

## METHODOLOGICAL ISSUES AND RESEARCH RECOMMENDATIONS FOR MILD TRAUMATIC BRAIN INJURY: THE WHO COLLABORATING CENTRE TASK FORCE ON MILD TRAUMATIC BRAIN INJURY

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**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. Of 743 relevant studies, 313 were accepted on scientific merit and comprise our best-evidence synthesis. The current literature on mild traumatic brain injury is of variable quality and we report the most common methodological flaws. We make recommendations for avoiding the shortcomings evident in much of the current literature and identify topic areas in urgent need of further research. This includes the need for large, well-designed studies to support evidence-based guidelines for emergency room triage of children with mild traumatic brain injury and to explore more fully the issue of prognosis after mild traumatic brain injury in the elderly population. We also advocate use of standard criteria for defining mild traumatic brain injury and propose a definition.**

*Key words:* mild traumatic brain injury, epidemiology, research recommendations.

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### INTRODUCTION

The literature on mild traumatic brain injury (MTBI) is large and of variable quality. The WHO Collaborating Centre for Neurotrauma Task Force on MTBI performed a comprehensive search and critical review of the methodological quality of the literature on this topic and accepted 42% of the 743 reviewed studies (1). Of the studies relating to incidence, risk factors and prevention of MTBI, 72% of the reviewed studies were judged by our task force as having acceptable scientific merit and included in our best-evidence synthesis (2). However, only 44% of the studies on economic costs, 36% of the studies on treatment (3), 32% of studies on the diagnosis of MTBI (4) and

28% of the studies on prognosis after MTBI (5) were accepted as being sufficiently methodologically sound to be included in our report. Despite the abundance of published studies on MTBI, fundamental questions remain about important clinical questions, such as the best method of screening children for referral to diagnostic imaging and what forms of intervention, if any, enhance recovery. Based on a critical assessment of the evidence, we make a number of general comments on the methodological strengths and weaknesses of the existing literature. We outline some of the more problematic methodological flaws in the research in each of the topic areas of epidemiology, diagnosis, prognosis and intervention, and make suggestions on what we view as priority areas of research to fill some of the more important gaps in knowledge.

### CASE DEFINITIONS OF MTBI

One major issue is the wide range of conditions considered to comprise MTBI and the heterogeneity in case definitions of MTBI (Table I). This problem has a negative impact on the interpretation and comparison of findings on MTBI (6, 7). Table I lists the MTBI case definitions used in each of the studies comprising our best-evidence synthesis. In a number of studies, the relevant injuries were described only as concussion, with no further definition, while head injuries sustained in sports were frequently described as a head blow causing cessation of play, missed games or requiring assessment and treatment. Other studies provided specific information on a wide spectrum of brain injury severity, including those usually considered mild, without explicitly defining these as MTBI (see Table I).

Of the studies comprising our best-evidence synthesis that provided explicit case definitions for MTBI, 62% incorporated Glasgow Coma Scale (GCS) scores as part of the case definition, though the specific definitions varied (see Table I). Some considered the spectrum of GCS 13–15 to be mild, some considered only GCS 14 and 15 to be mild, and others defined their cases using a GCS score of 15 only. Loss of consciousness (LOC) or amnesia was required in some case definitions, although the length of altered consciousness varied. Other studies did not require either LOC or amnesia in the case definition, and some excluded complications such as focal

abnormalities and/or abnormalities on imaging and/or the need for surgery, while other case definitions included these.

The remaining 38% of studies did not use GCS scores to help define MTBI, and a number of these used LOC, post-traumatic amnesia (PTA) or both, with a variety of time periods specified as the minimal and maximal time of altered consciousness. Still other studies defined a mild brain injury based on hospital discharge codes (usually ICD-9 code 850) or by the patient's Abbreviated Injury Score (AIS) (usually AIS 1–2). However, this can result in problems of misclassification. For example, it

has been reported that ICD-10 codes identify less than 50% of all head injury admissions to hospital, which would lead to inaccurately low incidence rates (8). To further complicate the issue of valid case ascertainment when using ICD codes, the ICD-9 code 850 (concussion), which is the most frequently used ICD diagnostic code for identifying MTBI, appears to be both under-inclusive (false negatives) and over-inclusive (false positives). One study found that only 23% of MTBI cases were classified as ICD code 850 (9). At the same time, 13% of severe and 29% of moderate traumatic brain injury (TBI) cases

Table I. Mild traumatic brain injury (MTBI) case definitions in studies included in the best-evidence synthesis

| MTBI case definition   | Studies (ref.) |
|--|----------------|
| Glasgow Coma Scale (GCS)   |                |
| GCS 12–15  | 20             |
| GCS 13–15 (or GCS 13–14 on 14-point scale)   | 21–62          |
| GCS 13–15 with head specific AIS 2 or more   | 63, 64         |
| GCS 13–15 with LOC   | 65–76          |
| GCS 13–15 with LOC, PTA, brief anterograde amnesia or other neurological symptoms (e.g. dizziness or memory, speech or vision problems). Length of LOC ranges from undefined, <5 to <30 minutes. Length of PTA ranges from undefined, <1 to <24 hours.   | 9, 77–93       |
| GCS 13–15 with LOC, PTA, skull fracture, seizure or neurological findings  | 94–97          |
| GCS 13–15 with LOC or PTA, but no complications (e.g. no focal abnormalities on neurological exam, abnormal imaging, need for surgery, seizures, depressed skull fracture and/or prolonged hospital stay). Length of LOC ranges from undefined, "brief", <15 to <30, length of PTA ranges from undefined to <5 minutes to <24 hours. | 15, 98–128     |
| GCS 15   | 129–133        |
| GCS 15 without LOC or PTA  | 134            |
| GCS 15 with LOC or PTA   | 135–140        |
| GCS 15 with LOC or amnesia for event and without complications (e.g. no focal deficits on neurological exam, normal imaging)   | 14, 141–144    |
| GCS 15 without complications (e.g. no focal deficits on neurological exam, normal imaging)   | 145, 146       |
| GCS 14–15  | 6, 147         |
| GCS 14–15 with LOC or PTA  | 148–151        |
| GCS 14–15 with LOC or skull fracture   | 152            |
| GCS 14–15 without complications (e.g. no focal deficits on neurological exam, normal imaging)  | 153, 154       |
| ICD codes  |                |
| ICD code 850   | 155–168        |
| ICD code 850 with LOC <1 hour  | 169            |
| ICD codes 850 and 780  | 170            |
| Abbreviated Injury Score (AIS) or Maximum AIS (MAIS) of traumatic brain injury   |                |
| AIS or MAIS 1–2  | 171–177        |
| AIS 1–3  | 178            |
| AIS 2 with LOC   | 179            |
| Alterations in consciousness (no GCS specified)  |                |
| LOC <5 minutes   | 180            |
| LOC <15 minutes  | 181, 182       |
| LOC <15 minutes (or brief LOC or amnesia for event), PTA <15 minutes, no skull fracture or neurological signs  | 183, 184       |
| LOC <20 minutes, PTA <60 minutes   | 185            |
| LOC <30 minutes, PTA <30 minutes   | 186–188        |
| LOC <30 minutes, PTA <24 hours   | 189            |
| LOC <30 minutes, PTA <30 minutes, no skull fracture  | 190            |
| Some LOC and PTA 1–24 hours  | 191            |
| PTA (or altered consciousness) <1 hours  | 192–201        |
| PTA <24 hours  | 202–212        |
| Head trauma without LOC, no skull fracture, no need for hospital admission   | 213            |
| Head trauma with certain or possible LOC and no more than 2 days in hospital   | 214            |
| Head trauma with PTA and/or LOC and/or other symptoms (e.g. dizziness, confusion)  | 215–230        |
| Head trauma leading to transient altered consciousness and/or period of complete amnesia and/or symptoms (e.g. headache, dizziness, visual symptoms) and/or skull fracture and/or ambulatory medical care or hospitalization up to 2 days.   | 231–237        |
| Head trauma in an infant or young child who is alert or awakens to voice or light touch  | 238            |
| Other*   | 239–325        |

\*Other includes concussion defined as head blow causing cessation of play/competition, or concussion causing missed game or practice, or concussion requiring assessment or treatment, or no explicit definition of MTBI or concussion. AIS = abbreviated injury score; LOC = loss of consciousness; PTA = post-traumatic amnesia; ICD = International Classification of Diseases.

were also coded as 850. The same study found that over 70% of MTBI cases were coded as ICD-9854 (intracranial injury of other and unspecified nature), and that code also included over 25% of the severe and over 60% of the moderate TBI cases. Another important source of variability in assignment of ICD codes is variability across settings in the training of hospital personnel assigning ICD codes from written diagnoses.

An in-depth discussion of the strengths and weaknesses of the existing criteria for classifying a TBI as mild is beyond the scope of this paper. However, the literature would greatly benefit by common criteria. Our task force recommends the following operational definition of MTBI:

“MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.”

This definition is derived from the definition developed by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (10) and has similarities with the conceptual definition of MTBI produced by a panel of experts from the US Centers for Disease Control and Prevention’s (CDC) MTBI Working Group (11). We agree with the American Congress of Rehabilitation Medicine definition, which specifies that the GCS score of 13–15 be assessed after 30 minutes post-injury. However, we recognize the practical concern that individuals with MTBI will rarely be assessed at an emergency department within this time frame. Therefore, although an assessment of GCS score just after 30 minutes post-injury remains the ideal, our proposed definition permits diagnostic use of a GCS score assessed by a qualified healthcare provider at the first opportunity.

## QUALITY OF EXISTING RESEARCH

Apart from the problems created in not having a universally accepted case definition for MTBI, we found many important flaws in the existing literature on MTBI. The most common deficiencies in the published research reports on MTBI were as follows:

- The purpose of the study or research question was not clearly stated, leaving questions about whether the methodology was

appropriate and whether the findings addressed the research question(s) or hypotheses.

- Lack of information about source population and sampling frame. Lack of information about selection of subjects into a study makes it difficult to determine to what population the study’s findings would legitimately generalize. In addition, in incidence studies, lack of information about the source population also impacts adversely on defining a valid population at risk (denominator).
- Research design sub-optimal or inappropriate to test the research question. Examples include the use of cross-sectional designs to assess recovery; use of a convenience sample of referrals to specialty clinics to determine frequency of symptoms; and use of case series to establish treatment effectiveness or rate of complications.
- Losses to follow-up without consideration of whether these losses were selective and would substantially bias the outcome. We assessed many studies with attrition rates of over 50%, where no attempt was made to investigate factors associated with attrition.
- Substandard or inappropriate analysis strategies. Often this was due to little or no consideration of confounders that might account for apparent relationships. In general, many studies presented only univariable statistical analyses, where multivariable techniques would be more appropriate. In other studies, multiple *t*-tests were used instead of analysis of variance or multivariable approaches. Tests of diagnostic procedures did not always report diagnostic test statistics, such as sensitivity, specificity, predictive values or likelihood ratios. Where multivariable analyses were performed, they were frequently underpowered, including too many explanatory variables for the sample size. This can lead to unstable models with misleading results (12), and this problem was especially frequent in the literature on prognosis of MTBI.
- Sub-optimal reference or comparison groups. Investigations of outcome after MTBI frequently use comparisons between MTBI cases and control groups to aid in identifying sequelae specific to MTBI. Because most problems reported after MTBI are not specific to the brain injury, but occur in the general population as a whole, comparison with appropriate controls can assist in distinguishing and quantifying MTBI-specific outcomes (i.e. control for confounding factors). However, differences in outcome between MTBI cases and a comparison group might also be due to systematic group differences in pre-injury characteristics or non-MTBI related post-injury factors, rather than to the MTBI itself. Some of this confounding may be adjusted in the analysis, but this is not always the case and comparison groups should come from the same general source population as MTBI cases. In particular, MTBI should not be identified as the cause of a particular outcome unless there has been adequate consideration of other group differences that might account for the observed outcome.
- Inadequate consideration of sources of information bias. An example of information bias is recall bias, where cases are

likely to recall past events differently from controls. Another example is observer bias, which might occur when the individual assessing the outcome is not blinded to group status of the participants. We also observed the use of outcome measures that had uncertain reliability and validity.

- Use of small samples leading to inadequate statistical power. This is especially problematic where adverse outcomes are rare or where small to moderate effect sizes are clinically important or are important from a public health perspective. Many times, we reviewed studies where the authors did not consider sample size issues at all.

## METHODOLOGICAL ISSUES AND RESEARCH PRIORITIES FOR EPIDEMIOLOGY OF MTBI

### *Methodological issues*

There is a substantial literature on the epidemiology of mild traumatic brain injury, and much of it (72%) was of sufficient quality to be included in our best-evidence synthesis (2). However, despite the methodological quality of this literature, it is difficult to form consistent conclusions about the incidence, risk and prevention of MTBI because of heterogeneity in the studies (2). Differences in criteria used to define MTBI (discussed above) are an important source of this heterogeneity in incidence rates of MTBI. The heterogeneity and lack of clear case definitions was especially problematic in the sports concussion literature. In these studies, concussion was often unclearly defined or not defined at all, resulting in uncertainty about both the lower and the upper limits of injury severity included in the study. Researchers exploring the incidence of MTBI frequently use ICD codes for case finding, since they are often the only readily available data. However, as discussed previously, this can result in misclassification of MTBI and widely varying incidence rates, depending on how these codes are assigned. We recommend that future authors consider the validity of their case definitions of MTBI and discuss this issue in their publications.

Another source of variability in the findings on incidence, risk and prevention of MTBI is the method used to ascertain cases. Studies using hospital discharge records for case finding produce the lowest incidence rates, and miss those cases presenting to emergency departments but not admitted. Studies using emergency department records to identify cases of MTBI, in turn, miss those individuals treated at clinics and those who do not seek medical treatment at all. In addition, where case finding is through hospital admission, changes in hospital admission policies over time and differences across locations must be considered. Such changes in admission policies could lead to falsely concluding that there is an increasing or decreasing trend in MTBI occurrence, or alternatively may mask true trends in incidence.

Producing a valid incidence rate not only requires accurate and complete ascertainment of cases, it also requires obtaining an accurate estimate of the population at risk. Cases must be

drawn from that population at risk. One example of a situation in which this is problematic is when tourists and transients are included in the MTBI cases, if the defined population at risk does not include such individuals. Another example is where individuals forming part of a defined study population at risk are transported to hospitals outside of the study setting, resulting in missing cases. We recommend that authors clearly state their source populations and discuss issues around their sampling frames for inclusion into their studies.

There is a great deal of interest in the literature in sports concussions. This is an important topic to study since these injuries generally affect the young and healthy. Understanding the absolute and relative risks of various sports can be of great assistance in developing strategies for improving safety within those sports. Studies that stratify their findings by whether the injury occurred in practice or competition, by gender, by amateur or professional play and by age are more informative, since these factors lead to important differences in incidence rates. In addition, one of the strengths of the sports concussion literature is the frequency with which incidence density is reported, that is, reporting incidence rates considering time at risk for injury. At the same time, there are some important gaps in the literature concerning the risk of MTBI in certain sports, such as professional football (American), hockey and boxing.

### *Research priorities*

We found relatively few studies on incidence and risk of MTBI in the paediatric population or the elderly, and we recommend that this be a research priority. We also recommend that studies be done to delineate the incidence and risk of concussions in professional football (American), professional soccer, professional hockey and professional boxing. Studies of incidence and risk of concussion in these sports should provide clear definitions of concussion.

Another important gap in the literature on epidemiology of MTBI is the paucity of information on risk factors for MTBI. At best, incidence rates are stratified by age, gender and race, but within these broad categories, we have little useful information about specific risk factors. We also recommend an increased focus on the study of modifiable risk factors in MTBI; such as alcohol or drug use, or environmental factors. More extensive information about populations at higher risk for MTBI could assist in development of primary prevention programs, especially where modifiable risk factors are identified. Given the paucity of research on risk factors for MTBI, we strongly recommend the implementation of studies that are large enough to assess the independent importance of various risk factors for MTBI.

## METHODOLOGICAL ISSUES AND RESEARCH PRIORITIES FOR DIAGNOSIS OF MTBI

### *Methodological issues*

Predicting acute complications of MTBI is a crucially important

clinical issue because they can be extremely serious if not identified. Computerized tomography (CT) scans are frequently employed in the developed nations as a diagnostic tool in MTBI. However, studies need to clearly track the linkages between CT abnormalities in general, CT abnormalities leading to decisions regarding further diagnostic or evaluation procedures (such as in-hospital observation), and CT abnormalities necessitating active intervention (such as surgery).

Diagnostic procedures such as CT scans can be expensive to use with all patients presenting with MTBI and impractical in locations where CT scanners are less easily accessible. We have strong evidence on the use of clinical risk factors to screen for intracranial lesions in adults, and therefore the need for CT scan (4). However, the evidence regarding use of clinical risk factors to make the decision to discharge home without observation is weaker, and this should be an important priority area for future research.

In general, the literature on MTBI diagnosis is weak, and we accepted only 32% of the studies reviewed on the usefulness of diagnostic procedures or screening strategies. Many of the studies we could not accept as evidence were single case reports or small case series. Other studies were underpowered to identify the rare complications of interest in this topic. Of the studies that form our best-evidence synthesis, only two could be classified as phase III diagnostic studies (4, 13). That is, they utilized a sample of patients clinically suspected of having the disorder in question, the diagnostic test and gold standard were administered independently of each other (e.g. administration of the gold standard was not dependent on the findings of the diagnostic test, and administration and interpretation of the test was blinded to the gold standard and vice versa) (4). We found no phase IV studies, i.e. studies that confirm the usefulness of the diagnostic procedure in improving patients' health and outcomes. Unlike most other studies of diagnostic procedures, which can be cross-sectional in design, a phase IV diagnostic study requires a longitudinal design (e.g. cohort or randomized controlled trial), with the diagnostic procedure in question as the exposure variable, and the outcome assessed over time.

#### *Research priorities*

A research area that deserves immediate attention is an investigation of the usefulness of clinical variables to predict intracranial complications in children. Although there are a number of exploratory studies addressing this issue (phase I and phase II studies), we need phase III and IV studies to provide more definitive guidelines for emergency room triage of children with MTBI. We need large, well-designed studies addressing the predictive value of negative CT scan in children. There is also little strong evidence available about the diagnostic value of cognitive function assessments, biochemical markers of brain injury or imaging techniques other than CT in acute MTBI. We recommend that phase III studies be performed to address these topics. Although we have strong studies on clinical predictors of need for CT scanning in adults with GCS score

of 15 (14) and in adults with GCS scores 13–15 (15), these findings should be validated in other samples and settings.

## METHODOLOGICAL ISSUES AND RESEARCH PRIORITIES FOR PROGNOSIS OF MTBI

### *Methodological issues*

Papers discussing prognosis after MTBI were the most frequent, indicating a substantial interest in this area. However, this area of research had the lowest proportion (28%) of accepted papers. Many of the papers not included in our best-evidence synthesis had substantial limitations, such as use of case series designs and non-representative samples to assess frequency of post-concussion symptoms. In addition, although cross-sectional studies can provide information on prevalence of symptoms in individuals with a history of MTBI, this design cannot clearly link these symptoms to the injury, so they are of limited value as prognostic studies.

Psychological distress, medications, pain from associated injuries (such as soft-tissue injuries) and pre-injury characteristics were rarely considered, and most of the studies reporting disability after MTBI did not differentiate disability caused by the MTBI itself from disability due to associated injuries, pre-morbid factors (such as alcoholism), or even conditions that occurred subsequent to the index MTBI.

Research findings concerning prognosis of children with MTBI are strong and relatively consistent. However, there are some gaps in the literature. For example, the long-term consequences of MTBI in infants and very young children have not been well documented. Research on prognosis of adults with MTBI is weaker and needs to consider a wide range of factors such as pain, medication effects, psychological distress and litigation/compensation, as well as the more commonly considered factors such as age, gender and socio-economic status. Research designs in this area also need to carefully distinguish MTBI-specific outcomes from pre-existing characteristics. Failure to consider base rates of symptoms and cognitive deficits may result in erroneous amplification of MTBI sequelae. Where base rates are considered by comparing MTBI cases with a reference group, care must be taken to ensure the appropriateness of that reference group and to consider the issue of confounding. A recent study highlighting this reports that, in comparison with a normal control group of family practice patients, individuals making personal injury claims for emotional or industrial stress report a much higher rate of symptoms commonly associated with neuropsychological impairment (16). Clearly, then, if particular outcomes are attributed to MTBI on the basis of a comparison of MTBI cases with controls, confounding due to selection factors must be considered.

### *Research priorities*

Identification of prognostic factors is seen as a priority for research. Exploratory studies have suggested a number of

potential prognostic factors for recovery after MTBI. Confirmatory studies that explicitly control for confounding should be undertaken to assess the strength and independence of these relationships. The roles of pain, psychological distress and alcohol or drug abuse in recovery from MTBI are especially important topics to explore, especially since these factors are modifiable, at least to some extent. We also need high-quality studies on prognosis after MTBI in the elderly. These studies need to clearly differentiate outcomes attributable to the brain injury from outcomes attributable to such factors as pre-injury health problems or other injuries. In addition, there needs to be more exploration of the role of compensation/litigation issues in delayed recovery to better understand the mechanisms behind this association. Furthermore, we see the need in the immediate future to further examine the long-term consequences of MTBI in very young children.

## METHODOLOGICAL ISSUES AND RESEARCH PRIORITIES FOR TREATMENT OF MTBI

### *Methodological issues*

Research examining intervention in MTBI, either in the acute stage or, for those with poor outcome, the chronic stage, should ideally use a randomized controlled design with proper concealment of allocation to intervention groups, blind assessment of outcome and minimal loss to follow-up. Such trials should be large enough; not only for adequate power, but to maximize the likelihood that random assignment equalizes both known and unknown confounders at baseline. There are, however, instances in which random assignment to treatment groups is not possible or practical. In these cases, a large, well-designed cohort study can provide useful information on effectiveness of treatments in the community setting, although care must be taken to measure and adjust for important confounders in order to have some assurance that the outcome is a result of the intervention in question and not an artefact of baseline differences between the groups (17, 18).

A recent investigation of the size and quality of randomized controlled trials on intervention strategies for head injury of all severities reported that the currently available trials are too small and poorly designed (19). Our review of the literature also led us to the observation that one of the most striking features of the

intervention studies in MTBI is the small sample size of most of the studies (3, 19). This is especially problematic given the high loss to follow-up in many of the studies, which further decreases a trial's power to detect a meaningful treatment effect as well as introducing a selection bias. The clinical trials of non-surgical intervention for MTBI included in our task force report consist of sample sizes of between 39 and 1156 subjects at enrolment, with 32–478 subjects available for analysis at follow-up (Table II). Losses to follow-up can introduce important bias into the findings of a trial, and few studies adequately addressed this issue. In addition, few of these studies included a discussion of what a clinically meaningful treatment effect would be, or a report of what sample size would have been adequate to detect such a difference between intervention arms.

### *Research priorities*

We recommend that intervention trials give more consideration to the optimal target population and timing of an intervention. This necessitates consideration of the findings of studies on prognosis after MTBI in order to identify those at risk of difficulties for recovery and what factors to intervene on. Studies targeting interventions with those most likely to benefit from such intervention are more efficient. Identification of factors associated with poor prognosis, especially when those factors are modifiable, provide a useful target for an intervention study. Some of these factors may be unrelated to the MTBI itself (5), but might be related to factors that increase individuals' risk of poor outcome, such as emotional reactions to an injury or unrelated life events that impact on recovery.

## FUTURE LITERATURE REVIEWS

Finally, we recommend that our recommendations be updated in 5 years. Given the widespread interest of clinicians, researchers and policymakers in MTBI, we anticipate that research endeavours over the next five years will see new insights into MTBI and will lend more clarity to the issues we have identified. In addition, the volume of literature on MTBI is continuing to expand, and we believe that the volume of new literature in the next 5 years will justify another review of the evidence.

Table II. Size of clinical trials of intervention of mild traumatic brain injury

| Author(s)                          | Number enrolled at baseline | Number included in the analysis                |
|------------------------------------|-----------------------------|--|
| Bohnen et al., 1993 (77)           | 39                          | 32 at 3-month follow-up                        |
| Mittenberg et al., 1996 (85)       | 58                          | 58 at 6-month follow-up                        |
| Chapman et al., 1999 (86)          | 61                          | 50 at end of treatment period                  |
| Lowdon et al., 1989 (183)          | 111                         | 77 at 6-week follow-up                         |
| Paniak et al., 1998; 2000 (84, 81) | 119                         | 111 at 3-months and 105 at 1-year follow-up    |
| Relander et al., 2002 (321)        | 178                         | 178 at first follow-up, 59 at 1-year follow-up |
| Wade et al., 1998 (323)            | 314                         | 218 at 6-month follow-up                       |
| Casey et al., 1987 (213)           | 321                         | 204 at 1-month follow-up                       |
| Wade et al., 1997 (194)            | 1,156                       | 478 at 6-month follow-up                       |

## CONCLUSIONS

Future research on MTBI must avoid the shortcomings evident in much of the current literature. Clear and relevant research questions must be addressed with study designs appropriate to answer these questions. Studies must be reported with sufficient clarity to permit the reader to understand the source population and sampling frame, how subjects were selected, how the study was carried out and how it was analysed. Studies must be large enough to address the research question, and it must be clear that consideration was given to the number of participants needed to ensure adequate power to detect a clinically meaningful effect. It should be demonstrated that participants are representative of the population being generalized to, both at enrolment and, where appropriate, at follow-up. Attribution of outcomes to MTBI should be cautious and causal inferences made only when other possible aetiological factors have been considered. Finally, the conclusions reached in research reports should be based on the research findings, should fit the inherent restrictions imposed by the design used, and should not extend beyond this.

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