

## SYSTEMATIC SEARCH AND REVIEW PROCEDURES: RESULTS OF THE WHO COLLABORATING CENTRE TASK FORCE ON MILD TRAUMATIC BRAIN INJURY

Linda J. Carroll,<sup>1</sup> J David Cassidy,<sup>1,2,3</sup> Paul M. Peloso,<sup>4</sup> Chantelle Garritty<sup>5</sup> and Lori Giles-Smith<sup>1</sup>

From the <sup>1</sup>Alberta Centre for Injury Control and Research, Department of Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada, <sup>2</sup>Department of Medicine, University of Alberta, Edmonton, Alberta, Canada, <sup>3</sup>Section for Personal Injury Prevention, Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden, <sup>4</sup>Department of Internal Medicine, University of Iowa Health Center, Iowa City, Iowa, USA, <sup>5</sup>Institute for Work and Health, Toronto, Ontario, USA

**The WHO Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury performed a comprehensive search and critical review of the literature published between 1980 and 2002 to assemble the best evidence on the epidemiology, diagnosis, prognosis and treatment of mild traumatic brain injury. Our primary sources of literature were Medline, Cinahl, PsycINFO and Embase. Citations were screened for relevance to mild traumatic brain injury, using *a priori* criteria, and relevant studies were critically reviewed for scientific merit. We identified 38,806 citations, of which 671 studies were judged relevant to the mandate of the task force. These, plus 70 studies found by hand-searching reference lists and 2 original research reports performed as part of the task force mandate were subjected to critical reviews. After review, 313 (42%) were accepted on scientific merit and comprise our best-evidence synthesis. Ninety percent of the literature on mild traumatic brain injury was found in Medline and another 5% in PsycINFO.**

*Key words:* mild traumatic brain injury, systematic review, best-evidence synthesis.

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*Correspondence address:* Linda J. Carroll, Department of Public Health Sciences, 3080 RTF, 8308–114 St., Edmonton AB, Canada, T6G 2E1.  
*E-mail:* lcarroll@ualberta.ca.

### INTRODUCTION

The literature on brain injury is vast and not easily accessible to clinicians, researchers and policymakers. Over the past decade, systematic reviews, guidelines and best-evidence syntheses have become an option to summarize information and promote evidence-based decision-making (1–5). The focus of our initiative is mild traumatic brain injury (MTBI).

In 1997, the WHO Collaborating Centre for Neurotrauma at Karolinska Institute, Stockholm, Sweden, assembled an international task force of scientist-clinicians and methodologists with the mandate to make recommendations with the goal of reducing the medical, social and economic consequences of

MTBI. In order to fulfill this mandate, the task force undertook 3 phases of investigation: (i) a scientific review and synthesis of the world literature on MTBI (6); (ii) original research on MTBI in Sweden (7); and (iii) original research on traffic-related MTBI in the Canadian province of Saskatchewan (8). A working group called the Scientific Secretariat performed the scientific work of the task force. This work was overseen by the Advisory Committee, through provision of guidance and expert opinion on both clinical and methodological issues, and reviews of the work carried out by the Scientific Secretariat. Names and affiliations of task force members are listed at the beginning of this supplement.

The purpose of our literature search was to identify all relevant literature on prevention of MTBI; incidence of MTBI; risk factors associated with MTBI; diagnosis; intervention; prognosis of MTBI; economic costs; and existing clinical guidelines. In most systematic reviews of the literature, the topic areas to be addressed are narrow and sharply focused. However, because of the lack of prior efforts to systematically assemble knowledge on this topic, our focus was intentionally broad and the questions were more widely inclusive. Questions addressed in this systematic review include:

- What is the epidemiology of MTBI, i.e. what are its risk factors, incidence, determinants, economic costs and how can it be prevented?
- What are the best strategies and current technologies for diagnosis of MTBI?
- What is the prognosis for patients with MTBI? What are the determinants of recovery or symptom persistence? What are the common sequelae?
- What is the evidence regarding interventions for MTBI?

### METHODS

#### *Literature search*

The scientific literature published between 1980 and the present was systematically searched and seminal papers published prior to 1980 were identified and included in the critical review.

*Electronic literature databases.* The primary sources of literature were the electronic databases Medline, Cinahl, PsycINFO and Embase. The search strategy was developed in consultation with library and information scientists familiar with use of electronic health databases.

Each electronic database uses slightly different thesaurus terms and limiting functions, and the search strategy was developed and tested on Medline, then adapted accordingly for the other 3 databases. Medline and PsycINFO were searched for the years 1980 through 2000, and Cinahl and Embase were searched for the years they were available to us in electronic form, i.e. Cinahl for the years 1982 through 2000, and Embase from 1988 through 2000. The Medline search strategy included the use of the following thesaurus terms (i.e. Medical Subject Headings or MeSH terms for Medline): brain-concussion; brain-injuries; head-injuries; head-injuries, -closed; brain-damage, -chronic; and brain/injuries. In order to ensure that all relevant studies were identified in our search, text words were also used, including the terms concussion, post-concussion, postconcussion, mild head injury, minor brain injury, and other similar terms (9). All citations identified by this search were entered into a bibliographic management software program, Reference Manager<sup>®</sup>, and because there is overlap amongst the databases, duplicate entries were excluded.

*Screening for relevance to task force mandate.* Since the search strategy was by design comprehensive but not necessarily specific, only a minority of citations was expected to be relevant to our task force questions. Therefore, all citations identified in the electronic search were screened for relevance to our mandate using the inclusion/exclusion criteria listed below.

#### *Inclusion criteria*

- Studies published since 1980. Papers published before 1980 were included if they were considered seminal papers, that is, studies that continue to have a substantial impact on clinical practice or are cited consistently in current research papers.
- English language reports. Other languages were included if they were seminal papers.
- Studies published in a journal, systematic reviews, conference proceedings, technical reports, unpublished manuscripts and others.
- Studies that refer to concussion or MTBI; or refer to diagnostic criteria that are used for concussion or MTBI. For example, a study may provide information about patients with Glasgow Coma Scale scores of 13–15, without specifically identifying these as MTBI.
- Studies examining diagnosis, incidence, risk factors, prevention, prognosis, treatment and rehabilitation or economic costs of MTBI.
- Studies include at least 10 subjects with MTBI or pertain to the prevention of MTBI. Exceptions are case reports or small case series documenting rare complications of MTBI, such as second impact syndrome.

#### *Exclusion criteria*

- Studies were excluded if they did not include at least 10 subjects with MTBI, except as allowed in the inclusion criteria.
- Studies about penetrating brain injuries, birth injuries, brain damage from stroke or other cerebrovascular incidents, shaken baby syndrome or moderate to severe traumatic closed head injuries were excluded.
- Studies were excluded if they did not report findings specific to MTBI. For example, if all analyses in a study combined mild and moderate brain injuries, and no findings were reported that distinguished these 2 groups, the study was considered irrelevant. However, some studies on prevention of traumatic brain injury were included, even if they were not specific to MTBI (for example, studies of effectiveness of helmet laws in preventing traumatic brain injuries).
- Non-systematic review papers (narrative reviews) or clinical review papers were excluded. However, the most widely cited narrative review papers were circulated to the task force, and reference lists of review papers were examined to ensure that all relevant literature was included.
- Letters to the editors and editorials without data were excluded.
- Studies using cadavers or non-human subjects, such as crash test dummies, animals, or biomechanical simulations were excluded.

Each citation found in the electronic database search was reviewed by 3 task force members, in rotating groups, and deemed probably relevant, irrelevant or unknown based on agreement of at least 2 of the 3 members. A citation was rated as probably relevant if the information contained in the abstract indicated that it met the above inclusion/exclusion criteria. A citation was rated as unknown where the abstract was unavailable, where

insufficient information was available in the abstract, or where the abstract was not sufficiently clear with respect to the inclusion/exclusion criteria. A citation was rated as irrelevant if it was clear from the abstract that the paper was not relevant to the task force mandate; for example, if the study related to severe brain injury or brain damage from stroke, or if it was an opinion paper with no data. Disagreements among the 3 raters were resolved at face-to-face discussions. When there was doubt about the relevance of a study or where disagreements could not be resolved by reviewing the abstract, the citation was rated unknown. No attempt was made to judge scientific merit at this stage.

For each citation rated as probably relevant or of uncertain relevance (unknown) in this initial screening, the entire paper was obtained from the library, and there was a second level of screening to ensure relevance. This was done in the case of papers rated probably relevant because the description in the abstract was not always consistent with the contents of the study. This also served to screen out papers in which no MTBI specific findings were reported; for example, where mild injuries were combined with moderate or severe injuries in the findings, and the effects of the mild brain injury could not be evaluated separately. This second level of screening was performed with respect to the same inclusion/exclusion criteria used in the first screening process.

*Additional search procedures.* As an adjunct to searching the electronic databases, we also examined the reference lists of all relevant studies in order to identify potentially relevant citations that might have been missed in the electronic database search. In addition, while we were actively searching for literature, we posted a website soliciting other published or unpublished manuscripts. Experts in the field of MTBI and brain injury associations were also solicited for material. All papers obtained in this manner were subjected to screening for relevance, utilizing the inclusion/exclusion criteria. Unpublished dissertations were not included because Canadian copyright laws do not permit copying these documents for distribution and review.

#### *Critical review of the literature*

All studies judged as relevant in the second layer of screening were subjected to a data abstraction and critical review process. The critical review assessed scientific merit and clinical relevance by using *a priori* criteria and computerized critical review forms, similar to the review forms used by the Quebec Task Force on Whiplash Associated Disorders (10).

These critical review forms were intended as a guide to identification of methodological strengths and biases, and to facilitate the Scientific Secretariat members' discussions of the methodological and clinical features of the study, with a focus on assessing the presence of selection, information and confounding bias. In addition, issues of external validity (generalizability) were considered in the review process. The forms do not provide a rating scale for determining scientific acceptability. Instead, the forms were used to abstract information from the study and to comment on the presence or absence of important methodological flaws and biases. Thus the forms prompted the reviewer to focus on issues of study design, study population, issues related to conduct of the study, participation rates, follow-up rates (where relevant), measurement issues and analysis. Quality appraisal criteria identified in the critical review forms were derived from fundamental principals of epidemiological conceptualization, measurement and design (e.g. (11, 12)). The critical review forms themselves are too extensive to include in this chapter, but are available from the first author on request.

Rotating pairs of Scientific Secretariat members performed independent in-depth reviews and the remaining Secretariat members read the study. The review forms were programmed on an Access<sup>®</sup> database and Secretariat members completed the reviews electronically. The 2 reviewers presented their reviews to the rest of the Scientific Secretariat and then the merit of each study was discussed. Decisions about the study's methodological quality and scientific merit were made by consensus of the Secretariat, after a full discussion. Studies were considered scientifically admissible, which could include accepting part or all of the findings; or scientifically inadmissible due to fatal biases and methodological flaws. In some cases, partial findings from a paper (for example, findings from a short-term follow-up) might be considered to stem from scientifically acceptable methods, whereas other findings in the same study might be considered too flawed to accept (for example, findings from longer term follow-up where attrition rates were very

Table I. Number of citations in electronic database search and results of screening

| Database              | Number of citations | Number of relevant studies (% yield) |
|-----------------------|---------------------|--------------------------------------|
| Medline (1980–2000)   | 26,228              | 588 (2.2)                            |
| Medline (2001)        | 1431                | 16 (1.1)                             |
| PsycINFO (1980–2000)* | 1055                | 32 (3.0)                             |
| Cinahl (1982–2000)†   | 531                 | 19 (3.6)                             |
| Embase (1988–2000)‡   | 9561                | 16 (0.2)                             |
| Total                 | 38,806              | 671 (1.7)                            |

\*Unique citations after eliminating Medline duplicate entries.  
 †Unique citations after eliminating Medline and PsycINFO duplicate entries.  
 ‡Unique citations after eliminating Medline, PsycINFO and Cinahl duplicate entries.

high). One of the 2 main reviewers was then assigned the task of submitting the final consensus review, which incorporated all comments and the acceptance decision agreed upon by the full Secretariat. Where a Scientific Secretariat member was an author or co-author of a paper, he or she absented themselves from the room during presentation and discussions of the study.

We also performed critical reviews of the 2 research reports that are published as part of the task force mandate (7, 8). The authors of these reports were excluded from that review process. In addition, all members of the Advisory Committee reviewed the 2 reports.

Updating the literature review

Although our planned literature search methodology included studies published up to the year 2000, we updated our Medline search for the year 2001, in order to include significant recent publications that might impact on our findings. We screened these abstracts using the inclusion/exclusion criteria described above, but selected only high impact studies for review. High impact studies included randomized controlled trials; large, well-designed cohort studies and case-control studies; and studies about important issues on which we had found conflicting findings, or little or no information in the previous literature. Finally, we included high impact studies published in 2002 that came to our attention, although we did not complete a systematic search.

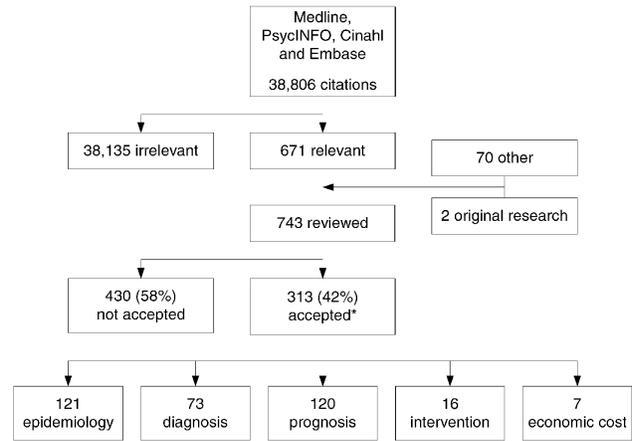
Evidence tables

Each study was identified as relating to incidence, risk, or prevention of MTBI; diagnosis of MTBI; prognosis or outcome after MTBI; and intervention or economic costs associated with MTBI. Data from accepted studies were then abstracted into evidence tables relating to each topic, and evidence from these studies was synthesized in our reports (13, 14). Some studies relate to more than 1 topic, and are therefore included in more than 1 set of evidence tables.

RESULTS

A total of 38,806 citations were identified in the search of the electronic databases. The results of the search and the application of inclusion/exclusion criteria for relevance are outlined in Table I.

Of the citations identified in electronic databases and rated in the initial citation screening as probably relevant or unknown, 671 were confirmed by the second level of screening as relevant to the mandate of the MTBI task force. This includes 16 studies identified as relevant and high impact in our search of the 2001 Medline citations. An additional 70 relevant studies were identified through hand searching the reference lists and through



\*Some studies relate to more than 1 topic area.

Fig. 1. Results of literature search and critical review.

our other searching procedures as outlined above. The primary reason for rating studies as irrelevant in the second level of screening, when they had been rated as probably relevant through abstract screening, was there were no findings specific to MTBI. For example, a number of studies combined mild and moderate injuries in the analysis, yielding no MTBI-specific information. Thus, 741 studies, plus the 2 original research reports, were subjected to our critical review process, and 313 studies (42%) were accepted as scientifically admissible (Fig. 1). These comprise our best-evidence synthesis. The breakdown of reviewed and accepted studies in each topic area is listed in Table II. The studies included in our best-evidence synthesis are listed in Appendix A. All other studies reviewed or cited in the chapters in this supplement are listed as a supplementary bibliography (Appendix B).

DISCUSSION

We performed critical reviews of 743 studies relating to the epidemiology, diagnosis, prognosis, treatment or economic costs of MTBI. Of these, 671 were identified in our electronic library database search. Medline contained 90% of these, PsycINFO another 5%, and the remaining 5% of identified

Table II. Number of appraised and accepted mild traumatic brain injury studies

| Topic area                | No. of studies critically appraised* | No. (%) of studies accepted as admissible* |
|---------------------------|--------------------------------------|--|
| Incidence/risk/prevention | 169                                  | 121 (72%)                                  |
| Diagnosis                 | 228                                  | 73 (32%)                                   |
| Prognosis                 | 428                                  | 120 (28%)                                  |
| Intervention or treatment | 45                                   | 16 (36%)                                   |
| Economic costs            | 16                                   | 7 (44%)                                    |

\*Some studies relate to more than 1 topic and are included in this table more than once.

studies were contributed by Cinahl and Embase together. There was significant overlap among the 4 databases. For example, of the almost 2700 citations identified in the PsycINFO search, 60% were also included in Medline. Clearly, searching only Medline and PsycINFO would provide the vast majority of the published literature in the area of MTBI.

The hand-searching process was also of some importance in identifying literature, with 70 studies identified through our other search strategies that had not been picked up through the electronic database searches. Some of these were, at the time of review, unpublished manuscripts identified by experts in the area of MTBI, but the majority was identified through reference lists of reviewed papers. Our website did not yield any literature that had not been identified through other sources.

Our methodology permitted a comprehensive search of the English literature and an in-depth review of the methodological and statistical quality of the studies relating to MTBI. However, our inability systematically to review literature in other languages may be considered a weakness. Although we had intended to review the non-English literature, professional language translation services proved prohibitively expensive. Attempts to solicit critical reviews by scientists fluent in other languages were only partially successful. The quality of the reviews was mixed, and data from these non-English studies were abstracted with varying levels of detail. In addition, there was no way of instituting the kind of quality control that was established for the English language reviews, i.e. 2 independent reviewers performing in-depth reviews with the remaining scientists reading each paper. This meant that discussions of non-English papers could not be adequately informed. The exception to this was the Swedish language, since 3 of the Scientific Secretariat members were Swedish. The decision not to include studies other than English and Swedish could potentially bias our findings. There is evidence that excluding non-English clinical trials from a meta-analysis has little effect on the summary treatment effect estimates, however it is unclear whether this applies in the area of MTBI, or for study designs other than clinical trials (15).

## CONCLUSION

We searched Medline, PsycINFO, Cinahl and Embase for literature relating to frequency, risk factors, diagnosis, intervention, prognosis and cost of MTBI. Literature was also obtained through searches of reference lists and soliciting published and unpublished manuscripts through personal communication with content experts and brain injury associations. After applying inclusion/exclusion criteria to identify studies with findings specific to the topic area, we found 671 relevant research studies. These studies, the 70 found through our other search procedures, and the 2 original research reports included in this supplement were subjected to a critical review process. We judged 313 studies as scientifically acceptable and summarized the findings

into evidence tables, which formed the basis for the findings and recommendations contained in this supplement.

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