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The course and prognostic factors of cognitive status after central nervous system trauma: A systematic review protocol

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Abstract

Introduction: Traumatic brain injury (TBI) is among the most disabling injuries, resulting in a range of cognitive impairments. Traumatic spinal cord injury (SCI) often occurs in conjunction with TBI; the two are best considered together in the context of trauma to the central nervous system (CNS). Despite strong indications of cognitive dysfunction in CNS trauma, little is known about its natural history or relationship with other factors. The current protocol outlines a strategy for a systematic review that will identify, assess, and critically appraise studies that assessed cognition in patients with CNS trauma on at least two separate time points post-injury.

Methods and and analysis*:* Medline, Central, Embase, Scopus, PsycINFO, and supplemental PubMed were systematically searched for peer-reviewed English language publications with a longitudinal design that focus on cognition in adults with either TBI, or SCI, or both from inception to December 2016. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines will be utilised in conducting and reporting the review. Results will be grouped by (a) prognostic factors of cognitive function; and (b) development of, or time until development of, cognitive deficit in patients with CNS trauma. To determine the course of cognitive status, matching assessment times will be grouped with their corresponding values and a sample size-weighted mean value will be calculated. Close attention will be paid to the properties of measurements used to assess cognition. Age and sex will be treated as covariates.

Ethics and dissemination: The authors will publish findings from this review in a peer-reviewed scientific journal and present the results at national and international conferences. This review will provide an increase in scientific certainty regarding prognostic factors and natural history of

cognitive status in males and females with CNS trauma, informing clinicians, policy makers, and future researchers on the topic.

Registration details: CRD42017055309.

Keywords: traumatic brain injury; spinal cord injury; cognition; dysfunction; prognosis; natural history; males, females; Ia level of evidence

Strengths and limitations of this study

- During the development phase of the project, concepts and hypotheses were formulated based on a synthesis of relevant discoveries across various disciplines and previous research
- The multilevel risk of bias assessment allows to detect main flaws in the individual studies' design and inform future research on the topic
- Special attention will be paid to measurements used to assess cognitive function in patients with CNS trauma
- We acknowledge expected heterogeneity in the primary studies, with variation between studies in sample characteristics, as well as in definitions of primary outcome
- Severe CNS trauma cases expect to be underrepresented in the inception cohorts and the majority of the patients expect to be men; this would limit the precision of estimates and generalizability of results
- We acknowledge chance for publication bias due to inclusion of only peer-reviewed studies published in English.

Introduction

Description of the condition

Central nervous system (CNS) trauma-- including traumatic brain injury (TBI) and traumatic spinal cord injury (SCI) [1]-- has been implicated as a risk factor for a range of cognitive impairments, particularly in the domains of attention, memory, emotion, and behaviour.[2-4] Recent studies have presented solid evidence that patients with a history of CNS trauma may develop various neurodegenerative disorders including Alzheimer's disease (AD).[4, 6] However, our understanding of *when* (i.e., post-injury timeframe) and *in whom* (i.e., characteristic of an injured person) AD develops after CNS trauma (TBI, SCI, or both) -- with respect to sustained and/or degrading cognitive impairment post-injury-- remains limited,[4, 7, 8] and reported rates of cognitive decline after TBI and traumatic SCI are quite variable.[9, 10] This variability has prompted interest in longitudinal studies that have focused on cognition in persons with CNS trauma across their lifespans post–injury.[11, 12] To assess longitudinal changes in cognitive status post-injury, evaluative instruments or composite tests able to measure changes in cognition after CNS trauma over time are crucial.[13] A recent study of factors associated with the rate of decline and evolution from mild cognitive impairment to AD dementia in elderly patients was performed, which estimated from three common global measures of cognition. This study appeared to have findings which varied depending on the evaluative measure used. [14] The study of measurements' properties of cognition in patients with CNS is still in its infancy, and-- when reporting cognitive decline associated with CNS-- evaluative properties of measurements have rarely been discussed or acknowledged. In order to come to a transparent

conclusion on the course of cognitive status after TBI, properly evaluating measurements' properties must be done in the process of data synthesis.

Description of measurements' needs

Under the framework of Kirshner and Guyatt, measurements used to evaluate change over time in any domain should be (1) reliable (i.e., possess adequate internal consistency and responsiveness test-retest reliability in the population of interest) and (2) correspond closely to the construct to be measured.[15] Until now, research on cognitive status after TBI has focused on patients' 'capacity' (i.e., what the patient can do when he or she is invited to), 'perceived ability' (i.e., what the patient thinks they can do), and 'cognitive activity' (i.e., what the patient can actually do), which are different constructs. As such, when assessing CNS trauma-related deficits in language, perception, memory, reasoning, attention, etc., a solid knowledge of the tests applied to measure these deficits is of great importance.

How sex might affect results

Another important area to consider in the study of cognition after CNS trauma and the risk of development of AD is sex (i.e., biological differences between men and women). Often, CNS trauma is considered to be an injury of males. Overall and in almost every age group, TBI and SCI more frequently occur in males than in females.[16, 17] These differences may reflect the high rate of general injuries among males and/or differences in risk taking societal roles and behaviours, relevant to the construct of gender, rather than sex.[18] In contrast, the preponderance of current evidence is that an increased risk of AD exists in women, which is even more pronounced in advanced age.[19] The reason behind sex differences in the risk of AD

is unknown, especially because many human studies support the notion that oestrogen, especially brain oestradiol, improves and conserves cognitive function including memory retention.[20,21] Consistent with this theoretical gap, women's traditional inequalities and disadvantages in access to and control of resources have resulted in the present scarcity of data on women with CNS trauma, and our knowledge of whether women and men are at different risks of developing cognitive impairment after CNS trauma due to differing gendered vulnerabilities (i.e., injury risk, severity, access to power and resources post-injury, help-seeking behaviours, health care system use, intervention response, and rehabilitation outcomes) or conversely, being protected from it, is limited. Therefore, an awareness of how cognitive status after CNS trauma varies or parallels by sex across time points when taking gender into account is critical to advance CNS trauma and AD research.

How age might affect results

Age is the single most important risk factor for various domains of cognitive decline across diverse cultural groups and geographic regions, including memory, language, processing speed, and executive functioning.[22] CNS neurogenesis is known to change during one's lifespan, and this is likely reflected in age-related risk for cognitive decline. However, research has highlighted that associations may vary across cohorts,[22] suggesting that different rates of cognitive decline might contribute to the global variation in age-related dementia prevalence. Likewise, consistent associations with genetics, cardiovascular health, and lifestyle and cognitive function have been accumulated in research, each of which is relevant to the discussion of the higher likelihood of being involved in an injury with CNS outcome.[23] The need to explore

how age-dependent associations with other risk factors in patients with CNS trauma cannot be undermined.

Objectives

The aim of the current study is to identify, appraise, and synthesize all available longitudinal studies relevant to the discussion of cognitive function in males and females following CNS trauma in an attempt to: (1) determine diagnostic/prognostic factors of development of cognitive deficits in patients with CNS trauma at the baseline and follow-up; (2) determine the course of cognitive function in patients with CNS trauma; and (3) summarize sex- and age-stratified results pertaining to the course of cognitive status in patients with CNS trauma. Finally, the current study intends to provide a systematic consideration, solid description, and in-depth understanding of the range of measurements utilized to assess cognition in CNS trauma research. This study also aims to report on these instruments' reliability and construct validity, which are key psychometric properties necessary for evaluative purposes. This study is operating under the hypothesis which states that acutely derived CNS trauma variables alone (i.e., age, sex, TBI mechanism, level of SCI, injury severity, etc.), are not sufficient to accurately predict cognitive status and/or its domains after CNS trauma. Furthermore, it is hypothesized that cognitive deficits following CNS trauma are the product of diverse external and internal influences acting on a genetically determined substrate and that many of these external influences are modifiable (Figure 1). The current protocol outlines a strategy for this systematic review.

Methods and analysis

The review will be conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] In accordance with these guidelines, the systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) [25] on January 16, 2017 (registration number, CRD42017055309).

Criteria for considering studies for this review

Types of studies

- Peer-reviewed published longitudinal studies (i.e., studies that have cognition* on at least two separate occasions) in English, conducted in adults with a clinical diagnosis of CNS trauma (TBI, or SCI, or both).
- Studies that were primarily designed to investigate the predictors and the course of cognitive deficits in patients with CNS trauma.

Participants and assessment

- Males and females aged 18 years or older, with TBI or SCI or both, defined by clinical criteria. We do not set limitations to the setting in which the research took place.
- Any means of diagnosis or assessment of cognition.

Types of outcome measures

The primary outcomes include (i) cognitive function or (ii) development of-- or time until development of-- possible or probable cognitive deficit in patients with CNS trauma.

*Cognitive function: cognitive function is referred to as the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.[26] It encompasses processes such as knowledge, attention, memory and working memory, judgment and evaluation, reasoning and "computation," problem solving and decision making, comprehension and production of language, etc.[26] Any measures of cognition (or its domain) (e.g., the presence or absence of cognitive deficits determined using a single question, a case definition of any measure of cognitive domain by a standardized clinical tool, or cognitive domain scores reported as a continuous variable) will be considered.

Development of cognitive deficit* in patients with CNS trauma will be assigned based on the DSM-V criteria for mild neurocognitive development, namely: (1) evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on: (i) concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and (ii) modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment; and (2) the cognitive deficits do not interfere with the capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required.[27]

Exclusion criteria

Types of studies:

- Studies investigating cognition after CNS trauma due to secondary pathological processes (e.g., oedema, intracranial haemorrhages, ischemia/infarction, and systemic intracranial conditions)
- Letters to editors and reviews without data, case reports, or reports; conference abstracts, articles with no primary data, theses, and unpublished manuscripts.

Search methods for the identification of studies

In collaboration with clinical experts and a medical information specialist, a comprehensive search strategy for studying cognitive function in CNS trauma was developed. All English language, peer-reviewed studies with prospective or retrospective data collection and a longitudinal design, found through Medline, Central, Embase, Scopus, PsycINFO, and supplemental PubMed, were eligible. Searches in individual databases covered publications' time frame from inception until early December 2016. The complete search strategy can be found in Supplementary File 1.

Searching other resources

Reference lists of included studies will be reviewed to identify any additional studies.

Selection of studies

All searches are saved in EndNote with duplicates removed. For the first level of screening, two reviewers (TM and SM, or TM and AD) will read the titles and abstracts of all the citations from the electronic database searches and remove all citations not related to the primary research objectives. For the second level of screening, each reviewer will independently assess the full

article. If the title or abstract suggests that the study might meet the inclusion criteria, each reviewer individually will assessed the full text; any conflicting views will be resolved by discussion between reviewers or by seeking advice from other researchers (AC) and experts (i.e., we are currently seeking support of the Cochrane Cognition team). Studies failing to meet the inclusion criteria will be excluded and the reason will be reported.

Data extraction and management

For studies fulfilling the inclusion criteria, two review authors (TM and SM for descriptive data, TM and AS for outcome data) will independently extract data into data collection forms grouped according to their design. The observational longitudinal studies data will be used to address all research objectives. Randomized control trial (RCT) studies will be treated as cohort studies by abstracting data from the control (e.g. untreated group) to address the second research objective (e.g. to determine the course of cognitive impairment) in patients with CNS trauma.

The abstracted data will include (1) study characteristics (author names, publication year, country of study, study setting, study design, sample size, method of measuring cognition and cognitive domains it covers, number of participants assessed for at each time point, time between assessments, and time since injury to each follow-up); (2) participant characteristics (mean age, sex, definition of CNS (i.e., TBI, SCI), localization/level of injury, and injury severity); (3) medication regimen, if reported; and (4) results (reported frequencies of cognitive impairments, and reported predictive associations between cognition and other variables) (Table 1).

Data synthesis

Results of each study will be divided into two main categories: prognostic factors of cognitive function across assessment times, and the course of cognitive (days)- function after CNS trauma.

To determine the course of cognitive dysfunction, matching assessment times (i.e. time since diagnosis when cognitive function was measured) will be grouped by their corresponding frequencies and a sample size-weighted mean frequency value will be calculated for time points with more than one contributing frequency value (i.e. more than one study reporting cognitive dysfunction at that time point). Results will also be grouped, if sufficient data exists, taking into account measurements used to assess cognitive function.

Prognostic factors associated with cognition and/or its domain(s) will be extracted from all cohorts (and untreated/without an effect RCTs). All factors influencing the course of cognitive values/status, as reported by the author, will be considered as prognostic factors. A prognostic association will be considered as significant if the reported *p*-value is ≤0.05, authors reported association as significant, or the 95% confidence intervals around a rate ratio or similar statistic did not exceed 1. Where a prognostic factor was assessed with respect to the outcome at several time-points in the same cohort, data will be extracted and reported for each follow-up time. Confounding factors (such as sex, heredity (if reported), sociodemographic characteristics, severity of injury, comorbid disorders, etc.) which may affect the generalizability of the study will be explored. The possible effects of measures used to assess cognition will be considered and special attention will be paid to measurements' psychometric properties, in particular, construct validity and reliability. Finally, given the nature of the research questions (i.e. prognostic factors, course) --which raises the issue of zero-time bias-- studies will be grouped

based on whether their baseline assessments were conducted before or after the one-month post-injury mark to best address the research questions. This time point was arbitrarily set.

Methodological quality and risk of bias assessment

Study quality will be assessed independently by two reviewers (TM and SM) using the guidelines developed by Hayden et al. (2006) for assessing prognostic studies.[28] The appraisal will consist of two steps: (1) assessment of six potential sources of bias (study participation and attrition, prognostic factors and outcome measurements, confounding measurement and account, and analyses), and designation to each "Yes," "Partly," "No," or "Unsure." Results will be assessed to determine if a study has a fatal flaw or bias; based on the results, each study would be assigned "high risk of bias" or "low risk of bias". To ensure the explicit basis for bias assessment, aspects of the trial methods on which the judgment for "high risk of bias" was based and the judgment itself-- including the trial method on which the decision of exclusion was based-- will be reported to the scientific community. For the "low risk of bias" studies, abstract data will be assessed on the relationships between measures of cognition and other variables. Any statistical measure of association (e.g., odds ratio, hazard ratio, or relative risk) will be reported (Table 2).

To summarize the level of evidence, the Scottish Intercollegiate Guidelines Network Methodology [29] will be utilized: (i) "++" when all or most of the quality criteria proposed by Hayden (2006) are fulfilled (allowing one "Partly" while appraising all potential sources of bias); (ii) "+" when some of the criteria are fulfilled; and (iii) "-" when few or none of the criteria are fulfilled (at least one "Yes"). Group (i) will be referred to as "high-quality studies" and group (ii) as "moderate-quality studies" (Table 2). Finally, the consistency of the level of evidence was

summarized. Evidence was designated "strong" when consistent findings were found in multiple "good" or one or more "excellent" quality studies and the total sample size of combined eligible studies was ≥100; "moderate" when consistent findings in multiple "fair" or one "good" quality study with a total sample ≥50, or at least one "good" or "excellent" quality study with a total sample of 50-99; "limited" when findings were found in at least one "fair," "good," or "excellent" quality study with total sample size between 25 and 49; and "unknown" when findings were of indeterminate rating, in studies with poor methodological quality or with a sample of <25.[30]

Measurements: description and properties evaluation

Using a standardized form developed for a previous systematic review on measurements' properties, [30] details of included measurements will be extracted from original studies and manuals-- where available-- and studies that evaluated their psychometric properties. The following descriptors will be extracted and reported: general characteristics, purpose and content, method of administration, respondent burden, language (and translations), psychometric properties, particularly reliability and construct validity, strength and caution for application in persons with CNS trauma.[31] Measurements will be then categorized into the following groups: (i) global measures of cognition; (ii) domain-specific measures of cognition; and (iii) multi-domain measures, which include items (subscales) of cognition among other functions.[32] Then, based on the above descriptors and using the Holmbeck et al. (2008) evidence-based assessment criteria, [33] a rating will be assigned – "well-established assessment," "approaching well-established assessment," or "promising assessment" in patients with CNS trauma-- to each included measurement.

Given the diversity in measurements of domains of cognitive function, severity and localization of CNS trauma, and the high likelihood of the diversity of statistical methodology used to express associations, a best-evidence synthesis approach [34] will be applied, synthesizing findings from studies with sufficient quality through tabulation and qualitative description. Some features falling under meta-analysis construct (i.e., sample size-weighted mean frequencies) will be considered only for the second research question (i.e., the course of cognitive deficits). As indicated above, for studies focusing on the same domain of cognitive deficits prevalence (i.e., executive function, etc.), sample size-weighted mean frequencies will be collected and matching assessment times (i.e. time post-injury that each domain of the cognitive function was measured) will be grouped with their corresponding frequencies. A sample size-weighted mean frequency value will be calculated for time points with more than one contributing frequency value (i.e. more than one study reporting values at that time point post-injury).

Dealing with missing data

Primary authors in cases of missing data will be contacted. The proportion of missing data will be reported along with reasons where indicated. In the case of duplicate publications and companion papers of a primary study, we will attempt to yield maximum scientific information by abstraction of all available data. Nonetheless, original publication (usually the oldest version) will take priority in data analysis.

Ethics and dissemination

This systematic review will provide increased scientific certainty about the prognostic factors and natural history of cognitive deficits in patients with CNS trauma, informing clinicians,

policy makers, and subsequent studies funded by the Alzheimer's Association. The strength of this systematic review protocol and research program is in its methodology, making it possible to identify associations longitudinally, thus improving the quality of inductive inferences about the natural progression of cognitive status in patients with CNS trauma. The multilevel risk of bias assessment will allow researchers to detect main flaws in the individual studies' design and inform future research on the topic of cognition in CNS trauma. During the development phase of the project, concepts and hypotheses were formulated based on a synthesis of relevant discoveries across various disciplines and previous research. The need to pay special attention to measurements used to assess cognitive function in patients with CNS trauma is noted and researchers will consider reliability and construct validity of each measure. It is evident that the content of measurements and their psychometric properties can influence estimates of cognitive impairment across time points (i.e., natural history research aim) as well and predictors of cognition in patients with CNS trauma. Likewise, earlier research highlighted that different domains of cognition are affected differently in TBI and SCI based on the injury, localization, and severity and that the perception of a person with CNS trauma can also be influenced by the duration of cognitive impairment (i.e., individuals could have adjusted to their long-term impairment, making them less likely to recognize their degree of impairment). To mitigate these issues, a variety of data related to domains of each measure will be collected and reported on. Such an approach will help researchers think about elements that constitute cognition in patients with CNS trauma, increasing the comprehensiveness of understanding and appreciation/relevance of measurement theory to the study of cognition. Further, the clinical criteria for the diagnoses of TBI and SCI will be collected and reported, as it is expected that they have a significant impact on the study results. Finally, multi-level knowledge translation

activities throughout of this research activity will be performed, ensuring that these results reach their intended knowledge users.

Limitations

Certain features of this review are open to debate. Those features include: (1) The assumption of expected heterogeneity in the primary studies with respect to sample characteristics (i.e. age, injury/localization of injury, time since injury) and the applied measurements of cognition properties and content; (2) potentially unequal sex distribution in primary studies, given that historically both TBI and SCI have been considered an injury of males; (3) age, a potential predictor of cognitive decline, may not be always reported as a continuous variable or in similar ranges; therefore, assessment of the age factor would be limited to those studies that reported it; (4) baseline assessments of cognition in patients with CNS trauma is expected to vary between studies: while the issue was predicted and attempts are to be made to mitigate the zero-time effect by reporting results with baseline assessments up to one month post-injury and after one month; separately, pre-morbid assessments of cognition are unlikely to be understood, and therefore, the generalizability of the results may remain unclear due to inadequate control of the confounding effects of premorbid cognitive functioning; (5) additional limitations relate to the inclusion of only English language articles which could affect the relevance of our findings to worldwide scientific community. Despite these limitations, this review is the first to consciously and comprehensively synthesize evidence on cognitive status in patients with CNS trauma, aiming to enrich science and advance care provided to patients with cognitive impairment stemming from traumatic brain and spinal cord injuries.

Implications

An aging population will increase the burden of CNS trauma as the number of people surviving after the injury progressively increases. While the neurological consequences of CNS trauma are well described, evidence is emerging on sex-/age-dependent associations between a prior injury (most frequently TBI) and the development of senile Alzheimer's-type dementia many years later. Diagnostic criteria, first established by the National Institute of Neurological and Communicative Disorders and Stroke, were revised in light of the discovery of new markers-- amyloid-B and tau proteins-- accumulation of which brings cognitive dysfunction and neuronal death. These markers, shown to be non-specific in Alzheimer's disease, appeared to be similar in persons with TBI and fatal familial insomnia. The reason behind these phenomena is not entirely clear. To fill the gap that is left by current evidence-based practice, the proposed study will lay the ground for further research aimed at determining the underlying basis behind any observed patterns. The significant economic and human costs of cognitive dysfunction years after CNS trauma merit the call for systematic efforts to understand the factors that contribute to its development. This research expects to motivate future investigations of AD and CNS trauma in numerous directions.

List of abbreviations

CNS, central nervous system; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RCT, randomized control trial; SCI, spinal cord injury; TBI, traumatic brain injury.

Competing interests

The authors have no conflicts of interest to declare pertaining to this research.

Authors' contributions

TM and AC contributed to the conception and design of the protocol. TM developed the idea, designed the protocol, and built the graphic data representation (e.g. tables, figure) AC provided expertise at each level and also reviewed the protocol. TM registered the protocol PROSPERO. TM wrote the first draft, which was reviewed by AC.

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Data sharing statement

Unpublished data from this study will be available will be shared with scientific/research community via Dryad digital repository (datadryad.org).

Additional material

File name: Additional file 1

File format: additional file 1.docx

Title of data: Search strategies.

Description of data: This file provides the list of search terms used to search Medline, Central, Embase, Scopus, PsycINFO, and supplemental PubMed.

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Table 1. Summary of study characteristics, including details on study sample, design, methods and results pertaining to cognitive status in patients with CNS trauma.

Author (year), Journal, Country, Setting	(1) Objective (2) Design (3) Follow up/assessment times (4) Inclusion/exclusion criteria	(1) Sample size (2) Attrition (3) Age (mean (SD)/ range), yrs (4) Sex (%M) (5) Education (6) Socioeconomic status (7) Injury severity (IS) (8) Time since injury (TSI) (9) Injury localization (IL) (10) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Confounders (1)Medications (2)Comorbidities/ measures (3) Others	Results	
					(1) Cognitive status definition (domain) (2) Frequencies, scores, cut-off score, if any	Score differences over time Notes

Table 2. Quality assessment of included studies using guidelines developed by Hayden et al, 2006.

N	Study	Study participation	Time-Zero	Study attrition	Prognostic factor	Outcome	Confounding measurement and account	Analysis	Reason for exclusion	Overall Assessment
1										

Yes – yes, sources of potential bias are presented
No – no potential bias
Not sure – not enough details were reported to make a decision (in some cases authors were contacted)
NA - not applicable according to the study design or type of analyses used

[a] – Not all required information about study attrition was provided
[b] - A study does not address the possibility of confounding
[c] – Some errors in analyses performed were observed: e.g. limited details about analyses
[d] – Completeness of follow-up was not adequate
[e] – Small sample size
[f] – Detail information about measure used was not provided or used measure was not validated
[g] – Analyses performed were not adequate
[h] – Not all important covariates were included or exclusion criteria are not completed
[i] – Baseline assessment performed after 1 month post injury

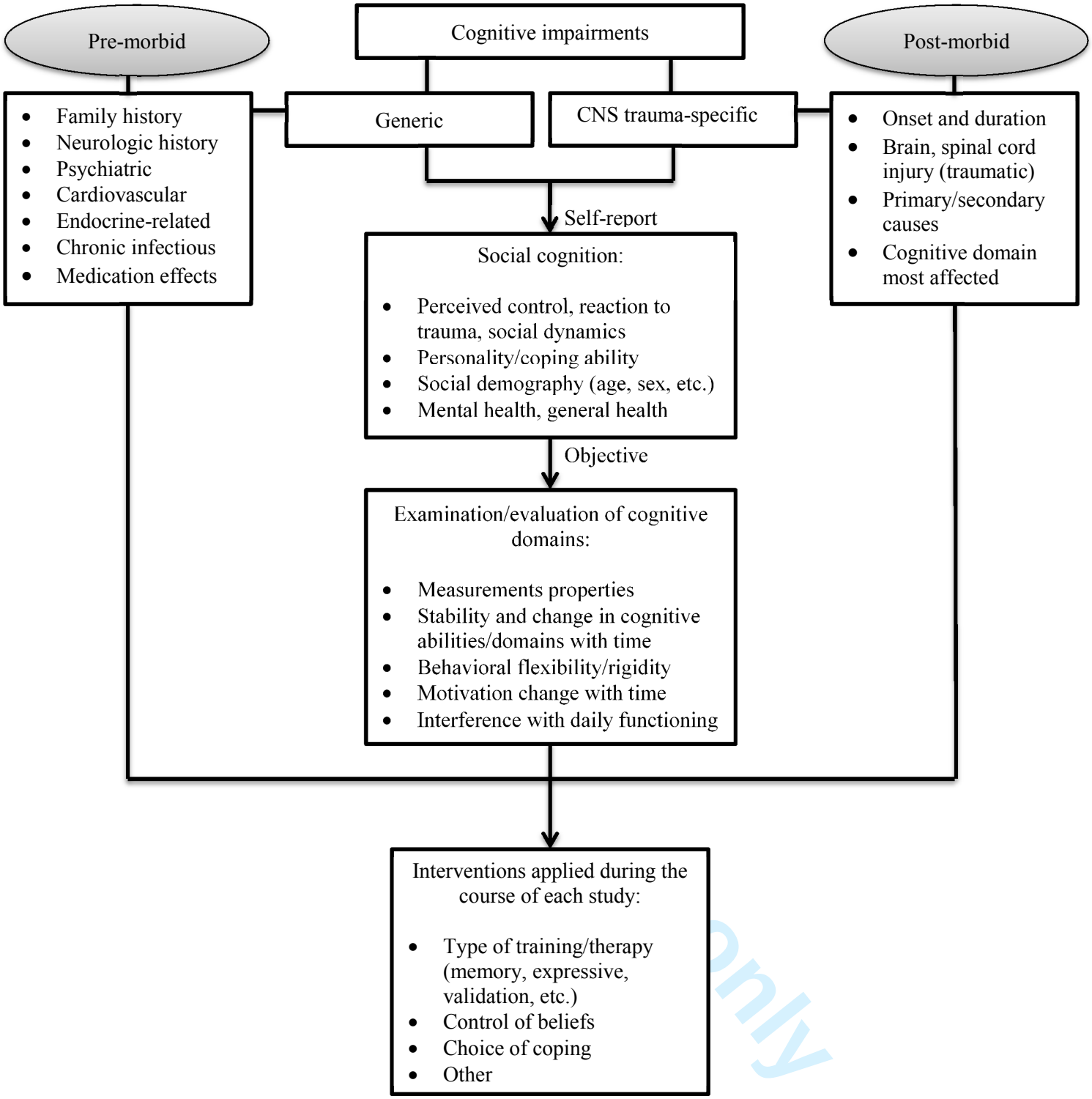


Figure 1. Conceptual model for summarizing longitudinal evidence on cognitive status in patients after central nervous system (CNS) trauma (i.e., traumatic brain injury (TBI), traumatic spinal cord injury (SCI) or both)

SEARCH DETAILS

Searches conducted in Medline and Medline in-process, Embase, Cochrane Central Register of Controlled Trials, PsycINFO. A supplemental search was conducted in Pubmed to identify non-Medline records. All searches were conducted from inception of the database to December 2016. All searches were limited to English. Searches were conducted by an Information Specialist (JB).

PRE-DUPLICATE REMOVAL

TOTAL Results: 29564

Medline: 9214

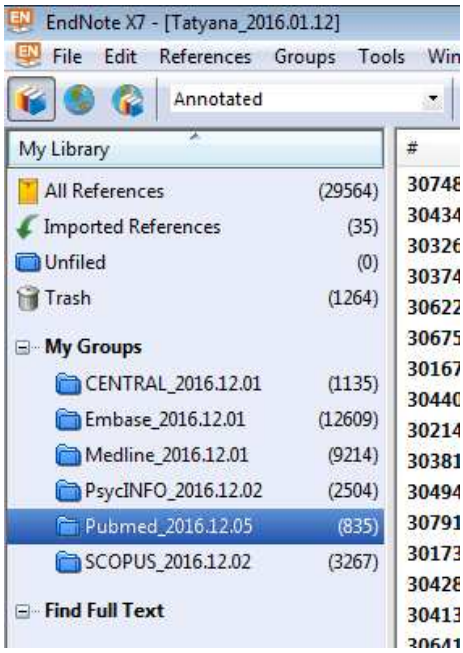
Embase: 12609

Central: 1135

PsycINFO: 2504

Scopus: 3267

Supplemental Pubmed search for NON-MEDLINE results: 835



POST-QUICK DUPLICATE REMOVAL

TOTAL Results: 22654

Duplicates Removed: 6910

Medline: 8197

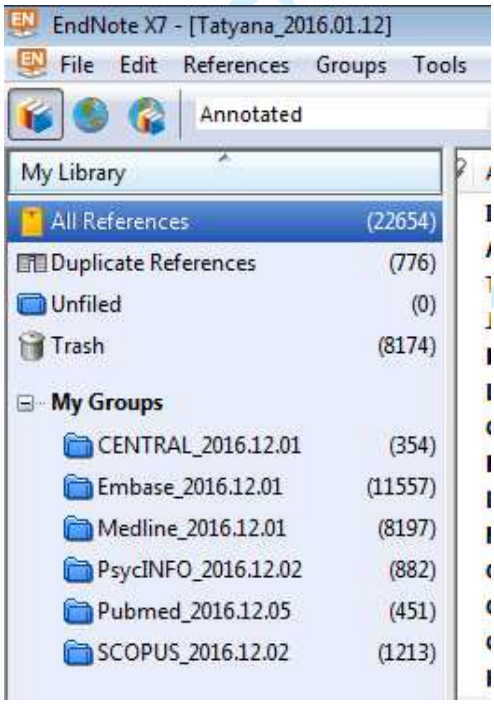
Embase: 11557

Central: 354

PsycINFO: 882

Scopus: 1213

Supplemental Pubmed search for NON-MEDLINE results: 451



SEARCH STRATEGIES

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

---

1 exp brain injuries/ (62019)

2 Craniocerebral Trauma/ (21460)

3 exp Head Injuries, Closed/ (9310)

4 exp Skull Fractures/ (20416)

5 mTBI*2.tw. (1804)

6 tbi*2.tw. (21603)
7 concuss*.tw. (6210)
8 ((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) adj2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)).tw. (175759)
9 ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)).tw. (76211)
10 or/1-9 (270610)
11 exp Spinal Cord Injuries/ (44778)
12 exp Central Cord Syndrome/ (83)
13 (myelopathy adj3 (traumatic or post-traumatic)).tw,kw. (98)
14 ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).tw,kw. (49823)
15 (spinal cord adj3 (contusion* or laceration* or transaction* or trauma* or ischemi*)).tw,kw. (7108)
16 SCI.tw,kw. (30348)
17 exp Paraplegia/ (12903)
18 exp Quadriplegia/ (7861)
19 (paraplegia* or quadriplegia* or tetraplegia*).tw,kw. (16952)
20 Spinal Cord Compression/ (10657)
21 exp Cervical Vertebrae/in (7544)
22 central spinal cord syndrome.tw,kw. (10)
23 central cord injury syndrome.tw,kw. (1)
24 or/11-23 (108760)
25 Brain Death/ (8074)
26 (brain adj2 (death or dead)).tw,kw. (7913)
27 ((vegetat* or unawareness* or "minimally conscious") adj2 state*1).tw,kw. (3285)
28 (prolonged adj2 unawareness*).tw,kw. (10)
29 25 or 26 or 27 or 28 (14590)
30 (central nervous system adj2 trauma*).tw,kw. (334)
31 (CNS adj2 trauma*).tw,kw. (529)
32 10 or 24 or 29 or 30 or 31 (384413)
33 exp Cognition/ (142070)
34 exp Cognition Disorders/ (85970)
35 neurocognit*.tw,kw. (17260)
36 (cognitive or cognition).tw,kw. (316220)
37 Executive Function/ (10349)

38 (executive adj2 (function* or control*)).tw,kw. (23269)
39 exp Arousal/ (114735)
40 arous*.tw,kw. (32131)
41 attention*.tw,kw. (343363)
42 vigilan*.tw,kw. (17025)
43 or/33-42 (818304)
44 32 and 43 (29440)
45 (dementi* or alzheim*).tw,kw. (188105)
46 exp dementia/ (154811)
47 45 or 46 (227210)
48 32 and 47 (8285)
49 exp clinical trial/ (816969)
50 exp Clinical Trials as Topic/ (323082)
51 multicenter studies as topic/ (17817)
52 (randomi?ed adj7 trial*).tw,kw. (309575)
53 (controlled adj3 trial*).tw,kw. (213828)
54 (clinical adj2 trial*).tw,kw. (309587)
55 ((single or doubl* or tripl* or treb*) and (blind* or mask*)).tw,kw. (174728)
56 ("4 arm" or "four arm").tw,kw. (928)
57 or/49-56 (1341652)
Annotation: Clinical trial SOURCE:
http://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters
58 Case-Control Studies/ (250991)
59 Control Groups/ (1791)
60 Matched-Pair Analysis/ (4926)
61 retrospective studies/ (643251)
62 ((case* adj5 control*) or (case adj3 comparison*) or control group*).tw,kw. (528797)
63 or/58-62 (1282282)
Annotation: Case control SOURCE:
http://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters
64 cohort studies/ (233586)
65 longitudinal studies/ (120931)
66 follow-up studies/ (595123)
67 prospective studies/ (464936)
68 cohort.tw,kw. (404386)
69 longitudinal.tw,kw. (206890)
70 prospective.tw,kw. (477259)

71 retrospective.tw,kw. (391544)

72 or/64-71 (1958903)

Annotation: Cohort source: http://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters

73 controlled before-after studies/ or interrupted time series analysis/ (462)

74 57 or 63 or 72 or 73 (3688853)

75 44 and 74 (8776)

76 48 and 74 (1798)

77 75 or 76 (9756)

78 limit 77 to english language (9214)

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Cochrane Central Register of Controlled Trials <October 2016>

Search Strategy:

---

1 exp brain injuries/ (1087)

2 Craniocerebral Trauma/ (244)

3 exp Head Injuries, Closed/ (156)

4 exp Skull Fractures/ (178)

5 mTBI*2.tw. (85)

6 tbi*2.tw. (1060)

7 concuss*.tw. (147)

8 ((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) adj2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)).tw. (5744)

9 ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)).tw. (4083)

10 or/1-9 (9638)

11 exp Spinal Cord Injuries/ (881)

12 exp Central Cord Syndrome/ (0)

13 (myelopathy adj3 (traumatic or post-traumatic)).tw,kw. (1)

14 ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).tw,kw. (2155)

15 (spinal cord adj3 (contusion* or laceration* or transaction* or trauma* or ischemi*)).tw,kw. (144)

16 SCI.tw,kw. (840)

17 exp Paraplegia/ (164)
18 exp Quadriplegia/ (142)
19 (paraplegia* or quadriplegia* or tetraplegia*).tw,kw. (355)
20 Spinal Cord Compression/ (77)
21 exp Cervical Vertebrae/in (3)
22 central spinal cord syndrome.tw,kw. (1)
23 central cord injury syndrome.tw,kw. (0)
24 or/11-23 (2772)
25 Brain Death/ (46)
26 (brain adj2 (death or dead)).tw,kw. (158)
27 ((vegetat* or unawareness* or "minimally conscious") adj2 state*1).tw,kw. (89)
28 (prolonged adj2 unawareness*).tw,kw. (0)
29 25 or 26 or 27 or 28 (254)
30 (central nervous system adj2 trauma*).tw,kw. (1)
31 (CNS adj2 trauma*).tw,kw. (3)
32 10 or 24 or 29 or 30 or 31 (12479)
33 exp Cognition/ (7913)
34 exp Cognition Disorders/ (3101)
35 neurocognit*.tw,kw. (1356)
36 (cognitive or cognition).tw,kw. (31319)
37 Executive Function/ (529)
38 (executive adj2 (function* or control*)).tw,kw. (2114)
39 exp Arousal/ (7319)
40 arous*.tw,kw. (3311)
41 attention*.tw,kw. (14257)
42 vigilan*.tw,kw. (1569)
43 or/33-42 (51427)
44 32 and 43 (1263)
45 (dementi* or alzheim*).tw,kw. (8989)
46 exp dementia/ (3609)
47 45 or 46 (9451)
48 32 and 47 (142)
49 44 or 48 (1328)
50 limit 49 to english language (1135)

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Embase <1974 to 2016 November 30>

Search Strategy:

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1 exp brain injury/ (158616)

2 head injury/ (47431)

3 mTBI*2.tw. (2626)

4 tbi*2.tw. (31097)

5 concuss*.tw. (7222)

6 ((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) adj2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)).tw. (215012)

7 ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)).tw. (97349)

8 or/1-7 (357773)

9 exp spinal cord injury/ (66659)

10 spinal cord ischemia/ (3451)

11 (myelopathy adj3 (traumatic or post-traumatic)).tw. (113)

12 ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).tw. (59117)

13 (spinal cord adj3 (contusion* or laceration* or transaction* or trauma* or ischemi*)).tw. (8264)

14 SCI.tw. (37297)

15 paraplegia/ (21869)

16 quadriplegia/ (15330)

17 (paraplegia* or quadriplegia* or tetraplegia*).tw. (19145)

18 central spinal cord syndrome.tw. (8)

19 central cord injury syndrome.tw. (1)

20 or/9-19 (136685)

21 brain death/ (12613)

22 (brain adj2 (death or dead)).tw. (10828)

23 ((vegetat* or unawareness* or "minimally conscious") adj2 state*1).tw. (4046)

24 (prolonged adj2 unawareness*).tw. (12)

25 21 or 22 or 23 or 24 (19386)

26 (central nervous system adj2 trauma*).tw. (360)

27 (CNS adj2 trauma*).tw. (602)

28 8 or 20 or 25 or 26 or 27 (499222)

29 exp cognition/ (1941327)
30 cognitive defect/ (138285)
31 neurocognit*.tw. (21396)
32 (cognitive or cognition).tw. (380936)
33 executive function/ (26536)
34 (executive adj2 (function* or control*)).tw. (28576)
35 arousal/ (41038)
36 arous*.tw. (38982)
37 attention*.tw. (399204)
38 vigilan*.tw. (21941)
39 or/29-38 (2408211)
40 exp dementia/ (300566)
41 (dementi* or alzheim*).tw. (224692)
42 40 or 41 (323799)
43 39 or 42 (2608334)
44 28 and 43 (96287)
45 exp clinical trial/ (1281583)
46 exp "clinical trial (topic)"/ (267609)
47 (randomi?ed adj7 trial*).tw. (373380)
48 (controlled adj3 trial*).tw. (250872)
49 (clinical adj2 trial*).tw. (384066)
50 ((single or doubl* or tripl* or treb*) and (blind* or mask*)).tw. (219774)
51 ("4 arm" or "four arm").tw. (1207)
52 exp case control study/ (140524)
53 control group/ (263620)
54 clinical study/ or retrospective study/ (765384)
55 ((case* adj5 control*) or (case adj3 comparison*) or control group*).tw. (668069)
56 cohort analysis/ (303792)
57 longitudinal study/ (106182)
58 follow up/ (1232689)
59 prospective study/ (388763)
60 cohort.tw. (568512)
61 longitudinal.tw. (231900)
62 prospective.tw. (629993)
63 retrospective.tw. (576605)
64 or/45-63 (4750710)
65 44 and 64 (27389)

66 limit 65 to english language (26109)
67 limit 66 to embase (12609)
****

PsycINFO <1806 to November Week 4 2016>
Search Strategy:
---
1 exp traumatic brain injury/ (15045)
2 exp head injuries/ (5474)
3 mTBI*2.tw. (1222)
4 tbi*2.tw. (8250)
5 concuss*.tw. (2204)
6 ((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) adj2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)).tw. (50900)
7 ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)).tw. (4816)
8 or/1-7 (55142)
9 exp spinal cord injuries/ (4891)
10 exp Spinal Cord/ and exp Ischemia/ (63)
11 (myelopathy adj3 (traumatic or post-traumatic)).tw. (7)
12 ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).tw. (5852)
13 (spinal cord adj3 (contusion* or laceration* or transaction* or trauma* or ischemi*)).tw. (848)
14 SCI.tw. (3541)
15 paraplegia/ (534)
16 quadriplegia/ (188)
17 (paraplegia* or quadriplegia* or tetraplegia*).tw. (1302)
18 central spinal cord syndrome.tw. (0)
19 central cord injury syndrome.tw. (0)
20 or/9-19 (9003)
21 (brain adj2 (death or dead)).tw. (581)
22 ((vegetat* or unawareness* or "minimally conscious") adj2 state*1).tw. (1069)
23 (prolonged adj2 unawareness*).tw. (2)
24 21 or 22 or 23 (1611)
25 (central nervous system adj2 trauma*).tw. (56)

26 (CNS adj2 trauma*).tw. (112)
27 8 or 20 or 24 or 25 or 26 (64469)
28 cognition/ (26647)
29 cognitive impairment/ (29197)
30 neurocognit*.tw. (11048)
31 (cognitive or cognition).tw. (385119)
32 exp executive function/ (11055)
33 (executive adj2 (function* or control*)).tw. (21794)
34 physiological arousal/ (6451)
35 exp attention/ (59769)
36 arous*.tw. (33693)
37 attention*.tw. (232302)
38 vigilan*.tw. (8933)
39 or/28-38 (631554)
40 (dementi* or alzheim*).tw. (82601)
41 exp dementia/ (63311)
42 alzheimer's disease/ (38544)
43 41 or 42 (63311)
44 39 or 43 (668410)
45 27 and 44 (17822)
46 clinical trials/ (10032)
47 (randomi?ed adj7 trial*).tw. (40375)
48 (controlled adj3 trial*).tw. (33223)
49 (clinical adj2 trial*).tw. (28656)
50 ((single or doubl* or tripl* or treb*) and (blind* or mask*)).tw. (25275)
51 ("4 arm" or "four arm").tw. (125)
52 experiment controls/ (867)
53 retrospective studies/ (381)
54 ((case* adj5 control*) or (case adj3 comparison*) or control group*).tw. (81862)
55 exp Longitudinal Studies/ (15780)
56 longitudinal studies/ (15306)
57 Followup Studies/ (12353)
58 cohort.tw. (49483)
59 longitudinal.tw. (90266)
60 prospective.tw. (48210)
61 retrospective.tw. (28144)
62 or/46-61 (341322)

63 45 and 62 (2588)

64 limit 63 to english language (2504)

****

SCOPUS (3267 results on 2016.12.02)

((((TITLE-ABS-KEY("central spinal cord syndrome")) OR (TITLE-ABS-KEY("central cord injury syndrome")) OR ((TITLE-ABS-KEY(mTBI* OR tbi* OR concuss*)) OR (TITLE-ABS-KEY(((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) NEAR/2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell*)))) OR (TITLE-ABS-KEY(((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) NEAR/2 (oedema* or edema* or fracture* or contusion* or commotion* or pressur*)))) OR (TITLE-ABS-KEY(((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) NEAR/2 (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)))) OR (TITLE-ABS-KEY((myelopathy NEAR/3 (traumatic or post-traumatic)))) OR (TITLE-ABS-KEY(((spine or spinal) NEAR/3 (fracture* or wound* or trauma* or injur* or damag*)))) OR (TITLE-ABS-KEY((spinal cord NEAR/3 (contusion* or laceration* or transaction* or trauma* or ischemi*)))) OR (TITLE-ABS-KEY((paraplegia* or quadriplegia* or tetraplegia*)))) OR (TITLE-ABS-KEY((brain NEAR/2 (death or dead)))) OR (TITLE-ABS-KEY(((vegetat* or unawareness* or "minimally conscious") NEAR/2 state*))) OR (TITLE-ABS-KEY((prolonged NEAR/2 unawareness*))) OR (TITLE-ABS-KEY((central nervous system NEAR/2 trauma*))) OR (TITLE-ABS-KEY((CNS NEAR/2 trauma*)))) AND (((TITLE-ABS-KEY(cognitive or cognition OR neurocogniti*) OR TITLE-ABS-KEY((executive NEAR/2 (function* or control*))))) OR (TITLE-ABS-KEY(arous* OR attention* OR vigilan* OR dementi* or alzheim*)))) AND (((TITLE-ABS-KEY((controlled NEAR/3 trial*)) OR TITLE-ABS-KEY((clinical NEAR/2 trial*)) OR TITLE-ABS-KEY(((single or doubl* or tripl* or treb*) and (blind* or mask*))) OR TITLE-ABS-KEY(("4 arm" or "four arm")) OR TITLE-ABS-KEY((case* NEAR/5 control*)) OR TITLE-ABS-KEY((case NEAR/3 comparison*)) OR TITLE-ABS-KEY(control group*) OR TITLE-ABS-KEY(cohort* OR longitudinal OR prospective OR retrospective))) OR (TITLE-ABS-KEY(random*)) OR (TITLE-ABS-KEY((randomized NEAR/7 trial*) OR (randomised NEAR/7 trial*)))) AND (LIMIT-TO(LANGUAGE,"English"))

Pubmed Supplimental Search (835 results on 2016.12.05)

((((((((((((((((((((mTBI[Text Word] OR TBI[Text Word] OR concuss[Text Word])))) OR ((((head*[Text Word] OR cerebr*[Text Word] OR cranium[Text Word] OR cranial[Text Word] OR capitis*[Text Word] OR brain*[Text Word] OR forebrain*[Text Word] OR skull*[Text Word] OR hemispher*[Text Word] OR intracran*[Text Word] OR orbit*[Text Word])) AND (injur*[Text Word] OR trauma*[Text Word] OR lesion*[Text Word] OR damag*[Text Word] OR wound*[Text Word] OR destruction*[Text Word] OR swell*[Text Word] OR oedema*[Text Word] OR edema*[Text Word] OR fracture*[Text Word] OR contusion*[Text Word] OR commotion*[Text Word] OR pressur*[Text Word]))))) OR (((brain*[Text Word] OR cerebr*[Text Word] OR intracerebr*[Text Word] OR cranium[Text Word] OR cranial[Text Word] OR intracran*[Text Word] OR head*[Text Word] OR subarachnoid*[Text Word] OR subdural*[Text Word] OR epidural*[Text Word] OR extradural*[Text Word])) AND (haematoma*[Text Word] OR hematoma*[Text Word] OR hemorrhag*[Text Word] OR haemorrhag*[Text Word] OR pressur*[Text Word] OR bleed*[Text Word]))) OR ((traumatic myelopathy[Text Word]) OR post-traumatic myelopathy[Text Word])) OR (((spine[Text Word] OR spinal[Text Word])) AND (fracture*[Text Word] OR wound*[Text Word] OR trauma*[Text Word] OR injur*[Text Word] OR damag*[Text Word]))) OR ((spinal cord[Text Word]) AND (contusion*[Text Word] OR laceration*[Text Word] OR transaction*[Text Word] OR trauma*[Text Word] OR ischemi*[Text Word]))) OR ((((SCI[Text Word]) OR (paraplegia*[Text Word] OR quadriplegia*[Text Word] OR tetraplegia*[Text Word])))))) OR (("central spinal cord syndrome"[Text Word]) OR "central cord injury syndrome"[Text Word])) OR ((brain death[Text Word]) OR brain dead[Text Word])) OR prolonged unawareness*[Text Word]) OR (((vegetat* state*[Text Word]) OR "state of unawareness"[Text Word]) OR minimally conscious state*[Text Word])) OR central nervous system trauma*[Text Word]) OR CNS Trauma*[Text Word])) AND (((((((neurocognit*[Text Word]) OR (cognition[Text Word] OR cognitive[Text Word])) OR executive function*[Text Word]) OR arous*[Text Word]) OR attention*[Text Word]) OR vigilan*[Text Word]) OR dement*[Text Word]) OR alzheim*[Text Word])))) AND ((((((trial*[Text Word] OR blind*[Text Word] OR mark*[Text Word] OR random*[Text Word])) OR case control*[Text Word]) OR case comparison*[Text Word]) OR control group*[Text Word]) OR (cohort[Text Word] OR longitudinal[Text Word] OR retrospective[Text Word] OR prospective[Text Word])))) AND ((((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])))) AND English[lang])) AND English[lang])

BMJ Open

The course and prognostic factors of cognitive status after central nervous system trauma: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017165.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Jun-2017
Complete List of Authors:	Mollayeva , Tatyana; Toronto Rehabilitation Institute, Research; University of Toronto, Rehabilitation Sciences Institute Pacheco, Nicole; Acquired Brain Injury and Society Research Toronto Rehabilitation Institute-University Health Network, McMaster University D'Souza, Andrea ; Acquired Brain Injury and Society Research Toronto Rehabilitation Institute-University Health Network, Research Colantonio, Angela; University of Toronto, Rehabilitation Science Institute
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Rehabilitation medicine, Research methods, Patient-centred medicine
Keywords:	traumatic brain injury, spinal cord injury, prognosis, cognition, Ia level of evidence, sex differences

Title: The course and prognostic factors of cognitive status after central nervous system trauma: A systematic review protocol

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Abstract

Introduction: Traumatic brain injury (TBI) is among the most disabling injuries, resulting in a range of cognitive impairments. Traumatic spinal cord injury (SCI) often occurs in conjunction with TBI; the two are best considered together in the context of trauma to the central nervous system (CNS). Despite strong indications of cognitive dysfunction in CNS trauma, little is known about its natural history or relationship with other factors. The current protocol outlines a strategy for a systematic review of the current evidence examining CNS trauma as a prognostic factor of cognitive status in the adult population.

Methods and analysis: The review will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. All peer-reviewed English language publications with a longitudinal design that focus on cognition in adults (ages 18 and older) with either TBI, or SCI, or both from inception to December 2016 found through Medline, Central, Embase, Scopus, PsycINFO, supplemental PubMed and bibliographies of identified articles will be considered eligible. Quality will be evaluated using published guidelines. Results will be grouped by: (a) prognostic factors of cognitive deficits; and (b) development of, or time until development of, cognitive deficit in patients with CNS trauma. Close attention will be paid to the evaluative properties of the measurements used to assess cognition.

Ethics and dissemination: The authors will publish findings from this review in a peer-reviewed scientific journal (s) and present the results at national and international conferences. This work will advance scientific certainty regarding natural history and prognostic factors of cognitive

status in males and females with CNS trauma, informing clinicians, policy makers, and future researchers on the topic.

Registration details: CRD42017055309.

Keywords: traumatic brain injury; traumatic spinal cord injury; cognition; Alzheimer's disease; prognosis; natural history; males, females; Ia level of evidence; systematic review

Strengths and limitations of this study

- During the developmental phase of the project, concepts and hypotheses were formulated based on a synthesis of relevant discoveries across various disciplines and previous research
- The multilevel risk of bias assessment allows to detect main flaws in the individual studies' design and inform future research on the topic
- Special attention will be paid to measurements used to assess cognitive function in patients with CNS trauma
- We acknowledge expected heterogeneity in the primary studies, with variation between studies in sample characteristics, as well as in definitions of primary outcome
- Severe CNS trauma cases are expected to be underrepresented in the inception cohorts and the majority of the patients are expected to be males; this would limit the precision of estimates and generalizability of results
- We acknowledge the chance of publication bias and a bias associated with exaggerating the estimate of the actual effect due to inclusion of only peer-reviewed studies published in English.

Introduction

Description of the condition

Central nervous system (CNS) trauma – including traumatic brain injury (TBI) and traumatic spinal cord injury (SCI) [1]– has been implicated as a risk factor for a range of cognitive impairments, particularly in the domains of attention, memory, emotion, and behaviour.[2-4] Recent studies have presented solid evidence that patients with a history of CNS trauma may develop various neurodegenerative disorders including Alzheimer's disease (AD).[4-6] However, our understanding of *when* (i.e., post-injury timeframe) and *in whom* (i.e., characteristic of an injured person) AD dementia develops after CNS trauma (TBI, SCI, or both) -- with respect to sustained and/or degrading cognitive impairment post-injury- remains limited,[4, 7, 8] and reported rates of cognitive decline after TBI and traumatic SCI are quite variable.[9, 10] This variability has prompted interest in longitudinal studies that have focused on cognition in persons with CNS trauma across their post-injury lifespans.[11, 12] To assess longitudinal changes in cognitive status post-injury, evaluative instruments or composite tests that are able to measure these changes in cognition after CNS trauma over time are crucial.[13] A recent study was conducted on the factors associated with the rate of decline and evolution from mild cognitive impairment (MCI) to AD dementia in elderly patients, estimated from three common global measures of cognition. This study appeared to have findings that varied depending on the evaluative measure used.[14] The study of measurements' properties of cognition in patients with CNS trauma is still in its infancy, and-when reporting cognitive decline associated with CNS trauma- evaluative properties of measurements have rarely been discussed or acknowledged. In order to come to a robust

conclusion on the course of cognitive status after TBI, appropriately evaluating the properties of measurements must be done in the process of data synthesis.

Description of measurements' needs

Under the framework of Kirshner and Guyatt, measurements used to evaluate change over time in any domain should be: (1) reliable (i.e., possess adequate internal consistency and responsiveness test-retest reliability in the population of interest) and (2) correspond closely to the construct to be measured. [15] Until now, research on cognitive status after TBI has focused on patients' 'capacity' (i.e., what the patient can do when he or she is invited to), 'perceived ability' (i.e., what the patient thinks they can do), and 'cognitive activity' (i.e., what the patient can actually do), which are different constructs.[16] As such, when assessing CNS trauma-related deficits in language, perception, memory, reasoning, attention, etc., a solid knowledge and understanding of the tests applied to measure these specific deficits is of great importance.

How sex might affect results

Another important area to consider in the study of cognition after CNS trauma and the risk of development of AD is sex (i.e., biological differences between males and females). Often, CNS trauma is considered to be an injury of males. Overall and in almost every age group, TBI and SCI more frequently occurs in males than in females.[17, 18] These differences may reflect the high rate of general injuries among males and/or differences in risk taking societal roles and behaviours, that are relevant to the construct of gender, rather than sex.[19] In contrast, the preponderance of current evidence indicates that an increased risk of AD exists in females, which is even more pronounced at an advanced age.[20] The reason behind sex differences in the

risk of AD is unknown, especially because many human studies support the notion that oestrogen, especially brain oestradiol, improves and conserves cognitive function including memory retention.[21,22] Consistent with this theoretical gap, women's traditional inequalities and disadvantages in access to and control of resources have resulted in the present scarcity of data on women with CNS trauma, [23-25] and our knowledge of whether women and men are at different risks of developing cognitive impairments after CNS trauma due to differing gendered vulnerabilities (i.e., injury risk, severity, access to power and resources post-injury, help-seeking behaviours, health care system use, intervention response, and rehabilitation outcomes) or conversely, being protected from it, is limited. [26] Therefore, an awareness of how cognitive status after CNS trauma varies by, or parallels by sex across time points when taking gender into account is critical to advance CNS trauma and AD research.

How age might affect results

Age is the single most important risk factor for various domains of cognitive decline across diverse cultural groups and geographic regions, including memory, language, processing speed, and executive functioning.[27] CNS neurogenesis is known to change during one's lifespan, and this is likely reflected in age-related risk for cognitive decline. However, research has highlighted that associations may vary across cohorts, [27] suggesting that different rates of cognitive decline might contribute to the global variation in age-related dementia prevalence. Likewise, consistent associations of cognitive function with genetics, cardiovascular health, and lifestyle have been accumulated in research, each of which is relevant to the discussion of the higher likelihood of being involved in an injury with CNS outcome.[28] The need to explore how

age-dependent factors associate with other risk factors in patients with CNS trauma cannot be undermined.

Objectives

The aim of the current study is to identify, appraise, and synthesize all available longitudinal studies relevant to the discussion of cognitive function in males and females following CNS trauma in an attempt to: (1) document the course of cognitive status (decline, improvement, stability, fluctuations, etc.) in patients with CNS trauma as time since injury progresses; (2) determine prognostic factors of development of cognitive deficits in patients with CNS trauma from the baseline to follow-up; and (3) summarize sex- and age-stratified results pertaining to the course of cognitive status in patients with CNS trauma. Finally, the current study intends to provide a systematic consideration, solid description, and in-depth understanding of the range of measurements utilized to assess cognition in CNS trauma research. This study also aims to report on these instruments' test-retest reliability and construct validity, which are key psychometric properties necessary for evaluative purposes. This study is operating under the hypothesis which states that acutely derived CNS trauma variables alone (i.e., age, sex, TBI mechanism, level of SCI, injury severity, etc.), are not sufficient to accurately predict cognitive status and/or its domains after CNS trauma. Furthermore, it is hypothesized that cognitive deficits following CNS trauma are the product of diverse external and internal influences acting on a genetically determined substrate and that many of these external influences are modifiable (Figure 1). The current protocol outlines a strategy for this systematic review.

Methods and analysis

The review will be conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] In accordance with these guidelines, the systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) [30] on January 16, 2017 (registration number, CRD42017055309).

Criteria for considering studies for this review

Types of studies and setting

- Peer-reviewed published longitudinal studies (i.e., studies that have cognition on at least two separate occasions) in English, conducted in adults with a clinical diagnosis of CNS trauma (TBI, or SCI, or both) regardless of research setting. Studies of SCI of only traumatic origin will be considered.
- Studies that were primarily designed to investigate the course and predictors of cognitive deficits in patients with CNS trauma.

Participants and assessment

- Males and females aged 18 years or older, with TBI or SCI or both, defined by clinical criteria.
- Any means of clinical diagnosis or standardised assessment of cognition. For more information, we refer the reader to section *Constructs of cognitive function, cognitive deficits, and AD*

Types of outcome measures

The primary outcomes include (i) cognitive function or (ii) development of-or time until development of-possible or probable cognitive deficit in patients with CNS trauma.

Constructs of cognitive function, cognitive deficits, and AD

Cognitive function is referred to as the mental action or process of acquiring knowledge and understanding through thoughts, experiences, and senses.[31] It encompasses processes such as knowledge, attention, memory and working memory, judgment and evaluation, reasoning and "computation," problem solving and decision making, comprehension and production of language, etc.[31] Any measures of cognition (or its domains) (e.g., the presence or absence of cognitive deficits determined using a single question, a case definition of any measure of cognitive domain by a standardized clinical tool, or cognitive domain scores reported as a continuous variable) will be considered.

Development of a cognitive deficit in patients with CNS trauma will be assigned based on the Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-V) criteria for MCI, namely: (1) evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on: (i) concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and (ii) modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment; and (2) the cognitive deficits do not interfere with the capacity for independence in everyday activities (i.e.,

complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required.[32]

Alzheimer's disease or dementia

This systematic review concerns sustained and/or degrading cognitive function post-injury, as well as cognitive complaints of uncertain clinical significance (i.e., MCI with questionable deficits on quantitative tests) starting early after the injury. While at this time, there is sparse data on how many individuals with CNS trauma will eventually progress to definite AD, some TBI patients with MCI have shown, on autopsy, findings of histopathological AD.[33, 34] The animal literature has also demonstrated evidence of features of AD arising shortly after the onset of TBI.[35, 36] These results suggest that in patients with CNS trauma, MCI detected very early post-injury may represent the initial clinical presentation of AD. As part of this review, close attention will be paid to patients at risk of having a high probability of AD – patients with MCI at baseline/early after injury (particularly mild injury severity cases) but who have progressed rapidly into cognitive deficits within first few years post-injury, characterized by uniform progression of cognitive impairments in several domains (i.e., memory, speech) and impaired activities of daily living. Further, the term dementia refers to a syndrome of brain dysfunction that is progressive, and has many possible causes; we intend to study CNS trauma as a risk for cognitive decline, with an open view to the natural course of cognitive status (improvement, decline, or relative stability) with time. Consequently, any sustained decline in cognitive status longitudinally is more reasonable in the discussion of risk of AD rather than dementia.

Exclusion criteria

Types of studies:

- Studies investigating cognition after CNS trauma due to secondary pathological processes (e.g., oedema, intracranial haemorrhages, ischemia/infarction, vegetative/minimally conscious state, and systemic intracranial conditions)..
- Letters to editors and reviews without data, case reports, or reports; conference abstracts, articles with no primary data, theses, grey literature, and unpublished manuscripts.
- Historical limiter (1993) is set to mTBI diagnosis, given that the diagnostic criteria for mTBI were introduced by the American Congress of Rehabilitation Medicine in 1993 only.[37]

Search methods for the identification of studies

In collaboration with clinical experts and a medical information specialist, a comprehensive search strategy for studying cognitive function in CNS trauma was developed. All English language, peer-reviewed studies with prospective or retrospective data collection and a longitudinal design, found through Medline, Central, Embase, Scopus, PsycINFO, and supplemental PubMed, were eligible. Searches in individual databases covered publications' time frame from inception until early December 2016. The complete search strategy can be found in Supplementary File 1. We refer the reader to the Cochrane handbook and other published sources for justification of the selected databases.

Searching other resources

Reference lists of included studies will be reviewed to identify any additional studies.

Selection of studies

All searches will be saved in EndNote with duplicates removed. For the first level of screening, two reviewers (TM and SM, or TM and AD) will read the titles and abstracts of all the citations from the electronic database searches and remove all citations not related to the primary research objectives. For the second level of screening, each reviewer will independently assess the full article. If the title or abstract suggests that the study might meet the inclusion criteria, each reviewer individually will assess the full text; any conflicting views will be resolved by discussion between reviewers and systematic review team members. If needed, clinical and research experts on the field will be contacted. Studies failing to meet the inclusion criteria will be excluded and the reason for exclusion will be reported.

Data extraction and management

For studies fulfilling the inclusion criteria, two review authors (AS or NP for descriptive data, TM and AS or NP for outcome data) will independently extract data into data collection forms grouped according to study design. The data from observational longitudinal studies will be used to address all research objectives. Randomized control trial (RCT) studies will be treated as cohort studies by abstracting data from the control (e.g. untreated group) to address the first research objective (e.g. to determine the course of cognitive deficits) in patients with CNS trauma.

The abstracted data will include: (1) study characteristics (author names, publication year, country of study, study setting, study design, sample size, method of measuring cognition and cognitive domains covered, number of participants assessed for at each time point, time between

assessments, and time since injury to each follow-up); (2) participant characteristics (mean age, sex, education, definition of CNS (i.e., TBI, SCI), localization/level of injury, and injury severity); (3) medication regimen, if reported; and (4) results (reported frequencies of cognitive impairments, and all reported predictive associations between cognition and other variables (i.e., age, sex, education, TBI severity, comorbidity, etc.).

Data synthesis

Results of each study will be divided into two main categories: the course of cognitive deficits after CNS trauma and prognostic factors of cognitive function across assessment times.

To determine the course of cognitive deficits, matching assessment times (i.e. time since diagnosis when cognitive function was measured) will be grouped by their corresponding frequencies and a sample size-weighted mean frequency value will be calculated for time points with more than one contributing frequency value (i.e. more than one study reporting cognitive deficit at that time point). Results will also be grouped, if sufficient data exists, taking into account measurements used to assess cognitive function.

Prognostic factors associated with cognition and/or its domain(s) will be extracted from all cohorts (and untreated/without an effect RCTs). All factors influencing the course of cognitive values/status, as reported by the author, will be considered as prognostic factors. A prognostic association will be considered as significant if the reported *p*-value is ≤0.05, authors reported association as significant, or the 95% confidence intervals around a rate ratio or similar statistic did not exceed 1, when adjusted for at least age and sex (i.e., minimum set of confounders) in a multivariable model. Where a prognostic factor was assessed with respect to the outcome at

several time-points in the same cohort, data will be extracted and reported for each follow-up time.

Confounding effect

To address our research objective regarding the effect of CNS trauma on cognitive status, we will evaluate the literature regarding putative negative effects in the light of other factors known to affect cognition; age and sex will be considered as the minimum set of confounders associated with cognition at each time point. All other confounding factors (such as medication/ illicit drug use effect, comorbidities) that may affect the generalizability of the study and interpretation of results will be explored and clearly described. In addition, the possible effects of measures used to assess cognition will be considered and special attention will be paid to measurements' psychometric properties, particularly construct validity and test-retest reliability. Finally, given the nature of the research questions (i.e. prognostic factors, course), which raises the issue of zero-time bias, studies will be grouped based on whether their baseline assessments were conducted before or after the one-month post-injury mark. This time point was arbitrarily set.

Methodological quality and risk of bias assessment

Study quality will be assessed independently by two experienced reviewers using the Quality in Prognosis Studies (QUIPS) guidelines.[38,39] The appraisal will consist of two steps: (1) assessment of six potential sources of bias (study participation and attrition, prognostic factors and outcome measurements, confounding measurement and account, and analyses), and (2) grading the presence of potential biases as "Yes," "Partly," "No," or "Unsure." To summarize the level of evidence, the Scottish Intercollegiate Guidelines Network Methodology [39] will be

utilized: (i) "++" when all or most of the quality criteria proposed by QUIPS are fulfilled (allowing one "Partly" while appraising all potential sources of bias); (ii) "+" when some of the criteria are fulfilled; and (iii) "-" when few or none of the criteria are fulfilled (at least one "Yes"). As proposed by Scottish Intercollegiate Guidelines Network (SIGN), studies with retrospective design will not receive a "++" rating. Group (i) will be referred to as "high-quality studies" and group (ii) as "moderate-quality studies". Results will be reported in a table format.

Finally, the consistency of the level of evidence will be summarized. Evidence will be designated "strong" when consistent findings are found in multiple "moderate-quality"" or one or more "high-quality" studies" and the total sample size of combined eligible studies is ≥100; "moderate" when consistent findings in multiple "moderate-quality" or one "high-quality" quality study with a total sample ≥50, or at least one "moderate-quality" or "high-quality" quality study with a total sample of 50-99; "limited" when findings are found in at least one "moderate-quality," or "high-quality" quality study with total sample size between 25 and 49; and "unknown" when findings are of indeterminate rating, in studies with poor methodological quality or with a sample of <25.[39] To ensure the explicit basis for bias assessment, aspects of the trial methods on which the judgment for "high risk of bias" will be based as well as the judgment itself- including the trial method on which the decision of exclusion was based- will be reported .

Measurements: description and properties evaluation

Using a standardized form developed for a previous systematic review on measurements' properties,[40] details of included measurements will be extracted from original studies and manuals-where available-and studies that evaluated their psychometric properties. The following descriptors will be extracted and reported: general characteristics, purpose and content, method

of administration, respondent burden, language (and translations), psychometric properties, particularly test-retest reliability and construct validity, and strengths and cautions for application in persons with CNS trauma.[40] Measurements will then be categorized into the following groups: (i) global measures of cognition; (ii) domain-specific measures of cognition; and (iii) multi-domain measures, which include items (subscales) of cognition among other functions.[41] Based on the above descriptors and using the Holmbeck et al. (2008) evidence-based assessment criteria, [42] a rating will be assigned – "well-established assessment," "approaching well-established assessment," or "promising assessment" in patients with CNS trauma– to each included measurement.

Given the diversity in measurements of domains of cognitive function, severity and localization of CNS trauma, as well as the high likelihood of the diversity of statistical methodology used to express associations, a best-evidence synthesis approach [43] will be applied, synthesizing findings from studies with sufficient quality through tabulation and qualitative description. Some features falling under meta-analysis constructs (i.e., sample size-weighted mean frequencies) will be considered only for the first research question (i.e., the course of cognitive deficits). As indicated above, for studies focusing on the same domain of cognitive deficits prevalence (i.e., executive function, etc.), sample size-weighted mean frequencies will be collected and matching assessment times (i.e. time post-injury that each domain of the cognitive function was measured) will be grouped with their corresponding frequencies. A sample size-weighted mean frequency value will be calculated for time points with more than one contributing frequency value (i.e. more than one study reporting values at that time point post-injury).

Dealing with missing data

In cases of missing data, primary authors will be contacted. The proportion of missing data will be reported along with reasons, where indicated. In the case of duplicate publications and companion papers of a primary study, we will attempt to yield maximum scientific information by abstraction of all available data. Nonetheless, original publication (usually the oldest version) will take priority in data analysis.

Ethics and dissemination

This systematic review will provide increased scientific certainty about the prognostic factors and natural history of cognitive deficits in patients with CNS trauma, informing clinicians, policy makers, and subsequent studies funded by the Alzheimer's Association. The strength of this systematic review protocol and research program is in its methodology, making it possible to identify associations longitudinally, thus improving the quality of inductive inferences about the natural progression of cognitive status in patients with CNS trauma. The multilevel risk of bias assessment will allow researchers to detect main flaws in the designs of individual studies and to inform future research on the topic of cognition in CNS trauma. During the development phase of the project, concepts and hypotheses were formulated based on a synthesis of relevant discoveries across various disciplines. It is evident that the content of measurements and their psychometric properties can influence estimates of cognitive impairment across time points (i.e., natural history research aim) as well as the predictors of cognition in patients with CNS trauma. Likewise, earlier research has highlighted that different domains of cognition are affected differently in TBI and SCI based on type, localization, and severity of injury and that the perception of a person with CNS trauma can also be influenced by the duration of cognitive impairment (i.e., individuals could have adjusted to their long-term impairment, making them less

likely to recognize their degree of impairment). To mitigate these issues, a variety of data related to the domains of each measure will be collected and reported on. This approach will help researchers think about elements that constitute cognition in patients with CNS trauma, increasing the comprehensiveness of understanding and the appreciation/relevance of the measurement theory in the study of cognition. Finally, multi-level knowledge translation activities (publications, presentations, research-knowledge user collaborations) throughout this research activity will be performed. This will ensure that the program results reach their intended knowledge users with the goal of informing innovations in AD and CNS trauma research, health policy and practice.

Limitations

Certain features of this review are open to debate. Those features include: (1) The assumption of expected heterogeneity in the primary studies with respect to sample characteristics (i.e. age, injury/localization of injury, time since injury) and the applied measurements of cognition properties and content; (2) potentially unequal sex distribution in primary studies, given that historically both TBI and SCI have been considered an injury specific to males; (3) age, a potential predictor of cognitive decline, may not be always reported as a continuous variable or in similar ranges; therefore, assessment of the age factor would be limited to those studies that reported it; (4) potential confounders, such as medication effects/illicit substance use and comorbidity load, may not be adequately explored given the lack of consistent reports and effect consideration in TBI research; [44] nonetheless, where possible, such effects will be explored; (5) baseline assessments of cognition in patients with CNS trauma are expected to vary between studies: while the issue was predicted and attempts will be made to mitigate the zero-time effect by reporting results with baseline assessments up to one month post-injury and after

one month; separately, pre-morbid assessments of cognition are unlikely to be understood, and therefore, the generalizability of the results may remain unclear due to inadequate control of the confounding effects of premorbid cognitive functioning; (6) additional limitations relate to the exclusion of grey literature, non- English language articles, and unpublished manuscripts and their potentially relevant results; this decision was based on the extensive number of studies identified within databases we have searched, as well as limited empiric evidence about the potential impact of selective searching and inclusion of these works on the results of systematic reviews.[45]

Despite the outlined limitations, this is the first review of its kind to consciously and comprehensively synthesize evidence on the cognitive status in patients with CNS trauma, aiming to advance scientific knowledge in the field and enrich the care provided to patients with cognitive impairments stemming from traumatic brain and spinal cord injuries.

Implications

An aging population will increase the burden of CNS trauma as the number of people surviving after the injury progressively increases. While the neurological consequences of CNS trauma are well described, evidence is emerging on sex-/age-dependent associations between a prior injury (most frequently TBI) and the development of senile Alzheimer's–type dementia many years later. Diagnostic criteria, first established by the National Institute of Neurological and Communicative Disorders and Stroke, were revised in light of the discovery of new markers--amyloid-B and tau proteins – accumulation of which brings cognitive dysfunction and neuronal death. These markers, shown to be non-specific in AD, appeared to be similar in persons with TBI and fatal familial insomnia. To fill the gap that is left by current evidence-based practice, the

proposed study will lay the ground for further research aimed at determining the underlying basis behind any observed patterns. The significant economic and human costs of cognitive dysfunction years after CNS trauma merit the call for systematic efforts to understand the factors that contribute to its development. This research looks to motivate future investigations of AD and CNS trauma in numerous directions.

List of abbreviations

AD, Alzheimer's disease; CNS, central nervous system; DSM-V, Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition; MCI, mild cognitive impairment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; QUIPS, Quality in Prognosis Studies; RCT, randomized control trial; SCI, spinal cord injury; SIGN, Scottish Intercollegiate Guidelines Network; (m)TBI, (mild) traumatic brain injury.

Competing interests

The authors have no conflicts of interest to declare pertaining to this research.

Authors' contributions

TM and AC contributed to the conception and design of the protocol. TM developed the idea, designed the protocol, and built the graphic data representation (e.g. figure). AC provided expertise at each level and also reviewed the protocol. TM registered the protocol PROSPERO. TM wrote the first draft, which was reviewed by AC. TM registered the protocol with PROSPERO. TM wrote the first draft, which was reviewed by AC. NP and AD contributed to

the revisions of the protocol and highlighted areas in need of refinement of scientific terms based on the results of the initial screening (i.e., first screen) that they performed.

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Data sharing statement

Unpublished data from this study will be available will be shared with scientific/research community via Dryad digital repository (datadryad.org). doi:10.5061/dryad.6pb54

Figure legends

File name: Figure 1

File format: Figure 1.tiff

Title of data: Conceptual model for summarizing longitudinal evidence on cognitive status in patients after central nervous system (CNS) trauma (i.e., traumatic brain injury (TBI), traumatic spinal cord injury (SCI) or both).

Description of data: This figure provides graphical representation of the conceptual model of longitudinal change in cognition and hypothesized associated factors in patients with CNS trauma.

Additional material

File name: Additional file 1

File format: additional file 1.docx

Title of data: Search strategies.

Description of data: This file provides the list of search terms used to search Medline, Central, Embase, Scopus, PsycINFO, and supplemental PubMed.

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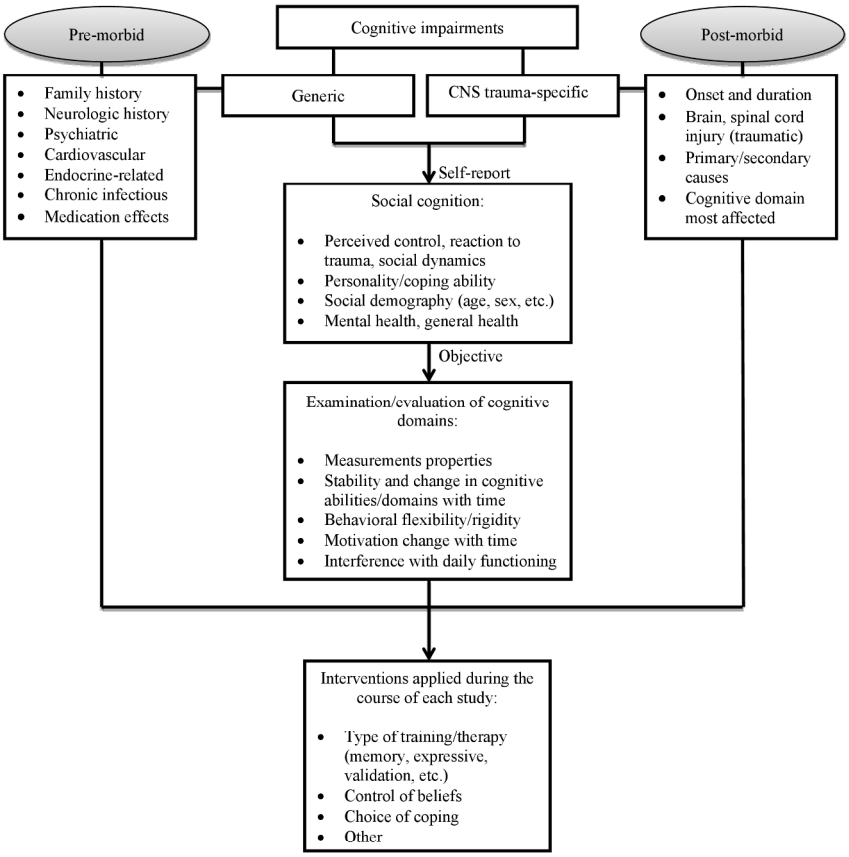


Figure 1. Conceptual model for summarizing longitudinal evidence on cognitive status in patients after central nervous system (CNS) trauma (i.e., traumatic brain injury (TBI), traumatic spinal cord injury (SCI) or both)

Conceptual model for summarizing longitudinal evidence on cognitive status in patients after central nervous system (CNS) trauma (i.e., traumatic brain injury (TBI), traumatic spinal cord injury (SCI) or both).

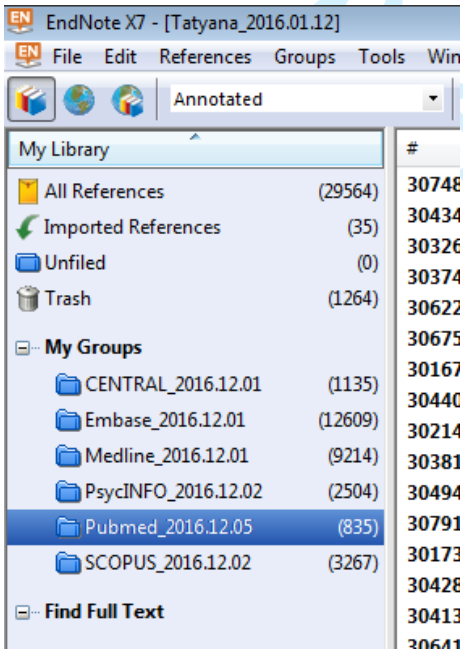
215x279mm (300 x 300 DPI)

SEARCH DETAILS

Searches conducted in Medline and Medline in-process, Embase, Cochrane Central Register of Controlled Trials, PsycINFO. A supplemental search was conducted in Pubmed to identify non-Medline records. All searches were conducted from inception of the database to December 2016. All searches were limited to English. Searches were conducted by an Information Specialist (JB).

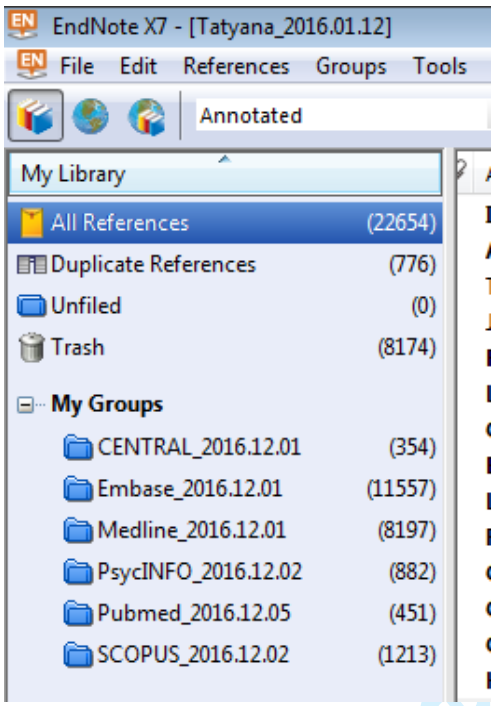
PRE-DUPLICATE REMOVAL

TOTAL Results: 29564
Medline: 9214
Embase: 12609
Central: 1135
PsycINFO: 2504
Scopus: 3267
Supplemental Pubmed search for NON-MEDLINE results: 835



POST-QUICK DUPLICATE REMOVAL

TOTAL Results: 22654
Duplicates Removed: 6910
Medline: 8197
Embase: 11557
Central: 354
PsycINFO: 882
Scopus: 1213
Supplemental Pubmed search for NON-MEDLINE results: 451



SEARCH STRATEGIES

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp brain injuries/ (62019)
2 Craniocerebral Trauma/ (21460)
3 exp Head Injuries, Closed/ (9310)
4 exp Skull Fractures/ (20416)
5 mTBI*2.tw. (1804)
6 tbi*2.tw. (21603)
7 concuss*.tw. (6210)
8 ((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) adj2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)).tw. (175759)
9 ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)).tw. (76211)
10 or/1-9 (270610)
11 exp Spinal Cord Injuries/ (44778)
12 exp Central Cord Syndrome/ (83)
13 (myelopathy adj3 (traumatic or post-traumatic)).tw,kw. (98)
14 ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).tw,kw. (49823)
15 (spinal cord adj3 (contusion* or laceration* or transaction* or trauma* or ischemi*)).tw,kw. (7108)

16 SCI.tw,kw. (30348)
17 exp Paraplegia/ (12903)
18 exp Quadriplegia/ (7861)
19 (paraplegia* or quadriplegia* or tetraplegia*).tw,kw. (16952)
20 Spinal Cord Compression/ (10657)
21 exp Cervical Vertebrae/in (7544)
22 central spinal cord syndrome.tw,kw. (10)
23 central cord injury syndrome.tw,kw. (1)
24 or/11-23 (108760)
25 Brain Death/ (8074)
26 (brain adj2 (death or dead)).tw,kw. (7913)
27 ((vegetat* or unawareness* or "minimally conscious") adj2 state*1).tw,kw. (3285)
28 (prolonged adj2 unawareness*).tw,kw. (10)
29 25 or 26 or 27 or 28 (14590)
30 (central nervous system adj2 trauma*).tw,kw. (334)
31 (CNS adj2 trauma*).tw,kw. (529)
32 10 or 24 or 29 or 30 or 31 (384413)
33 exp Cognition/ (142070)
34 exp Cognition Disorders/ (85970)
35 neurocognit*.tw,kw. (17260)
36 (cognitive or cognition).tw,kw. (316220)
37 Executive Function/ (10349)
38 (executive adj2 (function* or control*)).tw,kw. (23269)
39 exp Arousal/ (114735)
40 arous*.tw,kw. (32131)
41 attention*.tw,kw. (343363)
42 vigilan*.tw,kw. (17025)
43 or/33-42 (818304)
44 32 and 43 (29440)
45 (dementi* or alzheim*).tw,kw. (188105)
46 exp dementia/ (154811)
47 45 or 46 (227210)
48 32 and 47 (8285)
49 exp clinical trial/ (816969)
50 exp Clinical Trials as Topic/ (323082)
51 multicenter studies as topic/ (17817)
52 (randomi?ed adj7 trial*).tw,kw. (309575)
53 (controlled adj3 trial*).tw,kw. (213828)
54 (clinical adj2 trial*).tw,kw. (309587)
55 ((single or doubl* or tripl* or treb*) and (blind* or mask*)).tw,kw. (174728)
56 ("4 arm" or "four arm").tw,kw. (928)
57 or/49-56 (1341652)
Annotation: Clinical trial SOURCE:
http://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters
58 Case-Control Studies/ (250991)
59 Control Groups/ (1791)

60 Matched-Pair Analysis/ (4926)
61 retrospective studies/ (643251)
62 ((case* adj5 control*) or (case adj3 comparison*) or control group*).tw,kw. (528797)
63 or/58-62 (1282282)
Annotation: Case control SOURCE: http://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters
64 cohort studies/ (233586)
65 longitudinal studies/ (120931)
66 follow-up studies/ (595123)
67 prospective studies/ (464936)
68 cohort.tw,kw. (404386)
69 longitudinal.tw,kw. (206890)
70 prospective.tw,kw. (477259)
71 retrospective.tw,kw. (391544)
72 or/64-71 (1958903)
Annotation: Cohort source: http://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters
73 controlled before-after studies/ or interrupted time series analysis/ (462)
74 57 or 63 or 72 or 73 (3688853)
75 44 and 74 (8776)
76 48 and 74 (1798)
77 75 or 76 (9756)
78 limit 77 to english language (9214)

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Cochrane Central Register of Controlled Trials <October 2016>
Search Strategy:
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1 exp brain injuries/ (1087)
2 Craniocerebral Trauma/ (244)
3 exp Head Injuries, Closed/ (156)
4 exp Skull Fractures/ (178)
5 mTBI*2.tw. (85)
6 tbi*2.tw. (1060)
7 concuss*.tw. (147)
8 ((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) adj2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)).tw. (5744)
9 ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)).tw. (4083)
10 or/1-9 (9638)
11 exp Spinal Cord Injuries/ (881)

12 exp Central Cord Syndrome/ (0)
13 (myelopathy adj3 (traumatic or post-traumatic)).tw,kw. (1)
14 ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).tw,kw. (2155)
15 (spinal cord adj3 (contusion* or laceration* or transaction* or trauma* or ischemi*)).tw,kw. (144)
16 SCI.tw,kw. (840)
17 exp Paraplegia/ (164)
18 exp Quadriplegia/ (142)
19 (paraplegia* or quadriplegia* or tetraplegia*).tw,kw. (355)
20 Spinal Cord Compression/ (77)
21 exp Cervical Vertebrae/in (3)
22 central spinal cord syndrome.tw,kw. (1)
23 central cord injury syndrome.tw,kw. (0)
24 or/11-23 (2772)
25 Brain Death/ (46)
26 (brain adj2 (death or dead)).tw,kw. (158)
27 ((vegetat* or unawareness* or "minimally conscious") adj2 state*1).tw,kw. (89)
28 (prolonged adj2 unawareness*).tw,kw. (0)
29 25 or 26 or 27 or 28 (254)
30 (central nervous system adj2 trauma*).tw,kw. (1)
31 (CNS adj2 trauma*).tw,kw. (3)
32 10 or 24 or 29 or 30 or 31 (12479)
33 exp Cognition/ (7913)
34 exp Cognition Disorders/ (3101)
35 neurocognit*.tw,kw. (1356)
36 (cognitive or cognition).tw,kw. (31319)
37 Executive Function/ (529)
38 (executive adj2 (function* or control*)).tw,kw. (2114)
39 exp Arousal/ (7319)
40 arous*.tw,kw. (3311)
41 attention*.tw,kw. (14257)
42 vigilan*.tw,kw. (1569)
43 or/33-42 (51427)
44 32 and 43 (1263)
45 (dementi* or alzheim*).tw,kw. (8989)
46 exp dementia/ (3609)
47 45 or 46 (9451)
48 32 and 47 (142)
49 44 or 48 (1328)
50 limit 49 to english language (1135)

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Embase <1974 to 2016 November 30>
Search Strategy:

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1 exp brain injury/ (158616)
2 head injury/ (47431)
3 mTBI*2.tw. (2626)
4 tbi*2.tw. (31097)
5 concuss*.tw. (7222)
6 ((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) adj2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)).tw. (215012)
7 ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)).tw. (97349)
8 or/1-7 (357773)
9 exp spinal cord injury/ (66659)
10 spinal cord ischemia/ (3451)
11 (myelopathy adj3 (traumatic or post-traumatic)).tw. (113)
12 ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).tw. (59117)
13 (spinal cord adj3 (contusion* or laceration* or transaction* or trauma* or ischemi*)).tw. (8264)
14 SCI.tw. (37297)
15 paraplegia/ (21869)
16 quadriplegia/ (15330)
17 (paraplegia* or quadriplegia* or tetraplegia*).tw. (19145)
18 central spinal cord syndrome.tw. (8)
19 central cord injury syndrome.tw. (1)
20 or/9-19 (136685)
21 brain death/ (12613)
22 (brain adj2 (death or dead)).tw. (10828)
23 ((vegetat* or unawareness* or "minimally conscious") adj2 state*1).tw. (4046)
24 (prolonged adj2 unawareness*).tw. (12)
25 21 or 22 or 23 or 24 (19386)
26 (central nervous system adj2 trauma*).tw. (360)
27 (CNS adj2 trauma*).tw. (602)
28 8 or 20 or 25 or 26 or 27 (499222)
29 exp cognition/ (1941327)
30 cognitive defect/ (138285)
31 neurocognit*.tw. (21396)
32 (cognitive or cognition).tw. (380936)
33 executive function/ (26536)
34 (executive adj2 (function* or control*)).tw. (28576)
35 arousal/ (41038)
36 arous*.tw. (38982)
37 attention*.tw. (399204)
38 vigilan*.tw. (21941)

39 or/29-38 (2408211)
40 exp dementia/ (300566)
41 (dementi* or alzheim*).tw. (224692)
42 40 or 41 (323799)
43 39 or 42 (2608334)
44 28 and 43 (96287)
45 exp clinical trial/ (1281583)
46 exp "clinical trial (topic)"/ (267609)
47 (randomi?ed adj7 trial*).tw. (373380)
48 (controlled adj3 trial*).tw. (250872)
49 (clinical adj2 trial*).tw. (384066)
50 ((single or doubl* or tripl* or treb*) and (blind* or mask*)).tw. (219774)
51 ("4 arm" or "four arm").tw. (1207)
52 exp case control study/ (140524)
53 control group/ (263620)
54 clinical study/ or retrospective study/ (765384)
55 ((case* adj5 control*) or (case adj3 comparison*) or control group*).tw. (668069)
56 cohort analysis/ (303792)
57 longitudinal study/ (106182)
58 follow up/ (1232689)
59 prospective study/ (388763)
60 cohort.tw. (568512)
61 longitudinal.tw. (231900)
62 prospective.tw. (629993)
63 retrospective.tw. (576605)
64 or/45-63 (4750710)
65 44 and 64 (27389)
66 limit 65 to english language (26109)
67 limit 66 to embase (12609)
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PsycINFO <1806 to November Week 4 2016>
Search Strategy:
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1 exp traumatic brain injury/ (15045)
2 exp head injuries/ (5474)
3 mTBI*2.tw. (1222)
4 tbi*2.tw. (8250)
5 concuss*.tw. (2204)
6 ((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) adj2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)).tw. (50900)
7 ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)).tw. (4816)

8 or/1-7 (55142)
9 exp spinal cord injuries/ (4891)
10 exp Spinal Cord/ and exp Ischemia/ (63)
11 (myelopathy adj3 (traumatic or post-traumatic)).tw. (7)
12 ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).tw. (5852)
13 (spinal cord adj3 (contusion* or laceration* or transaction* or trauma* or ischemi*)).tw. (848)
14 SCI.tw. (3541)
15 paraplegia/ (534)
16 quadriplegia/ (188)
17 (paraplegia* or quadriplegia* or tetraplegia*).tw. (1302)
18 central spinal cord syndrome.tw. (0)
19 central cord injury syndrome.tw. (0)
20 or/9-19 (9003)
21 (brain adj2 (death or dead)).tw. (581)
22 ((vegetat* or unawareness* or "minimally conscious") adj2 state*1).tw. (1069)
23 (prolonged adj2 unawareness*).tw. (2)
24 21 or 22 or 23 (1611)
25 (central nervous system adj2 trauma*).tw. (56)
26 (CNS adj2 trauma*).tw. (112)
27 8 or 20 or 24 or 25 or 26 (64469)
28 cognition/ (26647)
29 cognitive impairment/ (29197)
30 neurocognit*.tw. (11048)
31 (cognitive or cognition).tw. (385119)
32 exp executive function/ (11055)
33 (executive adj2 (function* or control*)).tw. (21794)
34 physiological arousal/ (6451)
35 exp attention/ (59769)
36 arous*.tw. (33693)
37 attention*.tw. (232302)
38 vigilan*.tw. (8933)
39 or/28-38 (631554)
40 (dementi* or alzheim*).tw. (82601)
41 exp dementia/ (63311)
42 alzheimer's disease/ (38544)
43 41 or 42 (63311)
44 39 or 43 (668410)
45 27 and 44 (17822)
46 clinical trials/ (10032)
47 (randomi?ed adj7 trial*).tw. (40375)
48 (controlled adj3 trial*).tw. (33223)
49 (clinical adj2 trial*).tw. (28656)
50 ((single or doubl* or tripl* or treb*) and (blind* or mask*)).tw. (25275)
51 ("4 arm" or "four arm").tw. (125)

52 experiment controls/ (867)
53 retrospective studies/ (381)
54 ((case* adj5 control*) or (case adj3 comparison*) or control group*).tw. (81862)
55 exp Longitudinal Studies/ (15780)
56 longitudinal studies/ (15306)
57 Followup Studies/ (12353)
58 cohort.tw. (49483)
59 longitudinal.tw. (90266)
60 prospective.tw. (48210)
61 retrospective.tw. (28144)
62 or/46-61 (341322)
63 45 and 62 (2588)
64 limit 63 to english language (2504)

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SCOPUS (3267 results on 2016.12.02)

((((TITLE-ABS-KEY("central spinal cord syndrome")) OR (TITLE-ABS-KEY("central cord injury syndrome")) OR ((TITLE-ABS-KEY(mTBI* OR tbi* OR concuss*)) OR (TITLE-ABS-KEY(((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) NEAR/2 (injur* or trauma* or lesion* or damag* or wound* or destruction* or swell*)))) OR (TITLE-ABS-KEY(((head* or cerebr* or crani* or capitis* or brain* or forebrain* or skull* or hemispher* or intracran* or orbit*) NEAR/2 (oedema* or edema* or fracture* or contusion* or commotion* or pressur*)))) OR (TITLE-ABS-KEY(((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subarachnoid* or subdural* or epidural* or extradural*) NEAR/2 (haematoma* or hematoma* or hemorrhag* or haemorrhag* or pressur* or bleed*)))) OR (TITLE-ABS-KEY((myelopathy NEAR/3 (traumatic or post-traumatic)))) OR (TITLE-ABS-KEY(((spine or spinal) NEAR/3 (fracture* or wound* or trauma* or injur* or damag*)))) OR (TITLE-ABS-KEY((spinal cord NEAR/3 (contusion* or laceration* or transaction* or trauma* or ischemi*)))) OR (TITLE-ABS-KEY((paraplegia* or quadriplegia* or tetraplegia*)))) OR (TITLE-ABS-KEY((brain NEAR/2 (death or dead)))) OR (TITLE-ABS-KEY(((vegetat* or unawareness* or "minimally conscious") NEAR/2 state*))) OR (TITLE-ABS-KEY((prolonged NEAR/2 unawareness*))) OR (TITLE-ABS-KEY((central nervous system NEAR/2 trauma*))) OR (TITLE-ABS-KEY((CNS NEAR/2 trauma*)))) AND (((TITLE-ABS-KEY(cognitive or cognition OR neurocogniti*) OR TITLE-ABS-KEY((executive NEAR/2 (function* or control*))))) OR (TITLE-ABS-KEY(arous* OR attention* OR vigilan* OR dementi* or alzheim*)))) AND (((TITLE-ABS-KEY((controlled NEAR/3 trial*)) OR TITLE-ABS-KEY((clinical NEAR/2 trial*)) OR TITLE-ABS-KEY(((single or doubl* or tripl* or treb*) and (blind* or mask*))) OR TITLE-ABS-KEY(("4 arm" or "four arm")) OR TITLE-ABS-KEY((case* NEAR/5 control*)) OR TITLE-ABS-KEY((case NEAR/3 comparison*)) OR TITLE-ABS-KEY(control group*) OR TITLE-ABS-KEY(cohort* OR longitudinal OR prospective OR retrospective))) OR (TITLE-ABS-KEY(random*)) OR (TITLE-

ABS-KEY((randomized NEAR/7 trial*) OR (randomised NEAR/7 trial*)))) AND (LIMIT-TO(LANGUAGE,"English"))

Pubmed Supplimental Search (835 results on 2016.12.05)

((((((((((((((((((((mTBI[Text Word] OR TBI[Text Word] OR concuss[Text Word])))) OR ((((head*[Text Word] OR cerebr*[Text Word] OR cranium[Text Word] OR cranial[Text Word] OR capitis*[Text Word] OR brain*[Text Word] OR forebrain*[Text Word] OR skull*[Text Word] OR hemispher*[Text Word] OR intracran*[Text Word] OR orbit*[Text Word])) AND (injur*[Text Word] OR trauma*[Text Word] OR lesion*[Text Word] OR damag*[Text Word] OR wound*[Text Word] OR destruction*[Text Word] OR swell*[Text Word] OR oedema*[Text Word] OR edema*[Text Word] OR fracture*[Text Word] OR contusion*[Text Word] OR commotion*[Text Word] OR pressur*[Text Word])))) OR (((brain*[Text Word] OR cerebr*[Text Word] OR intracerebr*[Text Word] OR cranium[Text Word] OR cranial[Text Word] OR intracran*[Text Word] OR head*[Text Word] OR subarachnoid*[Text Word] OR subdural*[Text Word] OR epidural*[Text Word] OR extradural*[Text Word])) AND (haematoma*[Text Word] OR hematoma*[Text Word] OR hemorrhag*[Text Word] OR haemorrhag*[Text Word] OR pressur*[Text Word] OR bleed*[Text Word]))) OR ((traumatic myelopathy[Text Word]) OR post-traumatic myelopathy[Text Word])) OR (((spine[Text Word] OR spinal[Text Word])) AND (fracture*[Text Word] OR wound*[Text Word] OR trauma*[Text Word] OR injur*[Text Word] OR damag*[Text Word]))) OR ((spinal cord[Text Word]) AND (contusion*[Text Word] OR laceration*[Text Word] OR transaction*[Text Word] OR trauma*[Text Word] OR ischemi*[Text Word]))) OR ((((SCI[Text Word]) OR (paraplegia*[Text Word] OR quadriplegia*[Text Word] OR tetraplegia*[Text Word])))))) OR (("central spinal cord syndrome"[Text Word]) OR "central cord injury syndrome"[Text Word])) OR ((brain death[Text Word]) OR brain dead[Text Word])) OR prolonged unawareness*[Text Word]) OR (((vegetat* state*[Text Word]) OR "state of unawareness"[Text Word]) OR minimally conscious state*[Text Word])) OR central nervous system trauma*[Text Word]) OR CNS Trauma*[Text Word])) AND (((((((neurocognit*[Text Word]) OR (cognition[Text Word] OR cognitive[Text Word])) OR executive function*[Text Word]) OR arous*[Text Word]) OR attention*[Text Word]) OR vigilan*[Text Word]) OR dement*[Text Word]) OR alzheim*[Text Word]))) AND ((((((trial*[Text Word] OR blind*[Text Word] OR mark*[Text Word] OR random*[Text Word])) OR case control*[Text Word]) OR case comparison*[Text Word]) OR control group*[Text Word]) OR (cohort[Text Word] OR longitudinal[Text Word] OR retrospective[Text Word] OR prospective[Text Word]))) AND ((((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])))) AND English[lang])) AND English[lang])

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location; page(s) within the manuscript
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title, abstract, manuscript; pgs. 1-29 (for now)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA; original review protocol
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	PROSPERO: CRD42017055309
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page: 1-2, L1-L45
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Pg.22, Paragraph: 2, L451-457
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Pg. 22, Paragraph: 3, L458-462
Sponsor	5b	Provide name for the review funder and/or sponsor	Pg. 22, Paragraph: 3, L458-462
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Pg. 22, Paragraph: 3, L458-462
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Pg. 5, Paragraph: 1, L91-112
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Pg. 8, Paragraph: 1, L156-172
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting,	Pg. 9, L175-193

		time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Pg. 12, L285-299
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Pg. 12, L 248-255
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Pg. 13, Paragraph: 2, L260
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Pg. 13, Paragraph: 2, L260-268
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Pg. 13-14, L 270-283
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Pg. 14, Paragraph: 1, L 276-283
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Pg. 10-11, L195-236
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Pg. 15-16, L315-340
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Pg. 14-15, L285-299
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Pg. 14-15, L285-299
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Pg. 15, Paragraph: 2, L302-313
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication	N/A

		bias across studies, selective reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Pg. 15-18, L315-366

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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