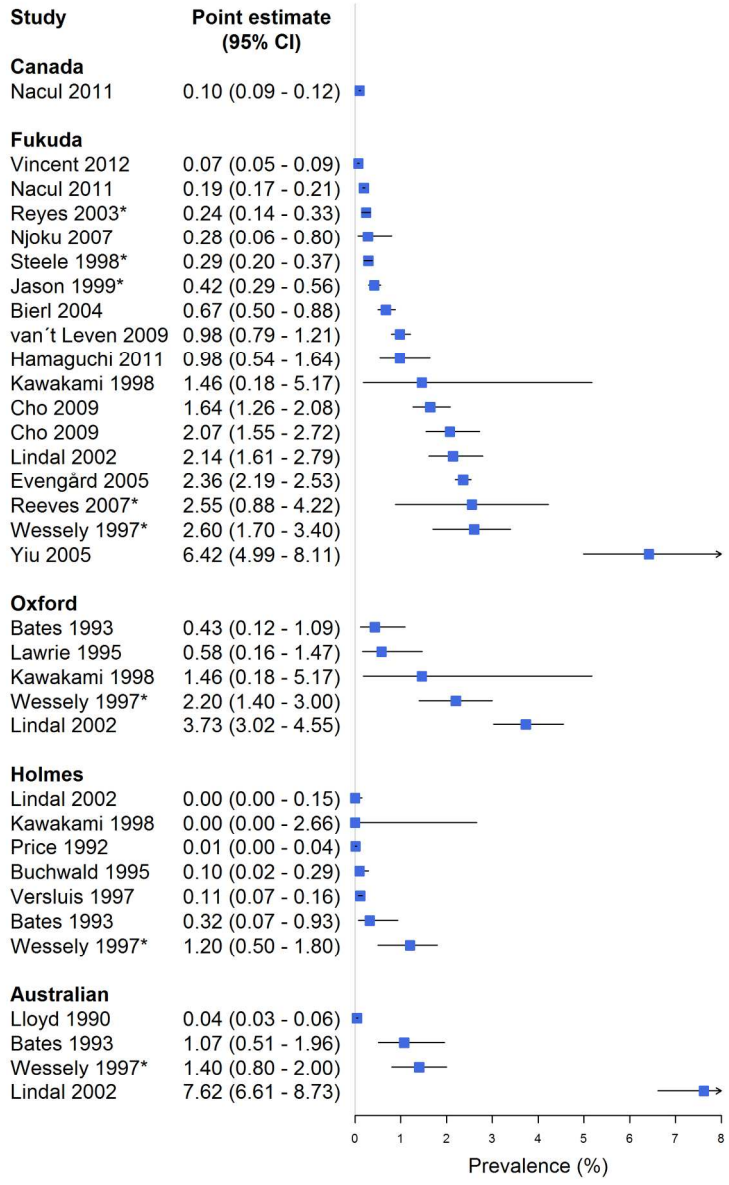
Model B: Evaluation design where different case definitions with assumed increasing specificity are applied sequentially on the same population
139x77mm (300 x 300 DPI)



Model C: Evaluation design with indirect comparisons of prevalence estimates from several case definitions applied on different populations
145x185mm (300 x 300 DPI)



Flow chart summarising the selection process
116x108mm (300 x 300 DPI)



Forest plot summarising indirect comparisons of prevalence estimates from different case definitions (Model C). Studies presenting point prevalence weighted for non-response are asterisked (*)
233x320mm (300 x 300 DPI)

Appendix 1

Search strategy CFS/ME Case Definitions

Total search hits: 2259 after the last update
Search hits after duplet removal: 1660 after the last update

AMED, EMBASE, MEDLINE, PsycINFO
Searched 25. November 2013
Total search hits: 1736
All the sources were search in Ovid simultaneously
Ovid AMED from 1985; 171 hits
Ovid EMBASE from 1980; 926 hits
Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE from 1946; 381 hits
Ovid PsycINFO from 1887; 258 hits

1. Fatigue Syndrome, Chronic/
2. (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or (chronic adj4 mononucleos*) or post infectious encephalo* or PVFS).tw.
3. 1 or 2
4. "diagnostic techniques and procedures"/
5. guideline/ or practice guideline/
6. (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics).tw.
7. 4 or 5 or 6
8. 3 and 7
9. 8 use prmz
10. chronic fatigue syndrome/
11. (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or (chronic adj4 mononucleos*) or post infectious encephalo* or PVFS).tw.
12. 10 or 11
13. diagnostic procedure/ or diagnostic test/ or physical examination/
14. (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics).tw.
15. 13 or 14
16. 12 and 15
17. 16 use emez

18. fatigue syndrome chronic/
19. (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or (chronic adj4 mononucleos*) or post infectious encephalo* or PVFS).tw.
20. 18 or 19
21. "diagnostic techniques and procedures"/ or patient assessment/ or physical examination/
22. (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics).tw.
23. 21 or 22
24. 20 and 23
25. 24 use amed
26. exp Chronic Fatigue Syndrome/
27. (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or (chronic adj4 mononucleos*) or post infectious encephalo* or PVFS).tw.
28. 26 or 27
29. medical diagnosis/ or diagnosis/ or physical examination/
30. (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics).tw.
31. 29 or 30
32. 28 and 31
33. 32 use psyf
34. 9 or 17 or 25 or 33
35. remove duplicates from 34

Cochrane Library

Searched 25. November 2013 back to 1898

Total search hits: 473

#1 (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or post infectious encephalo* or PVFS) .tw.
#2 (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics) .tw.
#3 MeSH descriptor: [Fatigue Syndrome, Chronic] explode all trees
#4 #1 or #3
#5 #2 and #4

CINAHL

Searched 25. November 2013 back to 1981

Total search hits: 27

S6 S3 and S4 Limiters - Exclude MEDLINE records

S5 S3 and S4

S4 S1 or S2

S3 TI (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics) OR AB (diagnostic procedure* or diagnostic technique* or diagnostic criteria or diagnostic definition or clinical definition or consensus definition or consensus criteria or case definition or clinical Guideline or clinical recommendation or clinical assessment or diagnostics)

S2 TI (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or post infectious encephalo* or PVFS) OR AB (chronic fatigue* or fatigue syndrome* or infectious mononucleos* or postviral fatigue syndrome* or myalgic encephalo* or CFIDS or CFS* or post infectious encephalo* or PVFS)

S1 (MH "Fatigue Syndrome, Chronic")

PEDro

Search 25. November 2013 back to 1929

Total search hits: 23

Search phrases and words: chronic fatigue syndrome and diagnos*

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1,2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2, 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5, 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8,9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2-4, Fig 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9,10,11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11,12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16,17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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