Author's response to reviews

Title: Perception versus polysomnographic assessment of sleep in CFS and non-fatigued controls: results from a population-based study

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Liz Hoffman
Assistant Editor
BMC-series journals

Dear Ms. Hoffman,

We are resubmitting the manuscript entitled "Perception versus polysomnographic assessment of sleep in CFS and non-fatigued control subjects: results from a population based study", manuscript number 1805351722143351.

This note includes the responses to the reviewer's comments.

Dr. Reeves will be away until September 18. In his absence, I will serve as the corresponding author.

Thank you for your assistance.

James F. Jones, MD

Reviewer 1

1. The most important problem is that the subjective data and the
polysomnographic data do not correspond to the same time period. The only way one could accurately compare self-report experiential material and objective sleep patterns reflected by PSG and sleep laboratory observation is to have the participant report on exactly the night during which the objective sleep parameters were assessed. This is usually done by sleep diary completed the morning after the overnight study. As a consequence of this important omission, the title of the paper is not accurate.

We understand the concerns of the reviewer. We think that our original approach, using PSG data to search for objective sleep abnormalities to correlate with self-reported sleep experience for the prior month, does provide some insight into the discrepancy between perceived and measured sleep problems. However, using data from the nap booklet and sleep booklets that were completed for each MSLT and PSG, was an equally important approach that we overlooked. Based on the reviewer’s suggestion we examined this data. The nap booklet assessed latency to fall asleep during each nap. The sleep booklets were completed the morning after each PSG and evaluated sleep qualities during the night, sleep onset latency, and total sleep time. An analysis of these data is seen on page 12. This analysis provided one of the most unique observations in our study; i.e. that the CFS subjects actually had a more accurate assessment of sleep latency than control subjects. T

2. An additional point related to subjective measurement in this study, is only retrospective questionnaires were used. It is known that on-going (i.e. diary measures) and retrospective questionnaires yield different data for the same experience. Symptoms in CFS are also somewhat cyclical in nature, and again this could only be captured by using sleep diaries for some consecutive number of days or weeks.

We agree that symptoms in CFS subjects vary with time but as major components of the illness, they are present throughout the illness when it is examined as a chronic process. We added a citation, reference 8, a paper that describes the clinical course in this population, in the introduction that addresses this point. The questionnaire data include subject responses to questions posed about cumulative sleep experiences as experienced over the month prior to questioning using the CDC Symptom Inventory, the Toronto Sleep Assessment Questionnaire and the Epworth Sleepiness Scale that reflect an illness of greater than 6 months duration that was present for a mean duration of 7.3 years.

3. With respect to the objective data, the study did demonstrate that participants with CFS and controls did not differ in gross sleep architecture and parameters. Even without doing a spectral analysis of the PSG data (which might have revealed the illusive correlates of CFS-related sleep complaints), one could have noted alpha intrusions, which would indicate some subtler undermining of sleep quality. Since alpha/delta

sleep has long been of interest in the related condition of fibromyalgia, and somewhat more recently in CFS, it was a bit surprising that this was not reported in this study.
Alpha intrusion was recorded during the study and is now included in the results section.

4. Both participants with CFS and controls appear to spend at least 1 hour of nocturnal wakefulness during the measured sleep period (if one adds the times for SOL and WASO). The data suggest that both samples have similarly mild sleep disruption; rather both have equally non problematic sleep. This again highlights how essential it is to have both samples report on their perceived sleep lab sleep quality.

Perceived sleep quality in the sleep lab is now included in the results as is a statement regarding awake time during the night as noted in this comment.

5. A more minor point is that there was no information about the timing of the sleep lab experience. Were participants awakened early (as is usual clinical practice), and sent home? This would have made a difference to the total sleep time measure, particularly since individuals with CFS often sleep late in the morning.

The sleep lab experience is now detailed in the methods section. Each subject had the opportunity to sleep 9 hours.

6. The fact that the MSLT did not reflect sleep deprivation in participants with CFS is not surprising. Individuals who report insomnia typically have difficulty falling asleep in the daytime as well.

We did not specifically address insomnia as part of the study design; subjects were entered based on complaints of insomnia per se, but rather as individuals who fulfilled or did not fulfill criteria for CFS. As seen in the text in this version the coincidental identification of subjects fulfilling a general definition of insomnia is discussed.

Reviewer 2

Major Compulsory Revisions

The Method section is too sketchy. While the authors note that aspects of the investigation were published elsewhere, it is not possible to understand the findings without additional information about the subjects, the measures and the procedure.

The methods section has been expanded with the requested details.

For example, were individuals who had CFS as well as fibromyalgia included? What proportion of the sample had fibromyalgia?
Fibromyalgia is another illness construct that in an expanded definition shares symptoms with CFS, however a history of fibromyalgia was uncommon in the CFS or control groups. Since fibromyalgia is not considered as an exclusionary illness in the diagnostic process of CFS, our study design did not include evaluation of features required to specifically diagnose fibromyalgia.

What was the age range?
The demographic information is included in the results section. It is placed in this section because the subjects described in this report were not identified until the sleep data had been analyzed.

Was the control group a healthy control group or simply ¿non-fatigued¿?
As described in the text on page 7, control subjects were ¿Participants whose scores were in the normal range on all of the above mentioned instruments (diagnostic) and who had no exclusionary medical or psychiatric conditions identified were classified as non-fatigued.¿

How were they recruited?
Please see page 5 for a description of acquisition of subjects.

The ¿surveillance study¿ in which subjects participated seems to have started in 1999-2000. What was investigated in this study?
Please see page 5 for a description of the aims of the surveillance study.

When were participants tested for the current investigation?
The study dates were between January and July of 2003 (page 5).

Also, I am not clear about what the measures measured or about the psychometric properties of the instruments.

The questionnaires used in this study to obtain participant histories and perceptions have been used in previous studies. The Multidimensional Fatigue Inventory is one of several well established instruments used to quantify self-perceived fatigue-reference 18. The SF-36 is perhaps the most commonly used instrument to assess health status. The psychometric properties of the CDC Symptom Inventory has been described and validated ¿ reference 20. The Epworth sleepiness scale (1991) and the Toronto Sleep Assessment Questionnaire (1996) have likewise been described. The Sleep and Nap Booklets were and are in use in the Emory University School of Medicine sleep center.

I am also confused about what, exactly, the dependent variables were and how many of these were used evaluated. These aspects of the Method should be clarified.
First we used logistic regression to analyze CDC symptom scores for unrefreshing sleep and problems sleeping as well as sleep booklet scores for latency to fall asleep, total sleep time, and sleep quality. For the first ANOVA's we used the polysomnographic variables listed on page 8. Paired sample t-tests were used to compare objective and subjective mean sleep latencies as measured by MSLT on day 2 and the total sleep time, and sleep onset time both measured by PSG and estimated for days 1 and 2. For the factor analysis we used questionnaire data from the Toronto sleep assessment instrument and the Epworth sleepiness scale.

The medications listed, which the authors grouped overall as medication that affects sleep used/not used and which they used in several analyses, include both sedating and stimulating substances (e.g., pseudoephedrine, hypnotics). Frankly, I do not understand the rationale for combining sedating and stimulating medications for these analyses. Sedating and stimulating medications should either be examined separately or these medications should eliminated altogether from the analyses.

Specific medication use in these subjects was not the topic of this report. We had previously found that in another publication regarding these subjects (Jones et. al., Medication use by persons with chronic fatigue syndrome: Results of a randomized telephone survey in Wichita, Kansas. Health Qual Life Outcomes, 2003;1(1):74.), medication use was widespread in both CFS and control subjects and not always given or taken for specific reasons. Therefore we chose to address medication use simply as a binary variable.

Sleep state misperception refers to insomnia. Yet, the investigators do not indicate how they defined, diagnosed or measured insomnia, be it primary or secondary (see Table 1), using either PSG or self-report.

Our analysis included two questionnaire items from the CDC Symptom Inventory that assess subjective sleep qualities over the preceding month, unrefreshing sleep and problems sleeping (getting to sleep, not sleeping through the night, or waking up on time). These items are also used in several definitions of insomnia (references 9, 18, and 36). The row in Table 1 describing a subject with Primary/Secondary insomnia has been removed because we cannot clarify further.

The sleep lab allowed participants approximately 7.5 hours in bed. People without insomnia often sleep more than this, and individuals with CFS often spend as much as 9-10 hours in bed. Thus the protocol did not allow for the evaluation of insomnia in the two populations, even if the conditions in the lab had been conducive to ¿normal¿ sleep. In this context it should be noted that according to the consensus conference, insomnia should not be diagnosed using PSG.
The new information provided in the methods section describes the sleep lab opportunity to sleep as 9 hours. We did not allow for the diagnosis of insomnia as it was not a goal of the study. The reviewer is correct that the diagnosis of insomnia is not strictly based on a PSG.

As for nonrefreshing sleep, to the best of my knowledge there are no acceptable self report or PSG based measures to evaluate this construct and in the present investigation this was evaluated by a single self report item.

Non-refreshing sleep is a component of the CDC Symptom Inventory, reference 20. In this context, it simply reflects the subject’s perception of the success of their sleep. The question was “During the last month, has unrefreshing sleep been a problem for you?”

Sleep state misperception in the present study refers to misperception of what? Total sleep time? Total wake time? Nonrefreshing sleep? Frequency of arousals? This central concept is never operationally defined!

As used in the original submission, misperception was simply a descriptive term that signified a difference between the subject’s impression of their sleep and the measured outcome. Because of the confusion that it introduced, “misperception” is not used in this version.

Also, I do not believe that any of the self-report measures evaluated sleep during the nights of PSG evaluation, a requirement if one is to conclude that sleep parameters are being misperceived.

This omission has been corrected in the Methods, Results, and Discussion sections by inclusion of the Nap and Sleep Booklet data.

Also, the data do not allow us to determine if there were significant numbers of participants who had discrepancies between insomnia parameters, such as total sleep and wake items, and PSG results.

We examined such relationships in two parameters, latency to fall asleep and total sleep time and we found a significant difference between the two subject groups. Please see new material on pages 12 and 13.

Given these considerations, I find it difficult to understand how the authors concluded that individuals with CFS suffer from sleep state misperception.

As stated above, the original manuscript used the term misperception in its general sense and it is no longer a part of this submission. As a result of the additional analyses the CFS subjects are now described as having an altered sleep perception state of unknown origin.

Yet, in the Discussion (page 11 bottom) the authors argue that type
of ¿underlying wakefulness at sleep onset (that characterizes insomnia ¿ not sleep state misperception ¿ italics mine) might also interfere with nonrefreshing sleep.¿ Why?

The sentence in question on page 11 reads as follows: ¿This type of underlying wakefulness at sleep-onset might also interfere with refreshing sleep.¿ It refers to a citation by others and was placed here to suggest that if underlying wakefulness was present or perceived it might interfere with subject perception of refreshing sleep. The topic has been removed from this version.

Do we know that the CFS participants complained of insomnia according to any standard definition (e.g., duration 3 months, three nights per week of undesired wakefulness lasting 31 minutes of more, distress related to sleep problems)?

Again, describing insomnia was not the objective of this study. We do know that CFS subjects and patients complained of un-refreshing sleep and problems sleeping for prolonged periods of time (loose definitional criteria for insomnia). The definition of CFS requires that diagnostic symptoms accompany the fatigue and that they contribute to the illness. Therefore if a subject fulfills diagnostic criteria multiple times over several years, and sleeping problems are part of that person¿s illness, those complaints will remain as part of the illness complex (reference 8). In addition, the definitional requirements for CFS include greater than 6 months fatigue and interference with normal function, components that certainly are distressful and consequences of insomnia.

Is there any evidence that nonrefreshing sleep is associated with misperception of anything?

Since I have strong concerns that the authors have failed to show that there is sleep state misperception in CFS I clearly do not agree with the conclusions.

We used the ¿unrefreshing sleep¿ and other self-report measures of sleep to compare with objective sleep studies. The marked difference between CFS and controls in self-reported measures of sleep and the lack of difference between the groups in objective measures, is the discrepancy reported. Because of this confusion, as noted above, the concept of misperception has been excluded from the report.

Yet, I feel strongly that additional information about sleep in CFS, both measured via PSG and questionnaire, is needed. An organizing framework other than sleep state misperception should, however, be used.

Hopefully, the new material added to the report satisfies these suggestions.

Minor Essential Revisions

I am not sure what ¿frequency matched¿ (p. 5) and ¿case status¿ (p. 9) mean ¿ please clarify.
This term ‘frequency matched’ has been removed. Case status is now explained in the text on page 9.

The section on Statistical Analyses would fit better in the results where the findings are detailed.

Our standard organization is inclusion of the Statistics section in the description of Methods.

The first paragraph of Results belongs in Method.

The demographic information is included in the results section. It is placed in this section because the subjects described in this report were not identified until the sleep data had been analyzed.

Alpha level was set at .05. I do not think this is appropriate given the number of comparisons. A Bonferroni correction to the alpha level would be useful.

Most of the comparisons of the sleep variables were non-significant (see Tables 1 and 2). Therefore a Bonferroni correction did not seem necessary. For the comparison between objective and subjective variables we only made a few comparisons. Of the significant p-values reported, only the difference between measured latency to fall asleep on night #1 and the corresponding questionnaire variable for the non-fatigued control group would survive a Bonferroni correction for multiple comparisons at the $\alpha = .05$ level. The Bonferroni procedure represents a conservative lower bound, however. Employing the method of Benjamini and Hochberg and controlling the false discovery rate to $< 10\%$, then all of the p-values reported above are still significant.

In the Discussion (last paragraph p. 11) the authors indicate that insomnia is associated with underestimation of total sleep time and overestimation of wake after sleep onset. But in the present study they did not report on sleep diary vs PSG findings for the same night so I don’t see the relevance of this statement. It should be deleted. Also, the literature shows that most medical patients have higher anxiety and depression scores than controls. So this type of evidence cannot be used to infer that individuals with CFS have insomnia or sleep state misperception.

The statement in question has been removed.

Page 12 bottom paragraph I do not understand how hypnotic medication is expected to improve unrefreshing sleep. If anything, sleep meds increase morning grogginess and fatigue.

The statement in question has been removed.

Page 12 -13 several statements about the findings are not presented in the Results (e.g., medication use was more common in CFS sample (top para) and median duration of illness was 7. 3 years). These should be included.
These errors have been corrected

Discretionary Revisions (which the author can choose to ignore)

I believe that the factor analysis was done for the two samples combined. The authors may want to examine factor structure separately for the two samples. Factor structure and loadings for people with dysfunctions are often different from those of controls.

We did a factor analysis for the individual groups that showed similar factor structure and loadings. We decided to combine the groups in order to statistically compare factor scores between the groups.

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