[Word count: (excluding appendices and references for petition): 1259 words]

Tom Kindlon's Written Testimony: CFSAC Meeting May 2009

My name is Tom Kindlon. I have CFS for over 20 years, having previously been healthy (and very "sporty"). Unfortunately it took me over 5 years to get diagnosed. By the time I was diagnosed I was virtually bedbound and I have only improved a small bit since then i.e. I have been housebound with CFS for nearly 15 years.

Before my CFS deteriorated, I was studying Mathematical Sciences in Trinity College Dublin (I got straight Firsts in the last year I did there – second year exams) so have some knowledge of mathematical and statistical methodologies.

I have been on the committee of the Irish ME/CFS Association (formerly the Irish ME/CFS Support Group) since 1996 and have been Assistant Chairperson since 1997. Amongst other things, I have helped organise the Association's response to thousands of enquiries in that period and have talked with hundreds of people with the condition. I have also been on Internet CFS forums since 1995 and thus heard people from around their world describe their illness and the effect it has had on them, as well as participating in many interesting discussions. I believe I have a lot of useful knowledge and experience in the area. In the last twelve months, I have had two letters on the subject of CFS published in Pubmed-listed journals.

I am very concerned about the "empirical" definition (Reeves, 2005) the CDC has adopted for CFS research in recent years.

I have posted numerous online comments to papers relating to the definition but the CDC has never responded to any of the points.

Frustrated by the CDC's continued use of the definition, I set up a petition on the issue on the 15th of April, 2009 (i.e. last month). This petition is summarized in 10 words as,
"CDC CFS Research should not involved the empirical definition (2005)"

http://www.ipetitions.com/petition/empirical_defn_and_CFS_research/index.html

The petition

We call on the Centers for Disease Control and Prevention (CDC) to stop using the "empirical" definition[1] (also known as the Reeves 2005 definition) to define Chronic Fatigue Syndrome (CFS) patients in CFS research.

The CDC claim it is simply a way of operationalizing the Fukuda (1994) definition[2]. However the prevalence rates suggest otherwise: the "empirical" definition gives a prevalence rate of 2.54% of the adult population[3] compared to 0.235% (95% confidence interval, 0.142%-0.327%) and 0.422% (95% confidence interval, 0.29%-0.56%) when the Fukuda definition was used in previous population studies in the US[4,5].

The definition lacks specificity. For example, one research study[6] found that 38% of those with a diagnosis of a Major Depressive Disorder were misclassified as having CFS using the empirical/Reeves definition.

References

[1] Reeves WC, Wagner D, Nisenbaum R, Jones JF, Gurbaxani B, Solomon L, Papanicolaou DA, Unger ER, Vernon SD, Heim C. Chronic fatigue syndrome--a clinically empirical approach to its definition and study. BMC Med. 2005 Dec 15;3:19. Link: http://www.biomedcentral.com/1741-7015/3/19

[2] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome; a comprehensive approach to its definition and study. Ann Int Med 1994, 121:953-959.

[3] Reeves WC, Jones JF, Maloney E, Heim C, Hoaglin DC, Boneva RS, Morrissey M, Devlin R. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul Health Metr. 2007 Jun 8;5:5.

[4] Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC: Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Int Med 2003, 163:1530-1536.

[5] Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor RR, McCready W, Huang CF, Plioplys S. A community-based study of chronic fatigue syndrome. Arch Intern Med. 1999 Oct 11;159(18):2129-37.

[6] Jason, LA, Najar N, Porter N, Reh C. Evaluating the Centers for Disease Control's empirical chronic fatigue syndrome case definition. Journal of Disability Policy Studies 2008, doi:10.1177/1044207308325995.

Further reading:
Problems with the New CDC CFS Prevalence Estimates
Leonard Jason, Ph.D., DePaul University
tinyurl.com/2qdgu4 i.e.
http://www.iacfsme.org/IssueswithCDCEmpiricalCaseDefinitionandPrev/tabid/105/Default.aspx

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I'm the first to admit that this isn't exactly the "catchiest" petition that has ever been created. One might think it would be lucky to get a few dozen responses.

However already, in just over a month, 651 people have signed (at the time of writing). Many have left comments which can be read on the site:
http://www.ipetitions.com/petition/empirical_defn_and_CFS_research/index.html
[Aside: other people have also left comments but for some reasons the comments have not gone up].

I believe this shows the depth of feeling there is on this issue.

If one looks at the CFSAC function, it is clear that the issues relating to the definition are fairly central:

Function
The Committee shall advise and make recommendations to the Secretary, through the Assistant Secretary for Health, on a broad range of topics including: (1) the current state of knowledge and research about the epidemiology and risk factors relating to chronic fatigue syndrome, and identifying potential opportunities in these areas; (2) current and proposed diagnosis and treatment methods for chronic fatigue syndrome; and (3) development and implementation of programs to inform the public, health care professionals, and the biomedical, academic and research communities about chronic fatigue syndrome advances.

For example, as I pointed out, prevalence estimates from CDC research jumped from 235 per 100,000 to 2540 per 100,000! That is to say that nearly 11 times as many people are diagnosed with the new "definition" as the old definition. This is clearly relevant for point 1. Who are these people? Do they all really have the same illness? I find it strange that, for example, somebody can score 100 out of 100 on the physical functioning subscale of the SF-36 (as well scoring the maximum on other subscales) but if they score low on the Role Emotional Subscale, they can be classed as being functionally impaired and hence satisfy that important part of the CFS definition. I believe this allows too many people who may not have CFS to satisfy the criteria. This concern has been demonstrated to be valid by the study by Leonard Jason and colleagues (2008) which found that 38% of those with Major Depressive Disorder were misclassified as having CFS using the new definition.

One of the external reviewers for the CDC program highlighted this problem when he was a reviewer for the Georgia prevalence study paper published in 2007. Leonard Jason alluded to this in a piece he wrote that year:
In Peter White's Dec. 3. 2006 review (http://www.biomedcentral.com/imedia/1083914155124266_comment.pdf) of Reeves et al.'s (2007) article, he states: The use of physical function, role physical and social function sub-scales is consistent with the International Study criteria for CFS, which states that the illness "results in substantial reduction in previous levels of occupational, educational, social, or personal activities." (Reeves et al, 2003). The use of role emotional is not, since it specifically asks about change in function "as a result of any emotional problems". And later White states that "In order to make these important criteria consistent with other studies, I think the authors need to re-analyse their data, omitting this sub-scale."
Prof. White made other criticisms of the definition in his reviews – I'm including as an appendix one of his reviews on the issue.

If one has a heterogeneous group of patients, it can mean that in intervention trials, if "true" CFS patients only make up a tiny fraction of the cohort, useful interventions could come up as showing no effect (or even being detrimental); alternatively, interventions may come up as being useful for CFS when in fact if one had only looked at those with "true" CFS, the intervention may have made no difference or may even have been detrimental. So you can see it is a serious issue.

Similarly with regard to risk factors for the illness, incorrect information could be gathered. For example, the CDC have now done not one but two studies looking at the relationship

between CFS and Childhood trauma. However the results may have looked very different had a different definition been used. The same applies to biological testing and also the search for biomarkers – having a very broad and inexact definition means progress in that area may never occur.

I am unsure of the specifics of how the CFSAC acts but I hope it will be able to do something on this issue. My views are inline with what I have read by Dr Leonard Jason on the issue so I would ask people to listen carefully to whatever points he has to make on the issue.

I am appending comments I have posted on articles, which show my general concerns. These are generally referenced comments, which had to be reviewed before they were posted (beside the CDC papers). The method the CDC is using to define Chronic Fatigue Syndrome can be a bit difficult to understand so the comments may also help people understand what the definition actually is.

Thank you for your time.

Tom Kindlon

Appendix 1: Comments I have been made on the "empirical definition" (Reeves, 2005) that have been "published" online beside CDC papers.

[Aside: I have not actually included all of the comments here]

http://www.biomedcentral.com/1741-7015/3/19/comments

Comments

Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study

William C Reeves, **Dieter Wagner**, **Rosane Nisenbaum**, **James F Jones**, **Brian Gurbaxani**, **Laura Solomon**, **Dimitris A Papanicolaou**, **Elizabeth R Unger**, **Suzanne D Vernon** and **Christine Heim**

BMC Medicine 2005, **3**:19doi:10.1186/1741-7015-3-19

- MDDm should be resolved for more than 5 years before a CFS diagnosis can be given
- Data from another population study found scores on the RE subscale are similar in CFS patients to those found in healthy controls
- This may not be a representative group of those who would be diagnosed in a random sample using the "standardized clinically empirical criteria"
- Why is this definition being referred to as an "empirical definition"?
- Using two MFI scales ("General Fatigue" or "Reduced Activity") to ensure patients satisfying the definition have "severe fatigue"
- Analyses of 2 separate CFS cohorts found 6 of the 8 SF-36 subscales group together - two that don't are MH and RE (the latter is being used in this definition)
- Another CFS study raises questions about the use of the RE subscale in a definition of CFS
- Research Study finds 38% of those with a Major Depressive Disorder satisfied these criteria for CFS (i.e. they lack specificity)

MDDm should be resolved for more than 5 years before a CFS diagnosis can be given

Tom Kindlon (26 June 2007) Irish ME/CFS Support Group

In this paper, it says:

"Following recommendations of the International CFS Study Group, only current MDDm was considered exclusionary for CFS."

However, part of the specific recommendations of the International CFS Study Group [1] was that MDDm had to have been resolved for more than 5 years:

"The 1994 case definition stated that any past or current diagnosis of major depressive disorder with psychotic or melancholic features, anorexia nervosa, or bulimia permanently excluded a subject from the

classification of CFS ... we now recommend that if these conditions have been resolved for more than 5 years before the onset of the current chronically fatiguing illness, they should not be considered exclusionary."

It might not be important to point this out for definitions for some illnesses: however if one looks at table 2, 6 of the 16 who are said to have CFS using the "current classification" of CFS, had been diagnosed with MDDm at a previous assessment which suggests it is important in this context.

Tom Kindlon

[1] Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, Evengard B, White PD, Nisenbaum R, Unger ER, International Chronic Fatigue Syndrome Study Group: Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution.

BMC Health Services Research 2003, 3:25.

http://dx.doi.org/10.1186/1472-6963-3-25

Competing interests

No Competing Interests

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Data from another population study found scores on the RE subscale are similar in CFS patients to those found in healthy controls

Tom Kindlon (09 July 2007) Irish ME/CFS Support Group

In a previous comment I said that I questioned the value of using the Role Emotional (RE) subscale to satisfy functional impairment criteria.

Researchers deciding whether to follow the method of operationalizing the Fukuda [1] used in this study, might be interested at looking at Table 2 in Jason et al [2]. The subjects were also obtained from a random-digit population study.

Here is what the authors said in the text on this part of the results:

"A MANCOVA for the Medical Outcomes Study SF-36 Health Survey (controlling for the effects of work status) revealed significant differences in gradations of disability across the diagnostic categories of CFS only, MCS only, FM only, more than one diagnosis, and no diagnosis on seven of the eight subscales ($F(4,208) = 1.82$, $p < .05$). The role-emotional scale was the only scale that did not reveal significant differences between the groups (see Table 2). Significant post hoc tests revealed that individuals with CFS demonstrated greater disability than those with no diagnosis on the role-physical; bodily pain; vitality; and social functioning scales. Individuals with MCS demonstrated greater disability than the no diagnosis group on the physical functioning; role-physical; bodily pain; general health; vitality; social functioning; and mental health scales. Individuals with FM demonstrated greater disability than the no diagnosis group on the physical functioning; role-physical; bodily pain; and social functioning scales. In addition, individuals with more than one diagnosis demonstrated greater disability than those in the no diagnosis group on the physical functioning; role-physical; bodily pain; vitality; and social functioning scales. Means for each of the Medical Outcomes Study subscales are reported in Table 2."

This issue of how the Fukuda criteria [1] are operationalized is not a trivial matter. Using the previous method of operationalizing the criteria, a CDC team found a prevalence for CFS of 235 per 100,000 [3]. Using the method of operationalizing the criteria outlined in this study, the prevalence rate for CFS was found to be 2.54% or 2540 per 100,000 [4] or 10.81 times the previous prevalence rate!

Tom Kindlon

[1] Fukuda, K., Straus, S.E., Hickie, I., Sharpe, M.C., Dobbins, J.G., & Komaroff, A. (1994). The chronic fatigue syndrome: A comprehensive approach to its definition and study. Annals of Internal Medicine, 121 (12):953-959. http://www.annals.org/cgi/content/full/121/12/953

[2] Jason, L.E., Taylor, R.R., & Kennedy, C.L. "Chronic Fatigue Syndrome, Fibromyalgia, and Multiple Chemical Sensitivities in a Community-Based Sample of Persons With Chronic Fatigue Syndrome-Like Symptoms." Psychosomatic Medicine 62:655-663 (2000).

http://www.psychosomaticmedicine.org/cgi/reprint/62/5/655

[3] Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Intern Med. 2003;163:1530–1536. doi: 10.1001/archinte.163.13.1530.

[4] Reeves WC, Jones JF, Maloney E, Heim C, Hoaglin DC, Boneva RS, Morrissey M, Devlin R. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Population Health Metrics 2007, 5:5 doi:10.1186/1478-7954-5-5

Competing interests

No Competing Interests

top

This may not be a representative group of those who would be diagnosed in a random sample using the "standardized clinically empirical criteria"

Tom Kindlon (02 January 2008) Irish ME/CFS Association - for Information, Support & Research

This "empirical" method of operationalizing the CDC 1994 CFS criteria[1] has subsequently been used in a population study[2]. It found a prevalence rate for CFS of 2540 per 100,000 persons 18 to 59 years of age[2].

This is considerably higher than the prevalence rates found in earlier studies. For example, a previous study using this cohort using a "previous" method of operationalizing the CDC 1994 CFS criteria[1] found a prevalence rate of 235 per 100,000[3].

Given the way the cohort in this current study was drawn up, using 58 people who had previously been diagnosed using a "previous" method of operationalizing the CDC 1994 CFS criteria, the group satisfying the new method of operationalizing the CDC 1994 CFS criteria, the "empirical" criteria, in this study may well not be the same sort of people that would show up if the method was used on a random sample of the population. So for example the results in Table 6 may not be similar to the results one can get in a random sample.

Unfortunately the paper giving the prevalence rate for Georgia[2] does not give the same pieces of information as is in Table 6 in this study. However we do have a paper which uses a group from the Georgia cohort[4]. Table 1 of this study[4] includes similar data. Some of the numbers are somewhat similar. However one that particularly stands out is the Role Emotional score. It was 35.6 (95% CI: 26.3-44.8). That compares to the value in this paper of 55.8+/-42.2.

Perhaps other data will be published in time. The main point of this comment is to point out or remind people that the data presented in this paper may not be representative of those that would be diagnosed using the empirical criteria.

Tom Kindlon

[1] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, & Komaroff A. (1994). The chronic fatigue syndrome: A comprehensive approach to its definition and study. Annals of Internal Medicine, 121 (12):953-959. http://www.annals.org/cgi/content/full/121/12/953

[2] Reeves WC, Jones JF, Maloney E, Heim C, Hoaglin DC, Boneva RS, Morrissey M, Devlin R. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Population Health Metrics 2007, 5:5 doi:10.1186/1478-7954-5-5

http://www.pophealthmetrics.com/content/5/1/5

[3] Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC: Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Int Med 2003, 163:1530-1536.

[4] Nater UM, Maloney E, Boneva RS, Gurbaxani BM, Lin JM, Jones JF, Reeves WC, Heim C. Attenuated Morning Salivary Cortisol Concentrations in a Population-based Study of Persons with Chronic Fatigue Syndrome and Well Controls. J Clin Endocrinol Metab. 2007 Dec 26

Competing interests

No competing interests

top

Why is this definition being referred to as an "empirical definition"?

Tom Kindlon (18 June 2008) Irish ME/CFS Association - for Information, Support & Research

I believe most people's understanding of "empirical criteria" or an "empirical definition" would be that the data would speak for itself; it "would decide" the cut-off points through methods such as cluster analysis (for example).

Indeed this would seem to have been William Reeves' understanding of an empirical definition. For example, in a presentation on the CDC's CFS research program (to a Task Force Meeting on the Epidemiology of Interstitial Cystitis)[1], he said:

"The problem with the CFS criteria was that they were not specific enough and not empiric-based. For example, one of the criteria stated that the research subject must have at least four of eight symptoms, among them, impaired concentration or memory and postexertional worsening of physical or mental fatigue.

"The accompanying symptoms need to be defined in and of themselves," Dr. Reeves said. The 1994 International Study Group also hypothesized that fatigue led to patients' symptoms rather than the reverse. The CDC is currently conducting population studies to develop an empiric definition of CFS that is based on statistical modeling."

At the inaugural meeting of the US Department of Health and Human Services' Chronic Fatigue Syndrome Advisory Committee (CFSAC), Dr Reeves said the CDC team of research would *"derive an empirical case definition based on data".[2]*

The definition presented here does not seem to have been based either on "statistical modeling" or "data". It seems to involve relatively arbitrary cut-off points; for example, of the 8 subscales of the SF-36, four are chosen and, for each of these, the 25th percentile of the published US population is chosen as a cut-off point. A patient is required to be in the bottom quartile for just one of these subscales to satisfy the criteria. Where did this cut-off point come from? There is no mention of it in the paper that suggested the use of the SF-36[3]; nor is there any mention that these particular subscales should be chosen or that one would sufficient. One of the authors of the paper[3] has confirmed that cut-off points were never chosen nor was it decided which sub-scales would be used. Given that the CDC's definition of CFS tends to go on to be used in numerous studies, would it not be better to investigate which thresholds give a "better" definition e.g. with a higher specificity and sensitivity - for example, for some of the SF-36 subscales, perhaps (say) the 13th, 15th, 20th or even 30th percentiles may be more appropriate.

The cut-off points suggested in this paper may or may not be useful. But is it really accurate to suggest that they are "empirically" derived?

[1] Epidemiology of Interstitial Cystitis - Executive Committee Summary and Task Force Meeting Report October 29th, 2003. http://www.niddk.nih.gov/fund/reports/ic/task_force_summary.pdf

[2] US Department of Health and Human Services - Chronic Fatigue Syndrome Advisory Committee (CFSAC). Inaugural Meeting. September 29th, 2003

Meeting Summary. http://www.hhs.gov/advcomcfs/CSFAC_mins_2003.09.29R.pdf

[3] Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, Evengard B, White PD, Nisenbaum R, Unger ER, International Chronic Fatigue Syndrome Study Group: Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Services Research 2003, 3:25

Competing interests

No competing interests

top

Using two MFI scales ("General Fatigue" or "Reduced Activity") to ensure patients satisfying the definition have "severe fatigue"

Tom Kindlon (30 June 2008) Irish ME/CFS Association - for Information, Support & Research

Initially when I read this paper, where it says "we defined severe fatigue as >= medians of the MFI general fatigue (>=13) or reduced activity (>=10) scales", I thought this referred to medians of the general population.

Hearing other people commenting on it, that's how some other people have been interpreting it also. It is probably somewhat natural to do this as the sentence before reads: "We defined substantial reduction in occupational, educational, social, or recreational activities as scores lower than the 25th percentile of published US population [11] on the physical function (<=70), or role physical (<=50), or social function (<=75), or role emotional (<=66.7) subscales of the SF-36."

However from looking at the scores for controls in other papers, these MFI scores do not look like medians for the whole US population but in fact are medians for this particular group of patients. This seems a strange way to set cut-off points for a CFS definition that is used for numerous studies into the illness, given the cohort that is being used as a basis:

"This population-based case control study enrolled 227 adults identified from the population of Wichita with: (1) CFS (n = 58); (2) non-fatigued controls matched to CFS on sex, race, age and body mass index (n = 55); (3) persons with medically unexplained fatigue not CFS, which we term ISF (n = 59); (4) CFS accompanied by melancholic depression (n = 27); and (5) ISF plus melancholic depression (n= 28)." i.e. this is not a random sample of the US population but a group of people selected for a specific purpose (or purposes) (not necessarily to design a definition, but as a follow-up study of people previously diagnosed with CFS or given some other label). Some of the groups are of different sizes - if the relative size of these groups had been changed, with relatively more people taken from some classification groups and less people taken from other groups, the median scores would likely have been different.

It should also be remembered that in this context the categories listed in the last paragraph refer to their classification when they evaluated years before (from 1997 to 2000), and not necessarily at the time when they were evaluated in this study (December 2002 to July 2003) (as is clear from the tables in this paper).

I thought it would be interesting to look at MFI scores in some other papers on CFS that did not use the "empirical definition".

I don't claim this is a definitive list but, at the same time, mean MFI scores with standard deviations only seem to be listed in a small percentage of papers.

The papers use cohorts from a variety of locations: England [3], The Netherlands [4], Germany [5] and the USA (New Jersey) [6].

I did not see any ranges given which would be useful given the task at hand (selecting cut-off points for a definition).

Unfortunately not all of the papers I found used the Fukuda [1] definition for CFS; some also used the Sharpe [2] definition for CFS. I indicate which definition is used in each case.

MFI: General Fatigue

Sample Sample Size Mean SD (Mean - 13)/SD Definition

Weatherley-Jones [3] 53 18.4 1.7 3.176470588 Sharpe (1991)

Vermeulen (Group 1) [4] 30 18.6 1.9 2.947368421 Fukuda (1994)

Vermeulen (Group 2) [4] 30 18.4 1.8 3 Fukuda (1994)

Vermeulen (Group 3) [4] 30 19.1 1.4 4.357142857 Fukuda (1994)

Gaab [5] 21 17.7 0.5 9.4 Sharpe (1991) and Fukuda (1994)

Brimacombe [6] 65 18.41 2.02 2.678217822 Fukuda (1994)

Combining these give a sample of 229 patients with a mean "General Fatigue" score of 18.45655022.

This data suggests that a threshold of >=13 will have a very very high sensitivity. This would suggest that another measure would not be necessary (unless it was being used as an extra criterion to increase the specificity, which isn't done with this definition).

However for completeness, I'm including the "Reduced Activity" data from the same papers:

Reduced activity (MFI)

Sample Sample Size Mean Score SE (Mean-10)/SD Definition

Weatherley-Jones [3] 53 16.1 3.1 1.967741935 Sharpe(1991)

Gaab [5] 21 15 0.7 8.714285714 Sharpe (1991) and Fukuda(1994)

Brimacombe [6] 65 15.93 4.55 1.340659341 Fukuda 1994

Combining these give a sample of 139 patients with a mean Reduced Activity score of 15.85431655.

Note: the Vermeulen paper[4] did not collect the MFI scores for Reduced Activity, just "the fatigue axes of the Multidimensional Fatigue Inventory" (which they defined as the MFI scores for General fatigue, Physical fatigue, Mental fatigue). It seems strange in the definition of Chronic Fatigue Syndrome defined in this paper (i.e. Reeves et al) that the "severe fatigue" criterion can be satisfied by a patient having a low score on a subscale of the MFI testing activity levels (as opposed to one of the 3 subscales measuring fatigue), especially when the function of the SF-36 is to "measure functional impairment". Just because someone is inactive doesn't mean they have severe fatigue. Allowing patients to be included if they simply have a "Reduced Activity" score of 10 or more (without necessarily having a low score on one of the fatigue axes of the MFI) risks reducing the specificity of the definition.

[1] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome; a comprehensive approach to its definition and study. Ann Int Med 1994, 121:953-959.

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[3] Weatherley-Jones, E., Nicholl, JP., Thomas, KJ., Parry, GJ., McKendrick, MW., Green, ST., Stanley, PJ and Lynch, SPJ. A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. Journal of Psychosomatic Research, 2004, 56, 2, 189-197.

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Psychosom Med. 2002 Nov-Dec;64(6):951-62.

[6] Brimacombe, Michael; Lange, Gudrun; Bisuchio, Kim; Ciccone, Donald S.; Natelson, Benjamin. Cognitive Function Index for Patients with Chronic Fatigue Syndrome Journal of Chronic Fatigue Syndrome, 2004, vol 12; number 4, pages 3-24

Competing interests

No competing interests

top

Analyses of 2 separate CFS cohorts found 6 of the 8 SF-36 subscales group together - two that don't are MH and RE (the latter is being used in this definition)

Tom Kindlon (30 September 2008) Irish ME/CFS Association - for Information, Support & Research

This paper is supposed to operationalize the recommendations in the consensus paper by Reeves et al[1]. That paper suggested that the SF-36 could be useful as a measure of functional impairment but did not specify which subscales should be used.

The authors of the current paper chose to define *"substantial reduction in occupational, educational, social, or recreational activities"* as *"scores lower than the 25th percentile of published US population [11] on the physical function (less than or equal to 70), or role physical (less than or equal to 50), or social function (less than or equal to 75), or role emotional (less than or equal to 66.7) subscales of the SF-36."*

Priebe et al[2] have just published an analysis of a cohort of CFS patients from the UK. *"Principal-component analysis of all scale scores revealed 2 distinct components, explaining 53% of the total variance."*

"Component 1 comprised 14 variables and had an eigenvalue of 7.9 (32.9% of the variance). It had positive loadings of the SCL-90-R subscales depression, anxiety, obsessive-compulsive symptoms, psychoticism, hostility, phobic anxiety, interpersonal sensitivity, paranoid ideation, the Spielberger Trait Anxiety Questionnaire, Health Anxiety Questionnaire and Beck Hopelessness Scale, and negative loadings of the SF-36 subscales of mental health and emotional role fulfilling." (Remember that lower the scores on the SF-36, the lower the reported functioning in that domain).

The other component involved the other 6 SF-36 subscales, The Fatigue Visual Analogue Scale, SCL-90-R subscale somatization and the Somatic Discomfort Questionnaire (SDQ) (the authors say *"the majority of physical symptoms that were assessed was measured on only 2 scales, the somatization subscale of the SF-36* and the SDQ"*)

(*This is presumably a typo and what they are referring to is the SCL-90-R subscale somatization).

Hardt et al [3] have previously performed factor analyses on a large cohort of patients (740 CFS patients from the US, 82 from the UK, and 65 from Germany). They said: *"Overall, there was a remarkable similarity in HRQoL among all CFS patients, regardless of location. Patients scored two to three standard deviations below normal on six subscales and one standard deviation below normal on the other two subscales. Factor analysis suggested a two-factor model where the same six subscales* (i.e. Bodily pain, General health perception, Limitations due to physical problems, Physical functioning, Social functioning and Vitality)

constitute the first factor and the two others (i.e. limitations due to emotional problems (RE) and Mental health) *the second factor."*

These result bring into question the use of the role emotional subscale alongside the other three subscales (physical function, role physical and social functioning) being used in this so-called "empirical definition".

[1] Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, Evengard B, White PD, Nisenbaum R, Unger ER: International Chronic Fatigue Syndrome Study Group: Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution.

[2] Priebe S, Fakhoury WK, Henningsen P: Functional Incapacity and Physical and Psychological Symptoms: How They Interconnect in Chronic Fatigue Syndrome. Psychopathology. 2008 Sep 3;41(6):339-345.

[3] Hardt J, Buchwald D, Wilks D, Sharpe M, Nix WA, Egle UT: Health-related quality of life in patients with chronic fatigue syndrome: an international study. J Psychosom Res 2001; 51: 431-434.

Competing interests

No competing interests

Another CFS study raises questions about the use of the RE subscale in a definition of CFS

Tom Kindlon (23 January 2009) Irish ME/CFS Association - for Information, Support & Research

Firstly, apologies for sounding like a broken record but the definition the CDC proposes for CFS is an important issue - it tends to be the one adopted by researchers around the world. The definition laid out in this paper continues to be used in papers involving cohorts the CDC has gathered for CFS population studies such as the papers using this cohort (which has been analysed in numerous papers) as well as a later study in Georgia[1].

Fulcher (2000)[2] is another study which raises questions about the use of the Role Emotional (RE) subscale of the SF-36 to select patients with CFS. The study involved 66 patients with CFS without a current psychiatric disorder, 30 healthy but sedentary controls, and 15 patients with a current major depressive disorder. It found, amongst other things, that *"the two patient groups were significantly more incapacitated than the sedentary controls on all SF-36 measures (p<0.001),* ***except that the patients with CFS were not significantly different in emotional or mental function****."* Also, ***"the depressed subjects were significantly more incapacitated in emotional and mental functioning than the patients with CFS p<0.001)."*** These results suggest that low scores on the emotional and mental functioning subscales of the SF-36 do not seem to be an intrinsic part of CFS (if they're found, they could be related to comorbid psychiatric issues). They also points out the risks of using the RE subscale alone [especially given CFS shares some characteristics with depression and so some people with depression (but not CFS) could potentially score the required 25 points on the Symptom Inventory] i.e. one could inadvertently include some people who have depression but not CFS, as CFS patients.

[1] Reeves WC, Jones JF, Maloney E, Heim C, Hoaglin DC, Boneva RS, Morrissey M, Devlin R. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul Health Metr. 2007 Jun 8;5:5.

[2] Fulcher KY, White PD. Strength and physiological response to exercise in patients with chronic fatigue syndrome. J Neurol Neurosurg Psychiatry. 2000 Sep;69(3):302-7.

Competing interests

No competing interests

top

Research Study finds 38% of those with a Major Depressive Disorder satisfied these criteria for CFS (i.e. they lack specificity)

Tom Kindlon (17 March 2009) rish ME/CFS Support Group

An interesting study [1] has recently been published on this issue: It investigated 37 participants with a diagnosis of a Major Depressive Disorder and 27 participants with a diagnosis of CFS. It found that 38% of those with a diagnosis of a Major Depressive Disorder were misclassified as having CFS using this new CFS definition [2]. That is to say these criteria lack specificity.

The authors gave some background to the study pointing out that that there are several CFS symptoms that are not commonly found in depression and that there has been previous research which has distinguished between CFS and depressed patients.

The authors screened participants from the MDD group to ensure that they did not have CFS as defined by the Fukuda et al. (1994) criteria [3].

For the data, the authors subdivided the MDD group into two groups: those that satisfied the new definition [2], called "MDD/CFS" and those that did not, called "MDD".

There were large differences between the "pure" CFS patients and the other two groups across some of the measures that make up the Reeves (2005) definition [2]. There were also not surprisingly differences in the percentage scores satisfying the criteria from the Reeves (2005) definition.

For example, on the **Role Physical subscale of the SF-36**, the means scores (SDs) across the CFS, MDD/CFS and MDD groups were: 5.56 (16.01); 51.79 (40.98); 58.7 (45.61). (The data showed that there were the following statistically significant differences at the $p \leq 001$ level: CFS<MDD/CFS and CFS<MDD). The percentages satisfying the criteria (RP less than or equal to 50) were, respectively, 96%, 50% and 44% (The data showed that there were the following statistically significant differences for the percentages at the $p \leq .001$ level: CFS>MDD/CFS and CFS>MDD).

For the **SF-36 Physical Functioning subscale** the respective scores across the CFS, MDD/CFS and MDD groups were 37.41 (23.43); 70.36 (32.90); 76.74 (21.25). (The data showed that there were the following statistically significant differences at the $p \leq .001$ level.: CFS<MDD/CFS and CFS<MDD). The percentages satisfying the criteria (PF less than or equal to 70) were, respectively, 93%, 43% and 35% (The data showed that there were the following statistically significant differences for the percentages at the $p \leq .001$ level: CFS>MDD/CFS and CFS>MDD).

For the **CDC Symptom Inventory CDC scores** (i.e. for the 8 case-defining symptoms) the respective scores across the CFS, MDD/CFS and MDD groups were 43.97 (14.28); 37.56 (10.54); 17.05 (8.62). (The data showed that there were the following statistically significant differences at the $p \leq .001$ level: CFS>MDD and MDD/CFS>MDD). The percentages satisfying the criteria (CDC Symptom Inventory greater than or equal to 25) were, respectively, 100%, 100% and 9% - this part of the definition should naturally the first two groups would be 100% (The data showed that there were the following statistically significant differences for

the percentages at the $p \leq .001$ level: CFS>MDD and MDD/CFS>MDD).

However the differences were the opposite (or "backwards") for the **Role Emotional subscale of the SF-36** i.e. rather than the CFS group having the worst score, they actually had the best score - the scores across the CFS, MDD/CFS and MDD groups were: 69.14 (40.22); 19.05 (31.25); 30.43 (40.09) (The data showed that there were the following statistically significant differences at the $p \leq .001$ level: CFS>MDD/CFS and CFS>MDD). The percentages satisfying the criteria (RE less than or equal to 67) were, respectively, 44%, 93% and 78% (The data showed that there were the following statistically significant differences for the percentages at the $p \leq .001$ level: CFS<MDD/CFS and CFS<MDD).

For some subscales, there were no differences across the groups, which also brings about questions about their use in a CFS definition
e.g.

(i) for the **Social Functioning subscale of the SF-36**, the mean scores (SDs) across the CFS, MDD/CFS and MDD groups were: 30.09 (28.43); 41.96 (23.31); 40.22 (25.27). The percentages satisfying the criteria (SF less than or equal to 75) were, respectively, 96%, 100% and 91% (The data showed that there were also no statistically significant differences for the percentages).

(ii) for the **Reduced Activity scale of the Multidimensional Fatigue Inventory** the scores were: 14.44 (3.79); 13.64 (3.95); 13.17 (4.77). The percentages satisfying the criteria (Reduced Activity score greater than or equal to 10) were, respectively, 85%, 86% and 78% (The data showed that there were also no statistically significant differences for the percentages).

The authors also calculated the **total from each group that would satisfy each of the three criteria in the Reeves Definition[2]**. This showed how poor the SF-36 and MFI criteria are for differentiating between CFS and MDD.

Using the **SF-36 criteria**, every one of the 37 patients with a Major Depressive Disorder satisfied the criteria used in the Reeves (2005) definition.

With the **Multidimensional Fatigue Inventory criteria**, 34 of the 37 patients (92%) with a Major Depressive Disorder satisfied the Reeves criteria.

The only measure that had any power to distinguish between the two groups was the CDC Symptom Inventory where 16 of the 37 patients (43%) with a Major Depressive Disorder satisfied the criteria. Of course, this is still not a particularly good percentage.

The authors make many of the points that have been made already in these comments. They point out that to score 25 on the CDC Symptom Inventory, somebody doesn't have to be that severely affected by more classic CFS symptoms. They could endorse symptoms such as unrefreshing sleep, impaired memory, headaches and muscle pain and score 25 without too much difficulty (one can score 16 from any one symptom).

This study clearly demonstrates that there is plenty of potential for a CFS definition to be "better" than the Reeves (2005) definition[2].

[1] Jason, L.A., Najar, N., Porter, N., Reh, C. Evaluating the Centers for Disease Control's empirical chronic fatigue syndrome case definition. Journal of Disability Policy Studies 2008, doi:10.1177/1044207308325995.

[2] Reeves WC, Wagner D, Nisenbaum R, Jones JF, Gurbaxani B, Solomon L, Papanicolaou DA, Unger ER, Vernon SD, Heim C. Chronic fatigue syndrome--a clinically empirical approach to its definition and study. BMC Med. 2005 Dec 15;3:19.

[3] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome; a comprehensive approach to its definition and study. Ann Int Med 1994, 121:953-959.

Competing interests

No competing interests

From http://www.pophealthmetrics.com/content/3/1/8/comments

Comments

Psychometric properties of the CDC Symptom Inventory for assessment of Chronic Fatigue Syndrome

Dieter Wagner, Rosane Nisenbaum, Christine Heim, James F Jones, Elizabeth R Unger and William C Reeves

Population Health Metrics 2005, **3**:8doi:10.1186/1478-7954-3-8

- Observations on apparent changes in methods of assessing symptoms

Observations on apparent changes in methods of assessing symptoms

Tom Kindlon (06 July 2007) Irish ME/CFS Support Group

I notice that the *"Symptom Inventory collects information about the presence, frequency, and intensity of .. symptoms during the month preceding the interview"*.

However the Fukuda et al '94 definition [1] is supposed to look for *"the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue"*.

Was there a particular reason why a time frame of one month was chosen? This would suggest that relatively short-lived symptoms would be counted. If the reasoning was that asking people detailed questions about symptom severity and frequency over a longer period would might not be as accurate, perhaps a two-stage question could be asked: firstly asking whether symptoms "have persisted or recurred during 6 or more consecutive months of illness" and then asking a more detailed question about frequency and intensity.

I also see no mention of the requirement, that was in the initial definition [1], that the symptoms didn't predate the fatigue. Again, if this is a change, it would seem to risk reducing the specificity of the symptom criteria (i.e. increasing the chences that symptoms from other causes are counted) so perhaps again a yes/no question would be good.

Tom Kindlon

[1] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A: The chronic fatigue syndrome; a comprehensive approach to its definition and study. Ann Int Med 1994, 121:953-959.

Competing interests

No Competing Interests

http://www.pophealthmetrics.com/content/5/1/5/comments

Comments

Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia

William C Reeves, **James F Jones**, **Elizabeth Maloney**, **Christine Heim**, **David C Hoaglin**, **Roumiana S Boneva**, **Marjorie Morrissey** and **Rebecca Devlin**

Population Health Metrics 2007, **5**:5doi:10.1186/1478-7954-5-5

- Does the use of the "Role emotional" subscale of the SF-36 help with sensitivity and specificity rates? Can we find out the prevalence rate if this subscale hadn't been used?
- Questioning the use of the Role Emotional (RE) subscale of the SF-36 questionnaire in the diagnosis of CFS

Does the use of the "Role emotional" subscale of the SF-36 help with sensitivity and specificity rates? Can we find out the prevalence rate if this subscale hadn't been used?

Tom Kindlon (15 June 2007) Irish ME/CFS Support Group

It is to be welcomed that attempts are being made to operationalize the CDC (94) CFS criteria [1], enabling easier comparisons between studies and making it easier for researchers to try to replicate findings.

So for example, having some sort of numerical value on a symptom so that one can say whether a symptom is present or not in a patient seems to be a good idea.

However if one is aiming to do this, it would seem preferable to choose methods that have good sensitivity and specificity rates for the condition in question. And it's questionnable whether the methods used in this study have good sensitivity and specificity.

The authors claim that they *"used stringent (i.e., <= 25th percentile population norms on any of the 4 SF-36 scales) to define severe functional impairment"*. One of the SF-36 subscales in question is the "role emotional" subscale. This involves questions such as: "During the past 4 weeks, have you accomplished less than you would like as a result of any emotional problems?"

Does this really capture whether there has been a "substantial reduction in previous levels of .. personal activities"? [Full quote from paper[1]: *1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset [has not been lifelong]; is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities*]

Perhaps the other three sub-scales cover this? For example, a better measure of whether the condition is having an effect on somebody's "personal activities" might be got from using the physical functioning subscales which asks about ability to walk distances, bath or dress oneself, etc. If this score is low, it's likely one's ability to do "personal activities" has been impaired.

Baraniuk[2] used the CDC '94 not operationalized in the same way as this study and found that CFS patients scores did have lower scores on some of the SF-36 subscales - but role emotional was one of the ones that weren't different (the others that weren't different were mental health and general health change).

Would it be possible for the authors to calculate the all important overall prevalence rate if those people who only satisfied this part of the "functional impairment" criteria are excluded? This data would be be useful not just in the US but around the world - countries around the world have been depending on the US to undertake such large scale (and expensive) studies on CFS.

Even before the recent broadening of the criteria, it had been felt by some that the CDC '94 criteria lacked specificity.

For example, Kennedy[3] investigated *"patients with self-reported symptoms which developed sporadically (sCFS, n=48); after Gulf War service (GW, n=24); and following exposure to organophosphate insecticides (OP, n=25)"* all of whom fulfilled the CDC '94 criteria[1]. Based on their findings, they concluded that *"differences in simple, easily performed clinical outcome measurements can be observed between groups of patients, all of whom fulfill*

the CDC-1994 criteria for CFS. It is likely that their response to treatment may also vary. The specificity of the CFS case definition should be improved to define more homogeneous groups of patients for the purposes of treatment and research."

Perhaps what is required is a totally new set of criteria?

Tom Kindlon

[1] Fukuda, K., Straus, S.E., Hickie, I., Sharpe, M.C., Dobbins, J.G., & Komaroff, A. (1994). The chronic fatigue syndrome: A comprehensive approach to its definition and study. Annals of Internal Medicine, 121 (12):953-959. http://www.annals.org/cgi/content/full/121/12/953

[2] James N Baraniuk, Begona Casado, Hilda Maibach, Daniel J Clauw, Lewis K Pannell and Sonja Hess S. A chronic fatigue syndrome - related proteome in human cerebrospinal fluid

BMC Neurology 2005, 5:22 doi:10.1186/1471-2377-5-22

http://www.biomedcentral.com/1471-2377/5/22

[3] Kennedy G, Abbot NC, Spence V.A, Underwood C, Belch JJF. The specificity of the CDC-1994 criteria for chronic fatigue syndrome: comparison of health status in three groups of patients who fulfil the criteria. Ann Epidemiol 2004; 14: 95–100.

Competing interests

No competing interests

Questioning the use of the Role Emotional (RE) subscale of the SF-36 questionnaire in the diagnosis of CFS

Tom Kindlon (19 June 2007) Irish ME/CFS Support Group

As background to the previous two comments, I thought I'd point out that if people would like to see what makes up the Role Emotional (RE) subscale of the SF-36, a copy of a sample SF-36 questionnaire can be seen at: <http://www.nhlbi.nih.gov/resources/deca/wave/w11.pdf> .

It is question 6 i.e. 3 questions with only yes or no as possible answers.

The cut off point used in the current study is less than or equal to a score of 66 [1], so one* "yes" answer (out of the three questions) is the cut off point for functional impairment.

Tom Kindlon

[1] Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study.

William C Reeves, Dieter Wagner, Rosane Nisenbaum, James F Jones, Brian Gurbaxani, Laura Solomon, Dimitris A Papanicolaou, Elizabeth R Unger, Suzanne D Vernon and Christine Heim

BMC Medicine 2005, 3:19 doi:10.1186/1741-7015-3-19

<http://www.biomedcentral.com/1741-7015/3/19>

Competing interests

No competing interests

*I incorrectly wrote two initially

Appendix 2:

Prof. Peter White commenting on the empirical definition (Reeves, 2005)

http://www.biomedcentral.com/imedia/1083914155124266_comment.pdf

Reviewer's report
Prevalence of Chronic Fatigue Syndrome in Metropolitan, Urban, **Title:** and Rural Georgia
Version: 1 **Date:** 3 December 2006
Reviewer: Peter White
Reviewer's report:
1. Is the question posed by the authors new and well defined?
Yes, it is, in that the novel aspects are:
- the state-wide sampling
- the study of prevalence across metropolitan, urban and rural populations
- the screen question being unwellness, not fatigue
- the use of standardised questionnaires to measure symptoms
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
No; see major compulsory revisions.
3. Are the data sound and well controlled?
Not yet; I think the authors need to review their analyses.
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes.
5. Are the discussion and conclusions well balanced and adequately supported by the data?
I think the authors need to be more cautious in their interpretation of their findings of a much higher prevalence than previously found. They should also refer to similar findings of prevalence found in other countries.
6. Do the title and abstract accurately convey what has been found?
Yes
7. Is the writing acceptable?
Yes.
Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
1. The methods leave out non-English speaking people, which may have led to an under-sampling of ethnic minority groups, and possibly CFS, if there is a difference in those who do not speak the majority language. I note the authors weighted the sample to allow for ethnic differences. The authors should mention this in discussion.
2. The authors state that, "..those with a score ? well-population medians on the general fatigue or reduced activity scales of the MFI were considered to meet fatigue criteria of the 1994 case definition." This means that it would be possible to meet the fatigue criterion without significant fatigue; i.e. with reduced activity alone. This is inconsistent with the international study criteria for CFS, which require: "clinically evaluated, unexplained, persistent or relapsing chronic fatigue (of least 6 months duration) that is of new or definite onset" (Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, Evengard B, White PD, Nisenbaum R, Unger ER. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Services Research 2003;3:25 (published 31 December 2003).
http://www.biomedcentral.com/1472-6963/3/25). In order to provide prevalence data consistent with previous criteria for CFS, the authors need to re-analyse their data for general fatigue alone on the MFI, if that is their preferred sub-scale to measure the severity of fatigue.
3. The authors state that, "Functional impairment was assessed by the medical outcomes survey short form-36 (SF-36) [13]. For classification as CFS, those with a score ? 25th percentile of population norms in the physical function or role physical, or social function, or role emotional subscales of the SF-36 were

considered to have substantial reduction in activities as specified in the 1994 definition." The same criticism as in the paragraph above applies to their choice of SF36 subscales. The use of physical function, role physical and social function sub-scales is consistent with the International Study criteria for CFS, which states that the illness "results in substantial reduction in previous levels of occupational, educational, social, or personal activities..." (Reeves et al, 2003). The use of role emotional is not, since it specifically asks about change in function "as a result of any emotional problems". I note that "role emotional" had the lowest correlation coefficient of any of the SF36 subscale scores with any of the three measures of CFS in one of the authors' previous studies (Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC: Psychometric properties of the CDC symptom inventory for the assessment of chronic fatigue syndrome. Population Health Metrics 2005, 3:8). In order to make these important criteria consistent with other studies,
I think the authors need to re-analyse their data, omitting this sub-scale.
4. There is a further problem about the choice of thresholds for both fatigue and functional impairment. For fatigue, the authors have chosen a median split from population norms, i.e. 50 % of the population would have a score of equal or greater than this. In contrast, they have chosen the bottom quartile score of population means. Why the discrepancy? This needs justification. Since the criteria for CFS include "severe" fatigue and dysfunction, it makes sense to make both thresholds the lower quartile from a population sample.
5. Furthermore the authors need to refer to the studies from which they took these population norms. I am aware of several population studies of working age adults using the SF36, but they give slightly different results, and the readers need to know which one they chose and why. I am not aware of any population studies of working age adults using the MFI. This reference should be given.
6. The authors state that, "For classification as CFS, those reporting ? 4 case defining symptoms and who scored > 25 on the SI case definition subscale were considered to meet accompanying symptom criteria of the 1994 case definition." Having read the relevant paper, I am still uncertain by both what is meant by the "SI case definition subscale" and what a score of 25 means. This needs both clarifying and justifying.
7. What proportion of the three different geographical sample households did not have a working telephone at the time of sampling? This is important information in order to approximate the selection bias towards greater economic income. I would assume that this data would be available.
8. What proportion of those screened by telephone was fatigued but not "unwell"? This should be reported.
9. How did they work out the numeric value of the weightings? It would help the reader to give more details about this.
10. The authors give mainly univariate analyses results with limited interaction data. We need to see multivariate analyses to model all the examined factors that may influence the prevalence of CFS, so that confounding and interactions can be excluded or explored.
11. The authors describe similar findings across black and white people, but do not describe the ethnic groups adequately. What do they mean by "black"?
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. Reference 12 needs revision.
Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
1. The description of the numbers and proportions found in sampling, telephone assessment and clinical assessment is complicated and it is hard to follow the numerators and denominators. I think readers would be helped by an algorithmic figure with the numbers (%) at each stage, with both true and false negatives and positives given at each stage of assessment.
2. The difference between metropolitan and urban areas seems somewhat arbitrary to this non-American referee. I suspect some further justification would help non-American readers
Unable to decide on acceptance or rejection until the authors have responded **What next?:** to the major compulsory revisions
An article of importance **Level of interest:** in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.