Author's response to reviews

Title: Fatigue in Traumatic Brain Injury adults: predictors and consequences: a systematic review of longitudinal study protocols

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Author's response to reviews: see over
Dear Systematic Reviews Editorial Team,

We wish to extend our sincere gratitude for the helpful feedback from the reviewers, which contributed to the improvement of this protocol. We have addressed the concerns raised and our revisions are listed below. Please find enclosed a revised version of our paper.

We look forward to hearing from you soon.

Sincerely,

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Reviewer #2:

Major Compulsory Revisions -None

Minor Essential Revisions

1. I have looked through your search strategies and I notice that you have limited some to people "19 plus years" (MEDLINE) and others to adults aged 17 or over (PsycINFO). However, in the Methods section of the protocol you refer to "adults aged 18 years and over." Therefore, please double check the search strategy to ensure consistency across the included studies. It would also add to the systematic review to comment on your interest in adults only.

Response: The database age limiters were based on the filters developed by the databases - for example, in Medline, the "adult" heading is defined as 19+, whereas adult is defined differently in PsychInfo - the filters are preset, thus we were not able to manually change them.

To adjust the Medline search to also include studies that may have 18 year olds, we changed the searches to find articles that are "not children" rather than "only adults". This increased our numbers considerably, as it also includes articles that do not have adults or children participating. This strategy broadened the search by including teenagers, and resulted in a more consistent search including all 18+ participants.

We updated the title of the protocol to “Fatigue in Traumatic Brain Injury adults: predictors and consequences: a systematic review of longitudinal study protocols”.

2. In the exclusion criteria it is clear why you have excluded impaired alertness or vigilance but I am unsure the difference between fatigue and sleepiness. I know that there is not an accepted
definition of fatigue however; I think you should justify how it differs to sleepiness especially as one leads to exclusion and the other leads to inclusion.

Response: The following paragraphs were added to the manuscript:

For the purpose of this review we will consider “human fatigue” as “the undesirable state produced by effort- the physical or mental effort of doing work” [17].

The cause of the patient’s symptoms on a single item scale can be hard to determine as patients with TBI may use vague words to describe their state (e.g. sleepiness vs. fatigue). Sleepiness is a basic physiological state, the presence and intensity of which can be inferred by how readily sleep onset occurs, how easily sleep is disrupted, and how long sleep endures. [18]. The utilized measures (and items within them) can guide in distinguishing the fatigue phenomena from sleepiness. For example, the symptom related to sleepiness may be presented as unintended episodes of falling asleep in the daytime or elevated numbers on standardized sleepiness scales; symptoms related to fatigue will manifest as muscular weakness or lack of energy. We recognize that some fatigue scales may include items related to sleepiness. As part of our review we will report whether utilized fatigue scales were uni- or multi-dimensional.

Discretionary Revisions
1. I prefer the term "data extraction" rather than "data abstraction" but that's a personal opinion!
Response: Left as is
2. Abstract, background, line 1: I think "deliberating" should read "debilitating"
Response: This has been changed
3. Abstract, methods, line 3: I think it should be "focus" rather than "focuses"
Response: This has been changed
4. Data collection, Selection of studies, 8: I think the sentence should finish with "table".
Response: This has been added

Reviewer #1.
Abstract

Highlight comment SJN 5/10/2013 8:55:53 AM Should this read 'debilitating'?
Response: This has been changed.

Highlight comment SJN 5/10/2013 9:30:04 AM ? See comment in main body of text
Randomized controlled trial data will be treated as a cohort.
Response: We will extract the control (e.g. untreated group) data from RCTs to address the second research objective (e.g. to determine the course of fatigue) in patients with TBI. If the intervention in the trial has no effect, we will use both groups. The Hayden et al. guidelines will suit the purpose of assessing the risk of bias RCT data in this case, as we will treat them as cohort studies.
The following statement has been added to the manuscript:
…we will utilize the control (e.g. untreated group) data from RCT studies to address the second research objective (e.g. to determine the course of fatigue) if the intervention had an effect. If the trial is negative, both intervention and control groups will be used.
Highlight comment SJN 5/10/2013 8:58:53 AM Increase the understanding of readers also therefore 'our' is probably not necessary here)
Response: This (e.g. our) word has been removed.

Highlight comment SJN 5/10/2013 9:07:45 AM There are several Cochrane databases so please state which were searched (The Cochrane Database of Systematic Reviews according to Additional file 1
Response: This has been adjusted.

Highlight comment SJN 5/10/2013 9:12:08 AM Are there specific reasons for excluding non English studies or studies of children?
Response re studies on children: The focus of the review is fatigue in an adult population with TBI. Focus on children, although important, requires separate assessment. A key reason for that is that the child’s brain continues to change and develop throughout early adulthood. Therefore, it is imperative that fatigue in a children’s population with brain injury is assessed separately.
Response re non-English studies:

We understand the reviewer’s concern. However, trying to identify all relevant studies irrespective of the country in which they were conducted or the language in which they have been published is generally difficult with current electronic databases. We alternatively considered restricting the inclusion criteria by the country in which the studies were conducted. This however, may lead to even greater bias, as positive studies conducted in non-English-speaking countries are more likely to be submitted to an English-speaking journal. We therefore decided to report on studies published in English, but conducted in a non-English-speaking country in the table. We would not be able, however, to perform an extensive search for other studies conducted in that country, but not published in English, among which could potentially be studies with negative results. This remains one of the limitations, as outlined in the protocol.

We added the following paragraph to the manuscript:

An attempt will be made to identify non-English language papers (e.g. usually titles and abstracts are translated to English in many databases) and document their existence and reason for exclusion as “language” will be recorded.

Highlight comment SJN 5/10/2013 9:15:25 AM Any attempts to search for unpublished data (conference abstracts / contacting experts in the field etc)? Addressing publication bias?

Response: We agree with the reviewer that search for unpublished manuscripts will reduce the publication bias.

The following paragraph has been added to the manuscript:

**** To reduce the publication bias, we will use the following approaches to find unpublished studies: 1) will search in the Cochrane Handbook (through the Cochrane Library CD) for registries with completed and ongoing studies registered in the area of TBI and through the website www.controlled-trials.com, which provides online access to a listing of ongoing and completed control trials; and 2) will contact the principal investigators of relevant studies directly, asking whether they know of additional studies. We will also screen for the conference abstracts bearing in mind to contact the study authors to obtain full study details.
Designs of studies to be included? - I see the designs to be excluded are listed below, are all other designs to be included?)
Response: The designs of the studies that will enable us to answer the research questions have been provided.

Is a minimum time of follow up required?
Response: We did not pre-specify timelines for longitudinal studies. The reason for this is that one of our research questions relates to the natural course of fatigue in TBI. Lundin and colleagues (2006) followed 122 consecutive patients with mTBI and assessed symptoms (including fatigue) after 1, 7 and 14 days and 3 months post-injury. The natural history of fatigue has been reported as follows (0.61, 0.19, 0.42, and 0.11). As such, we decided to keep timelines open.

What about studies that consider fatigue as a secondary outcome? They could still contain relevant information
Response: We decided to consider studies that focus on fatigue as the primary outcome only. This is partially because they are expected to be more rigorous, and of better quality given the predefined hypothesis. In addition post-host analyses are not always accurate, and could potentially mislead readers.

Should this have two stars - relating to TBI? criteria*
Response: This has been corrected.

If fatigue doesn't have a 'generally accepted universal definition' as stated in the background section, can you be 100% sure that these studies aren't focusing on 'fatigue'? Is the use of the word 'fatigue' in the study part of the inclusion criteria?
Response: Sleepiness is defined as a basic physiological state, the presence and intensity of which can be inferred by how readily sleep onset occurs, how easily sleep is disrupted, and how long sleep endures\(^1\). The “human fatigue” term is difficult to define, although investigators at the Civil Aeromedical Institute described it as “the undesirable state produced by effort- the physical or mental effort of doing work”\(^2\). It is true that the cause of the patient’s symptoms can be hard to determine as patients with TBI may use vague words to describe their state. Nevertheless, utilized measures (and items within) can guide in distinguishing the phenomena from sleepiness and other parallel states. For example, the symptom related to sleepiness may be presented as unintended episodes of falling asleep during the daytime or elevated numbers on standardized sleepiness scales. On the other hand, symptoms related to fatigue will manifest as muscular weakness, lack or energy. We recognize that some fatigue scales, may include items in regards to sleepiness. As part of our review we plan to report whether utilized scales were uni- or multi-dimensional.


The following paragraphs have been added to the manuscript:

For the purpose of this review we will consider “human fatigue” as “the undesirable state produced by effort- the physical or mental effort of doing work” [17].

and

The cause of the patient’s symptoms on a single item scale can be hard to determine as patients with TBI may use vague words to describe their state (e.g. sleepiness vs. fatigue). Sleepiness is a basic physiological state, the presence and intensity of which can be inferred by how readily sleep onset occurs, how easily sleep is disrupted, and how long sleep endures [18]. The utilized measures (and items within them) can guide in distinguishing the fatigue phenomena from
sleepiness. For example, the symptom related to sleepiness may be presented as unintended episodes of falling asleep during the daytime or elevated numbers on standardized sleepiness scales; symptoms related to fatigue will manifest as muscular weakness or lack or energy. We recognize that some fatigue scales may include items related to sleepiness. As part of our review we will report whether utilized fatigue scales were uni- or multi-dimensional.

Highlight comment SJN 5/10/2013 9:22:43 AM Why exclude these types of study? Exclusion of unpublished data could lead to publication bias
Response: We updated our exclusion criteria:

****To reduce the publication bias, we will use the following approaches to find unpublished studies: 1) will search in the Cochrane Handbook (through the Cochrane Library CD) for registries with completed and ongoing studies registered in the area of TBI and through the website www.controlled-trials.com which provides online access to a listing of ongoing and completed control trials; and 2) will contact the principal investigators of relevant studies directly, asking whether they know of additional studies. We will also screen for the conference abstracts bearing in mind to contact the study authors to obtain full study details.

Highlight comment SJN 5/10/2013 9:25:03 AM This section would be more appropriate as 'Types of study design' in the inclusion criteria as it is not strictly 'Data Collection'
Response: The subtitle has been changed.

Highlight comment SJN 5/10/2013 9:54:13 AM Could pharmacological interventions in this area have side effects of fatigue, therefore confounding the disease process of fatigue following TBI?
Response: A detailed review of the medications (whenever available, and we will also contact authors) will be undertaken and reported, as many medications, including those commonly used in the TBI population (e.g. antiepileptics, antipsychotics, antihistamines, corticosteroids, antidepressants, etc.), can cause fatigue.
Highlight comment SJN 5/10/2013 9:32:18 AM I don't understand, are RCTs to be treated as if patients were not randomised? The design of the study / statistics used / results will be dependent on the randomisation so I would not recommend treating the data as observational I would recommend analysing randomised and observational data separately)

Response:
The following sentence has been added to the manuscript to clarify:

…we will utilize the control (e.g. untreated group) data from RCT studies to address the second research objective (e.g. to determine the course of fatigue) if the intervention had an effect. If the trial is negative, both intervention and control groups will be used.

The risk of will be assessed by Hayden’s criteria, separately for the observational studies and RCTs.

Highlight comment SJN 5/10/2013 9:37:17 AM Alternatively, to include all relevant evidence in the review, rather than excluding 'high risk of bias' studies straight away, sensitivity analysis could be performed excluding these studies and therefore assessing the robustness of the results and whether the biased studies are influencing the results

Response: Thank you for your comment. We agree that the basis for bias assessment should be made explicit, by recording the aspects of the trial methods on which the judgment was based and then the judgment itself. As such, we will report in the supplementary table the trial method on which the decision of exclusion was made.

The following sentence has been added to the protocol:

In order to ensure the explicit basis for bias assessment, we will record the reasons for our judgment of “high risk of bias,” including the main reasons why the decision of exclusion was made.

Highlight comment SJN 5/10/2013 9:39:58 AM Will origins of missing data be considered (e.g. data missing at random or not at random?)

Response: The following sentence has been added to the protocol:
Where possible, the proportion of missing data will be stated, along with possible reasons. If there is too much of missing data, the paper will be classified as “high risk of bias”.

Highlight comment SJN 5/10/2013 9:41:06 AM Is the word 'our' necessary here? Or it is referring to a universal 'our'?
Response: This has been changed.

Highlight comment SJN 5/10/2013 9:42:05 AM but unpublished data and conference abstracts are to be excluded?
Response: This has been addressed.

Highlight comment SJN 5/10/2013 9:43:14 AM Is there a reason for this criteria?
Response: Non peer-reviewed studies have greater potential for bias; the focus remains on peer-reviewed studies only.