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Time to Resolution of Symptoms and Recovery after Mild Traumatic Brain Injury: Protocol for a Systematic Review and Meta-Analysis

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Time to Resolution of Symptoms and Recovery after Mild Traumatic Brain Injury: Protocol for a Systematic Review and Meta-Analysis

Registration

PROSPERO registration number: CRD42023462797

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NIHR Clinical Lectureship awarded to Dr Richter

Conflicts of interest

Dr Virginia Newcombe holds a grant with Roche Pharmaceuticals for a study and an honorarium from Integra. These are unrelated to this manuscript.

Abstract

Introduction

Mild traumatic brain injury (mTBI) is a leading cause of morbidity and mortality, with approximately 1 out of 200 people each year sustaining a mTBI in Europe. There is a growing awareness that recovery may take months or years, however the exact time frame of recovery remains ill defined in the literature. This systematic review aims to record the range of outcome measures used for mTBI and understand the time to recovery for different outcomes.

Methods and analysis

This protocol complies with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline. A pre-specified literature search for articles in the English language will be conducted from database inception to the date of searches using MEDLINE and EMBASE. For each study, screening of title, abstract and full-text as well as data extraction will be done by two reviewers, with an adjudicating third reviewer if required. Risk of bias will be assessed with the Cochrane risk of bias tool for clinical trials, and the Newcastle Ottawa score for cohort studies. The primary outcome is the time to resolution of symptoms in mTBI patients who have a full recovery, using any validated outcome measure. Results will be categorised by symptom groups including but not limited to post-concussive symptoms, mental health, functional recovery and health related quality of life. For mTBI patients who do not recover, this review will also explore time to plateau of symptoms and sequalae of these symptoms. Where possible meta-analysis will be undertaken, with narrative review undertaken when this is not possible. Sub-group analyses of patients aged over 64 years, and patients with repetitive head injury, are planned.

Ethical review and dissemination

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

Prospero registration number

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Word count 305

Strengths and limitations of this study

- ⇒ We aim to provide a comprehensive and rigorous systematic review of recovery profiles following mTBI, informing clinicians on the expected recovery and identifying specific targets for further research on therapeutic intervention.
- ⇒ We will examine a wide range of outcome measures, in keeping with the heterogenous nature of deficits clinically observed following mTBI.
- ⇒ We will employ rigorous methodology, with results reported in keeping with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.
- ⇒ The search algorithm is open with wide inclusion criteria, allowing identification of a wide range of papers to best inform the reviews conclusions.
- ⇒ The heterogeneity of the included studies may limit the ability for quantitative summary in the form of meta-analysis, with a qualitative summary anticipated for a wide section of the literature.
- ⇒ The review will be limited to articles in English

Background

Traumatic brain inury (TBI) is a leading cause of morbidity and mortality worldwide, with a large associated economic burden to the global healthcare system.[1][2] TBI is classically defined as mild (mTBI), moderate and severe depending on clinical factors such as conscious level and neurological functioning.[3][4] Every year in Europe, approximately 1 out of 200 people are affected by mTBI.[5] Further, this is likely an underestimate, with mTBIs often undiagnosed and unrecorded.[6][7]

After excluding a need for admission or neurosurgical intervention, current practice commonly is to discharge patients who have mTBI with head injury advice and no routine follow-up unless specific concerns.[8] A widely held dogma is that the majority of patients with mTBI go on to make a full recovery.[8][9] However, “mild” TBI should not be underestimated, with this classification presenting somewhat of a misnomer.[9] A significant proportion of mTBI patients will continue to experience significant, life-changing problems that can last months to years, representing a significant individual burden for patients, families, and also a wider public health burden.[8] These symptoms can include severe fatigue, poor memory, headaches, and mental health issues (including anxiety, depression, and post-traumatic stress).[10] Further evidence, largely observed in the related field of sports related concussion, has highlighted potential long term complications with repetitive minor head injuries (two or more prior concussions).[11][12][13] However, the translation of this away from sport to the wider world of mTBI is less established.

There is increasing evidence of ongoing symptoms following mTBI.[8][14][15] High quality evidence has emerged from several large observational studies including CENTER-TBI, TRACK-TBI and UPFRONT, generally demonstrating that between 30-50% of patients demonstrate functional deficits 3-12 months following mTBI.[16][17][18][19][20][21][22] However, studies collecting serial outcome measurements represent a smaller pool of evidence.[23]Further, there is significant heterogeneity in the literature concerning outcome measurement tool, the timepoint of outcome measurement, and the definition of mTBI.

There is a need for a synthesis of the current literature, firstly to establish the landscape of outcome measures used in mTBI recovery, and secondly to summarise the temporal recovery profile across the variety of symptomatic outcomes a patient may experience. Greater understanding of this can aid in clinical discussion with patients at the time of injury over expected recovery, inform when to follow up patients with ongoing symptoms, and help in identification of patient groups and time-periods for further therapeutic studies.

This aims of systematic review and meta-analysis are

1. to explore the scope of outcome measures used in mTBI research, and
2. to build a picture of the temporal recovery profile of patients who have sustained a mTBI . .

Methods

The review will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study has been registered on the Prospero database (CRD42023462797).

Eligibility criteria

The Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) eligibility criteria are detailed in Table 1. Eligibility criteria for inclusion will include both observational and interventional studies, enrolling adults (age equal to or greater than 16) with mTBI and assessment of patient recovery. To reduce the risk chronological and selection bias associated with later recruitment only studies recruiting patients within one week of injury will be included. A wide range of mTBI definitions will be included:

- Presentation with a history of a head injury, GCS 13 to 15.[10][26]
- American Congress of Rehabilitation Medicine, revised by the World Health Organisation (WHO) definition: Glasgow coma score 13-15 at 30 minutes post-injury, and one or more of the following symptoms: 30 minutes loss of consciousness, 24 hours post-traumatic amnesia (PTA), impaired mental state after and temporally congruent with injury (confusion or disorientation) and/or transient neurological deficit.[27][28]
- Clinical records data definition (CDC): a documented Abbreviated Injury Severity Scale score of 2 for the head region.[29]
- An administrative data definition for surveillance or research: cases of mTBI were recognized if the patients were assigned certain diagnostic codes chosen by the authors to be consistent with the diagnosis of mTBI. These include the International Classification of Diseases ninth, and tenth edition.[30]

All reported outcomes and outcome measures will be included, including functional recovery, mental health, physical health symptoms, and health related quality of life. The reference list of review articles found in the search will be screened for further references that meet the inclusion criteria.

The exclusion criteria for study type will be case-control studies, case series, case reports, qualitative studies, review articles and cross-sectional studies. Other exclusion criteria include: paediatric studies or mixed populations where no separated results are reported for adults or children respectively, no follow up data, and no specification of TBI severity or separate results for mTBI patients specifically.

Where multiple articles report on the same outcome measure at the same timepoint for the same patient cohort, or overlapping patient cohorts, only one article will be included, prioritising larger sample sizes and more recent publication dates.

Information sources

A planned literature search for articles in the English language will be conducted from inception to the search date using Cochrane, MEDLINE and EMBASE. A trial search was conducted on 05/10/2023 with refinement of the search criteria following this.

Search strategy

The search strategy will use MeSH terms and text words to capture studies relating to mTBI, concussion, and outcomes. The search strategy can be found in Table 2.

Study records

Study selection will be performed using the online tool Rayyan (https://www.rayyan.ai) to allow for removal of duplicate articles and for initial screening of titles and abstracts. Each title and abstract will be reviewed independently by two reviewers.[31] Two votes will be required to exclude a paper with disagreements solved through discussion or consultations with a third reviewer (principle investigator). For abstracts meeting inclusion criteria, full texts will be retrieved, and each full text will again be independently reviewed against the inclusion and exclusion criteria by two reviewers and an adjudicating third reviewer if required. Reason for study exclusion will be recorded during the full-text screening.

To establish the landscape of outcomes measures used, and to facilitate appropriate categorisation of outcome measures, the review will be undertaken in two stages. The first stage will identify the outcome measures and study cohort characteristics reported across the studies. The second stage will synthesise the results of the outcome measures. A standardised data abstraction form will be created for each stage of data extraction, piloted on at least five articles by at least two reviewers each, and the forms be adjusted as required. Data will be extracted by two independent reviewers for each selected paper. The following data items will be extracted in stage one:

1. Study design
2. Study setting
3. Sample size
4. Definition of mTBI
5. Patient demographics (age, gender, population type (military, sport, community etc.))
6. Location of recruitment (emergency department, primary care, hospital admission, sporting field etc)
7. Glasgow Coma Score
8. Presence of abnormal CT head (percentage, attributable to TBI)
9. Presence (number, severity) of subjects with a prior history of TBI
10. Time of recruitment relative to time of injury
11. Timing(s) of outcome measured
12. Outcome measures collected

The exact data items recorded for stage two will depend on the range of outcome measures found in stage one. This will include:

1. Method of recording outcome measure (i.e.. total score, binary thresholds, clinical diagnosis)
2. Definition of complete recovery
3. Proportion of patients with complete symptom resolution at each measured time point and for each outcome measure
4. Loss to follow-up at each timepoint
5. Definition of complete recovery

Where information is not available from the published manuscripts, the authors will be contacted directly.

Outcomes and prioritisation

The overall primary outcome of this systematic review and meta-analysis is the time to resolution of symptoms following mTBI. For mTBI patients who do not recover, this review will also explore time to plateau of symptoms and sequalae of these symptoms.

Data synthesis

Data will be synthesised following PRISMA guidelines. [32] Studies will be assessed clinically (PICO) and methodologically (study design, comparability, outcome ascertainment, and risk of bias). For studies reporting on the same outcome measure the I^2 test will be conducted to assess heterogeneity.

Meta-analysis is intended and will be displayed using forest plots. A narrative synthesis and summary of effect measures will be conducted if heterogeneity or risk of bias precludes formal meta-analysis.

Meta-analysis or narrative synthesis of elements will focus on time to resolution of symptoms in patients who have a full recovery, and time to plateau of symptoms and sequalae in patients who do not recover. Subgroup analysis may be undertaken for patient age (65 years or over compared to younger adults) and patients who have sustained repetitive head injury (e.g. athlete populations) if data on these cohorts is able to be extracted.

Risk of bias

Risk of bias will be assessed for all included studies. Risk of bias will be assessed with use of the Cochrane risk of bias tool for clinical trials or the Newcastle Ottawa score for cohort studies.[33][34] Two reviewers will independently assess each included study for bias. Publication bias will be assessed using funnel plots for the most commonly recorded outcomes.

Patient and public involvement

This review has been discussed by a Patient and Public Involvment and Engagement (PPIE) focus group run in conjunction with the NIHR Brain Injury MedTech Co-operative who informed its content including ensuring that different outcome measures were included. A PPIE panel will be involved with interpretation and dissemination of results.

Ethics and Dissemination

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

Contributorship statement

AN, OH, DW, SR, and VN all contributed to the conceptualisation, design, data interpretation, critical revision and final approval of the protocol.

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Tables

Table 1. Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) Strategy for Inclusion and Exclusion

PICOS Strategy	Inclusion Criteria	Exclusion Criteria
P – Population	Aged 16 years or over Diagnosed with mild traumatic brain injury (mTBI) within a week of recruitment	No follow up data available Severity of traumatic brain injury is not specified No mild TBI specific data can be extracted
I – Intervention	No specific intervention	< 30 cases of mTBI
C – Comparator	No specific comparator Not limited to studies with a control group	N/A
O – Outcome	Any study that follows up the patient beyond the time of recruitment at least once, and reports on one or more outcome measures.	Outcome(s) not clearly stated
S – Study design	Systematic reviews and meta-analyses Randomised controlled trials Cohort studies	Cross-sectional studies Case-control studies Case series Case reports Qualitative studies Review articles

Table 2. Search strategy for a systematic review and meta-analysis exploring the time to recovery for adult patients with mild traumatic brain injury

	Medline	Embase
#1	exp post-concussion syndrome/ OR exp brain concussion/ OR exp brain injuries/ OR exp craniocerebral trauma/ OR exp brain injuries, traumatic/	exp concussion/ OR exp brain injuries/ OR exp head injury/ OR exp traumatic brain injury/
#2	("MTBI" OR "mild TBI" OR "TBI" OR "traumatic brain inj*" OR "mild traumatic brain injur*").ab,ti.	("MTBI" OR "mild TBI" OR "TBI" OR "traumatic brain inj*" OR "mild traumatic brain injur*").ab,ti.
#3	exp symptom assessment/ OR exp post-concussion syndrome OR exp mental disorders/ OR exp neurologic manifestations/ OR exp depression/ OR exp dizziness/ OR exp vertigo/ OR exp sleep wake disorders/ OR exp headache/ OR exp post-traumatic headache/ OR exp headache disorders, secondary/ OR exp fatigue/ OR exp mental fatigue/ OR exp memory/ OR exp memory disorders/ OR exp irritable mood/ OR exp anxiety/ OR exp anxiety disorders/ OR exp patient health questionnaire/ OR exp Glasgow outcome scale/ OR exp dissociative disorders/ OR exp stress disorders, post-traumatic/ OR exp return to work/ OR exp "Memory and Learning Tests"/ OR exp functional status/ OR exp "Recovery of Function"/ OR exp cognition/ OR exp mental health/ OR exp social status/ OR exp disease progression/ OR exp "Quality of Life"/ OR exp prognosis/ OR exp treatment outcome/ OR exp patient reported outcome measures/	exp symptom assessment/ OR exp postconcussion syndrome/ OR exp behaviour disorder/ OR exp neurologic disease/ OR exp depression/ OR exp mood disorder/ OR exp dizziness/ OR exp vertigo/ OR exp sleep disorder/ OR exp headache/ OR exp posttraumatic headache/ OR exp secondary headache/ OR exp fatigue/ OR exp mental fatigue/ OR exp memory/ OR exp cognition/ OR exp memory disorders/ OR exp irritability/ OR exp anxiety/ OR exp patient health questionnaire/ OR exp Glasgow outcome scale/ OR exp dissociative disorder/ OR exp mental disease/ OR exp posttraumatic stress disorder/ OR exp return to work/ OR exp cognitive

		function test/ OR exp functional status/ OR exp cognition/ OR exp mental health/ OR exp social status/ OR exp disease exacerbation OR exp "quality of life"/ OR exp prognosis/ OR exp treatment outcome/ OR exp patient-reported outcome/
#4	("symptom*" or "prognos*" or "quality of life" or "functional" or "mortality" or "GOSE" or "Rivermead" or "outcome*").ab,ti.	("symptom*" or "prognos*" or "quality of life" or "functional" or "mortality" or "GOSE" or "Rivermead" or "outcome*").ab,ti.
#5	exp time factors/ OR exp chronology as topic/ OR exp follow up studies/	exp time factor/ OR exp chronology/ OR exp follow up/
#6	("chronology" OR "time course" OR "recovery" OR "resolution" OR "rehabilitation").ab,ti.	("chronology" OR "time course" OR "recovery" OR "resolution" OR "rehabilitation").ab,ti.
#7	exp pediatrics/ OR exp child/ OR exp infant/ OR exp schools/	exp pediatrics/ OR exp child/ OR exp infant/ OR exp school/
#8	("p?ediatric*" OR "child*" OR "infant*").ab,ti.	("p?ediatric*" OR "child*" OR "infant*").ab,ti.

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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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review **Page 1**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **N/A**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number **Page 1**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **Page 1**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review **Page 6**
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 **Page 1**
Sponsor	5b	Provide name for the review funder and/or sponsor **Page 1**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **Page 1**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known **Page 2**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **Page 3**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review **Page 3**
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 **Page 4**
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 **Page 4**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **Page 4**

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) **Page 5**
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 **Page 5**
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 **Page 5**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **Page 6**
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 **Page 6**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **Page 6**
	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) **Page 6**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **Page 6 Page 6**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **Page 6**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) **Page 6**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **Page 6**

*** 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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Time to Resolution of Symptoms and Recovery after Mild Traumatic Brain Injury: Protocol for a Systematic Review and Meta-Analysis

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Time to Resolution of Symptoms and Recovery after Mild Traumatic Brain Injury: Protocol for a Systematic Review and Meta-Analysis

Registration

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Competing interest statement

Dr Virginia Newcombe holds a grant with Roche Pharmaceuticals for a study and an honorarium from Integra. These are unrelated to this manuscript.

Abstract

Introduction

Mild traumatic brain injury (mTBI) is a leading cause of morbidity and mortality, with approximately 1 out of 200 people each year sustaining a mTBI in Europe. There is a growing awareness that recovery may take months or years, however the exact time frame of recovery remains ill defined in the literature. This systematic review aims to record the range of outcome measures used for mTBI and understand the time to recovery for different outcomes.

Methods and analysis

This protocol complies with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline. A pre-specified literature search for articles in the English language will be conducted from database inception to the date of searches using MEDLINE and EMBASE. . A trial search was conducted on 05/10/2023 with refinement of the search criteria following this. For each study, screening of title, abstract and full-text as well as data extraction will be done by two reviewers, with an adjudicating third reviewer if required. Risk of bias will be assessed with the Cochrane risk of bias tool for clinical trials, and the Newcastle Ottawa score for cohort studies. The primary outcome is the time to resolution of symptoms in mTBI patients who have a full recovery, using any validated outcome measure. Results will be categorised by symptom groups including but not limited to post-concussive symptoms, mental health, functional recovery and health related quality of life. For mTBI patients who do not recover, this review will also explore time to plateau of symptoms and sequalae of these symptoms. Where possible meta-analysis will be undertaken, with narrative review undertaken when this is not possible. Sub-group analyses of patients aged over 64 years, and patients with repetitive head injury, are planned.

Ethical review and dissemination

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

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Strengths and limitations of this study

- ⇒ We aim to provide a comprehensive and rigorous systematic review of recovery profiles following mTBI, informing clinicians on the expected recovery and identifying specific targets for further research on therapeutic intervention.
- ⇒ We will examine a wide range of outcome measures, in keeping with the heterogenous nature of deficits clinically observed following mTBI.
- ⇒ We will employ rigorous methodology, with results reported in keeping with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.
- ⇒ The search algorithm is open with wide inclusion criteria, allowing identification of a wide range of papers to best inform the reviews conclusions.
- ⇒ The heterogeneity of the included studies may limit the ability for quantitative summary in the form of meta-analysis, with a qualitative summary anticipated for a wide section of the literature.
- ⇒ The review will be limited to articles in English

Background

Traumatic brain inury (TBI) is a leading cause of morbidity and mortality worldwide, with a large associated economic burden to the global healthcare system.[1] [2] Over 85% of TBI may be classified as mild (mTBI) according to conscious level and neurological functioning.[3] [4] mTBI leads to a significant public health burden. Every year in Europe, approximately 1 out of 200 people are affected by mTBI.[5] Further, this is likely an underestimate, with mTBIs often undiagnosed and unrecorded.[6] [7]

After excluding a need for admission or neurosurgical intervention, current practice commonly is to discharge patients who have mTBI with head injury advice and no routine follow-up unless specific concerns.[8] A widely held dogma is that the majority of patients with mTBI go on to make a full recovery.[8] [9] However, “mild” TBI should not be underestimated, with this classification presenting somewhat of a misnomer.[9] A significant proportion of mTBI patients will continue to experience significant, life-changing problems that can last months to years, representing a significant individual burden for patients, families, and also a wider public health burden.[2] [8] These symptoms can include severe fatigue, poor memory, headaches, and mental health issues (including anxiety, depression, and post-traumatic stress).[2] Further evidence, largely observed in the related field of sports related concussion, has highlighted potential long term complications with repetitive minor head injuries (two or more prior concussions).[10] [11] [12] However, the translation of this away from sport to the wider world of mTBI is less established.

There is increasing evidence of ongoing symptoms following mTBI.[8] [13] [14] High quality evidence has emerged from several large observational studies including CENTER-TBI, TRACK-TBI and UPFRONT, generally demonstrating that between 30-50% of patients demonstrate functional deficits 3 to12 months following mTBI. [15][16][17][18][19][20][21] However, studies collecting serial outcome measurements represent a smaller pool of evidence.[22] Further, there is significant heterogeneity in the literature concerning outcome measurement tool, the timepoint of outcome measurement, and the definition of mTBI.

There is a need for a synthesis of the current literature, firstly to establish the landscape of outcome measures used in mTBI recovery, and secondly to summarise the temporal recovery profile across the variety of symptomatic outcomes a patient may experience. Greater understanding of this can aid in clinical discussion with patients at the time of injury over expected recovery, inform when to follow up patients with ongoing symptoms, and help in identification of patient groups and time-periods for further therapeutic studies.

This aims of systematic review and meta-analysis are

1. to explore the scope of outcome measures used in mTBI research, and
2. to build a picture of the temporal recovery profile of patients who have sustained a mTBI

Methods

The review will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study has been registered on the Prospero database (CRD42023462797).

Eligibility criteria

The Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) eligibility criteria are detailed in Table 1. Eligibility criteria for inclusion will include both observational and interventional studies, enrolling adults (age equal to or greater than 16) with mTBI and assessment of patient recovery. To reduce the risk chronological and selection bias associated with later recruitment only studies recruiting patients within eight weeks of injury will be included; or has assessed participants prior to sustaining an injury. A wide range of mTBI definitions will be included:

- Presentation with a history of a head injury, GCS 13 to 15.[2] [23]
- American Congress of Rehabilitation Medicine, revised by the World Health Organisation (WHO) definition published in 1993[24] and revised in 2023[25]: Glasgow coma score 13-15 at 30 minutes post-injury or later upon presentation to health care, and one or more of the following symptoms: up to 30 minutes loss of consciousness, up to 24 hours post-traumatic amnesia (PTA), impaired mental state after and temporally congruent with injury (confusion or disorientation) and/or transient neurological deficit.[25] [26]
- Clinical records data definition (CDC): a documented Abbreviated Injury Severity Scale score of 2 for the head region.[27]
- An administrative data definition for surveillance or research: cases of mTBI were recognized if the patients were assigned certain diagnostic codes chosen by the authors to be consistent with the diagnosis of mTBI. These include the International Classification of Diseases ninth, and tenth edition.[28]

All reported outcomes and outcome measures will be included, including functional recovery, mental health, physical health symptoms, and health related quality of life. The reference list of review articles found in the search will be screened for further references that meet the inclusion criteria.

The exclusion criteria for study type will be case-control studies, case series, case reports, qualitative studies, review articles and cross-sectional studies. Other exclusion criteria include: paediatric studies or mixed populations where no separated results are reported for adults or children respectively, no follow up data, and no specification of TBI severity or separate results for mTBI patients specifically.

Where multiple articles report on the same outcome measure at the same timepoint for the same patient cohort, or overlapping patient cohorts, only one article will be included, prioritising larger sample sizes and more recent publication dates.

Information sources

A planned literature search for articles in the English language will be conducted from inception to the search date using Cochrane, MEDLINE and EMBASE. A trial search was conducted on 05/10/2023 with refinement of the search criteria following this.

Search strategy

The search strategy will use MeSH terms and text words to capture studies relating to mTBI, concussion, and outcomes. The search strategy can be found in Table 2.

Study records

Study selection will be performed using the online tool Rayyan (https://www.rayyan.ai) to allow for removal of duplicate articles and for initial screening of titles and abstracts. Each title and abstract will be reviewed independently by two reviewers.[29] Two votes will be required to exclude a paper with disagreements solved through discussion or consultations with a third reviewer (principle investigator). For abstracts meeting inclusion criteria, full texts will be retrieved, and each full text will again be independently reviewed against the inclusion and exclusion criteria by two reviewers and an adjudicating third reviewer if required. Reason for study exclusion will be recorded during the full-text screening.

To establish the landscape of outcomes measures used, and to facilitate appropriate categorisation of outcome measures, the review will be undertaken in two stages. The first stage will identify the outcome measures and study cohort characteristics reported across the studies. The second stage will synthesise the results of the outcome measures. A standardised data abstraction form will be created for each stage of data extraction, piloted on at least five articles by at least two reviewers each, and the forms be adjusted as required. Data will be extracted by two independent reviewers for each selected paper. The following data items will be extracted in stage one:

1. Study design
2. Study setting
3. Sample size
4. Definition of mTBI
5. Patient demographics (age, gender, population type (military, sport, community etc.), education level, employment status)
6. Mechanism of injury including intentional violence
7. Premorbid conditions (mental health (including post-traumatic stress disorder, depression and anxiety), sleep disorders, substance/alcohol use disorder, migraine, attention deficit disorder, dementia, other neurological conditions and other medical co-morbidities)
8. Other factors that may influence outcome: workers compensation, medico-legal action.
9. Location of recruitment (emergency department, primary care, hospital admission, sporting field etc)
10. Glasgow Coma Score
11. Presence of abnormal CT head (percentage, attributable to TBI)
12. Presence (number, severity) of subjects with a prior history of TBI
13. Time of recruitment relative to time of injury
14. Timing(s) of outcome measured
15. Outcome measures collected
16. Whether symptom or neurocognitive validity measures were collected and the result of such measures.

The exact data items recorded for stage two will depend on the range of outcome measures found in stage one. This will include:

1. Method of recording outcome measure (i.e. total score, binary thresholds, clinical diagnosis)
2. Definition of complete recovery
3. Proportion of patients with complete symptom resolution at each measured time point and for each outcome measure
4. Loss to follow-up at each timepoint
5. Definition of complete recovery

Where information is not available from the published manuscripts, the authors will be contacted directly.

Outcomes and prioritisation

The overall primary outcome of this systematic review and meta-analysis is the time to resolution of symptoms following mTBI. For mTBI patients who do not recover, this review will also explore time to plateau of symptoms and sequalae of these symptoms.

Data will be synthesised following PRISMA guidelines.[30]

Assessment of bias and heterogeneity

Studies will be assessed clinically and methodologically (study design, comparability, outcome ascertainment, and risk of bias). Risk of bias will be assessed with use of the Cochrane risk of bias tool 2.0 (ROB 2.0) for clinical trials, and the Newcastle Ottawa score for cohort studies.[31] [32] This will include assessment of the impact of missing data on effect estimates.[33] [34] Two reviewers will independently assess each included study for bias. Publication bias and small-study effects will be assessed using funnel-plots for the most commonly recorded outcomes for included RCTs. As funnel plots are difficult to interpret for observational studies they will not be used in this case. However potential for bias including reporting will be included in the discussion.[24] The Egger method to assess asymmetry will be used for any outcomes with more than ten individual studies.

For studies reporting on the same outcome measure the magnitude of variation or heterogeneity between studies will be measured by the index of heterogeneity (I^2 and its confidence intervals).[35] I^2 values of 25%, 50% and 75% are assumed to represent low, medium and high heterogeneity, respectively. The significance of the heterogeneity will be determined by χ^2 for Q statistics.

Data synthesis

Data extracted from included studies will be presented in evidence tables or as a narrative summary. We will analyse studies with one outcome time point and multiple outcome time points separately and then pool this data if appropriate. For statistical analyses p-value less than 0.05 will be considered significant.

If data are too heterogenous to pool then narrative synthesis of elements will be performed. This will focus on time to resolution of symptoms in patients who have a full recovery, and time to plateau of symptoms and sequalae in patients who do not recover. Tables of data extracted from each study will be presented.

Data analysis

Descriptive analysis will be performed. If studies have sufficiently homogenous populations, exposures and outcomes data will be pooled and meta-analysis performed to calculate summary measures of effect. To allow for expected differences between studies a random-effects model will be used.

For single outcome time point data a series of exploratory multivariate regression models will be used to understand the effects of participant demographics and premorbid/post morbid factors on outcome. If the relationship is not parametric other non-parametric methods of curve fitting will be used.

For studies with more than one outcome timepoint the recovery curve for each study will be presented graphically. If parametric data the equation will be reported and splines will be used for non-parametric data.

Subgroup analyses

Where possible prespecified subgroup analysis will be undertaken for key groups where differential extent and rate recovery may be expected. These groups have been chosen due to either prior literature supporting this (e.g. older age,[36] female sex,[24] repetitive TBI[11] [12] [37]) and/or them being discrete populations which have special characteristics (e.g. military/blast injuries and sports concussion).[2] The planned sub-analyses will therefore be: patient age (65 years or over compared to younger adults), sex, patients who have sustained more than one head injury, military and/or blast injuries, and sports concussion including sub-concussive injuries. Where appropriate sensitivity analyses will be performed using studies which have collected validity measures.

Sensitivity analysis

Sensitivity analyses will be performed if there is significant heterogeneity with outlying studies being removed. Studies at high risk of bias will also be excluded and main conclusions will be based on studies at low risk of bias.

Patient and public involvement

This review has been discussed by a Patient and Public Involvment and Engagement (PPIE) focus group run in conjunction with the NIHR Brain Injury MedTech Co-operative who informed its content including ensuring that different outcome measures were included. A PPIE panel will be involved with interpretation and dissemination of results.

Ethics and Dissemination

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

Contributorship statement

AN, OH, HH, DW, SR, and VN all contributed to the conceptualisation, design, data interpretation, critical revision and final approval of the protocol.

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Tables

Table 1. Population, Exposure, Comparison, Outcomes, and Study Design (PECOS) Strategy for Inclusion and Exclusion

PICOS Strategy	Inclusion Criteria	Exclusion Criteria
P – Population	Aged 16 years or over Sustained an injury consistent with mild traumatic brain injury (mTBI) within 8 weeks of recruitment or had assessment prior to sustaining a mTBI.	No follow up data available Severity of traumatic brain injury is not specified No mild TBI specific data can be extracted < 30 cases of mTBI
E – Exposure	Mechanism of injury consistent with mTBI	
C – Comparator	No specific comparator Not limited to studies with a control group	N/A
O – Outcome	Any study that follows up the patient beyond the time of recruitment at least once, and reports on one or more outcome measures.	Outcome(s) not clearly stated
S – Study design	Systematic reviews and meta-analyses Randomised controlled trials Cohort studies	Cross-sectional studies Case-control studies Case series Case reports Qualitative studies Review articles

Table 2. Search strategy for a systematic review and meta-analysis exploring the time to recovery for adult patients with mild traumatic brain injury

	Medline	Embase
#1	exp post-concussion syndrome/ OR exp brain concussion/ OR exp brain injuries/ OR exp craniocerebral trauma/ OR exp brain injuries, traumatic/	exp concussion/ OR exp brain injuries/ OR exp head injury/ OR exp traumatic brain injury/
#2	("MTBI" OR "mild TBI" OR "TBI" OR "traumatic brain inj*" OR "mild traumatic brain injur*").ab,ti.	("MTBI" OR "mild TBI" OR "TBI" OR "traumatic brain inj*" OR "mild traumatic brain injur*").ab,ti.
#3	exp symptom assessment/ OR exp post-concussion syndrome OR exp mental disorders/ OR exp neurologic manifestations/ OR exp depression/ OR exp dizziness/ OR exp vertigo/ OR exp sleep wake disorders/ OR exp headache/ OR exp post-traumatic headache/ OR exp headache disorders, secondary/ OR exp fatigue/ OR exp mental fatigue/ OR exp memory/ OR exp memory disorders/ OR exp irritable mood/ OR exp anxiety/ OR exp anxiety disorders/ OR exp patient health questionnaire/ OR exp Glasgow outcome scale/ OR exp dissociative disorders/ OR exp stress	exp symptom assessment/ OR exp postconcussion syndrome/ OR exp behaviour disorder/ OR exp neurologic disease/ OR exp depression/ OR exp mood disorder/ OR exp dizziness/ OR exp vertigo/ OR exp sleep disorder/ OR exp headache/ OR exp posttraumatic headache/ OR exp secondary headache/ OR exp fatigue/ OR exp mental fatigue/ OR exp memory/ OR exp cognition/ OR exp memory

	disorders, post-traumatic/ OR exp return to work/ OR exp "Memory and Learning Tests"/ OR exp functional status/ OR exp "Recovery of Function"/ OR exp cognition/ OR exp mental health/ OR exp social status/ OR exp disease progression/ OR exp "Quality of Life"/ OR exp prognosis/ OR exp treatment outcome/ OR exp patient reported outcome measures/	disorders/ OR exp irritability/ OR exp anxiety/ OR exp patient health questionnaire/ OR exp Glasgow outcome scale/ OR exp dissociative disorder/ OR exp mental disease/ OR exp posttraumatic stress disorder/ OR exp return to work/ OR exp cognitive function test/ OR exp functional status/ OR exp cognition/ OR exp mental health/ OR exp social status/ OR exp disease exacerbation OR exp "quality of life"/ OR exp prognosis/ OR exp treatment outcome/ OR exp patient-reported outcome/
#4	("symptom*" or "prognos*" or "quality of life" or "functional" or "mortality" or "GOSE" or "Rivermead" or "outcome*").ab,ti.	("symptom*" or "prognos*" or "quality of life" or "functional" or "mortality" or "GOSE" or "Rivermead" or "outcome*").ab,ti.
#5	exp time factors/ OR exp chronology as topic/ OR exp follow up studies/	exp time factor/ OR exp chronology/ OR exp follow up/
#6	("chronology" OR "time course" OR "recovery" OR "resolution" OR "rehabilitation").ab,ti.	("chronology" OR "time course" OR "recovery" OR "resolution" OR "rehabilitation").ab,ti.
#7	exp pediatrics/ OR exp child/ OR exp infant/ OR exp schools/	exp pediatrics/ OR exp child/ OR exp infant/ OR exp school/
#8	("p?ediatric*" OR "child*" OR "infant*").ab,ti.	("p?ediatric*" OR "child*" OR "infant*").ab,ti.

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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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review **Page 1**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **N/A**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number **Page 1**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **Page 1**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review **Page 8**
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 **Page 1**
Sponsor	5b	Provide name for the review funder and/or sponsor **Page 1**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **Page 1**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known **Page 3**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **Page 3**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review **Page 4**
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 **Page 5**
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 **Page 5**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **Page 5**

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) **Page 5**
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 **Page 5**
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 **Page 5**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **Page 6**
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 **Page 6**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **Page 7**
	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) **Page 7**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **Page 7**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **Page 7**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) **Page 7**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **Page 7**

*** 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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Time to Resolution of Symptoms and Recovery after Mild Traumatic Brain Injury: Protocol for a Systematic Review and Meta-Analysis

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Time to Resolution of Symptoms and Recovery after Mild Traumatic Brain Injury: Protocol for a Systematic Review and Meta-Analysis

Registration

PROSPERO registration number: CRD42023462797

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Competing interest statement

Dr Virginia Newcombe holds a grant with Roche Pharmaceuticals for a study and an honorarium from Integra. These are unrelated to this manuscript.

Abstract

Introduction

Mild traumatic brain injury (mTBI) is a leading cause of morbidity and mortality, with approximately 1 out of 200 people each year sustaining a mTBI in Europe. There is a growing awareness that recovery may take months or years. However, the exact time frame of recovery remains ill-defined in the literature. This systematic review aims to record the range of outcome measures used for mTBI and understand the time to recovery for different outcomes.

Methods and analysis

This protocol complies with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline. A pre-specified literature search for articles in the English language will be conducted from database inception to the date of searches using MEDLINE and EMBASE. A trial search was conducted on 05/10/2023 with refinement of the search criteria following this. For each study, screening of the title, abstract and full text, as well as data extraction, will be done by two reviewers, with an adjudicating third reviewer if required. The risk of bias will be assessed using the Cochrane risk of bias tool for clinical trials and the Newcastle Ottawa score for cohort studies. The primary outcome is the time to resolution of symptoms in mTBI patients who have a full recovery, using any validated outcome measure. Results will be categorised by symptom groups, including but not limited to post-concussive symptoms, mental health, functional recovery and health-related quality of life. For mTBI patients who do not recover, this review will also explore the time to the plateau of symptoms and the sequelae of these symptoms. Where possible, meta-analysis will be undertaken, with a narrative review undertaken when this is not possible. Sub-group analyses of patients aged over 64 years, and patients with repetitive head injury, are planned.

Ethical review and dissemination

Ethical review is not required, as no original data will be collected. Results will be disseminated through peer-reviewed publications and academic conferences.

Prospero registration number

CRD42023462797

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Strengths and limitations of this study

- ⇒ We aim to provide a comprehensive and rigorous systematic review of recovery profiles following mTBI, informing clinicians on the expected recovery and identifying specific targets for further research on therapeutic intervention.
- ⇒ We will examine a wide range of outcome measures, in keeping with the heterogenous nature of deficits clinically observed following mTBI..
- ⇒ The search algorithm is open with wide inclusion criteria, allowing identification of a wide range of papers to best inform the reviews conclusions.
- ⇒ The heterogeneity of the included studies may limit the ability for quantitative summary in the form of meta-analysis, with a qualitative summary anticipated for a wide section of the literature.

Background

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide, with a large associated economic burden on the global healthcare system.[1] [2] Over 85% of TBI may be classified as mild (mTBI) according to consciousness level and neurological functioning.[3] [4] mTBI leads to a significant public health burden. Every year in Europe, approximately 1 out of 200 people are affected by mTBI.[5] Further, this is likely an underestimate, with mTBIs often undiagnosed and unrecorded.[6] [7]

After excluding a need for admission or neurosurgical intervention, current practice commonly is to discharge patients who have mTBI with head injury advice and no routine follow-up unless specific concerns arise.[8] A widely held dogma is that the majority of patients with mTBI go on to make a full recovery.[8] [9] However, “mild” TBI should not be underestimated, with this classification presenting somewhat of a misnomer.[9] A significant proportion of mTBI patients will continue to experience substantial, life-changing problems that can last months to years, representing a significant individual burden for patients and families and also a wider public health burden.[2] [8] These symptoms can include severe fatigue, poor memory, headaches, and mental health issues (including anxiety, depression, and post-traumatic stress).[2] Further evidence, largely observed in the field of sports-related concussions, has highlighted potential long-term complications with repetitive minor head injuries (two or more prior concussions).[10] [11] [12] However, the translation of this away from sport to the wider world of mTBI is less established.

There is increasing evidence of ongoing symptoms following mTBI.[8] [13] [14] High-quality evidence has emerged from several large observational studies, including CENTER-TBI, TRACK-TBI and UPFRONT, generally demonstrating that 30-50% of patients demonstrate functional deficits 3 to 12 months following mTBI. [15][16][17][18][19][20][21] However, studies collecting serial outcome measurements represent a smaller pool of evidence.[22] Further, there is significant heterogeneity in the literature concerning outcome measurement tools, the timepoint of outcome measurement, and the definition of mTBI.

There is a need to synthesise the current literature to establish the landscape of outcome measures used in mTBI recovery and summarise the temporal recovery profile across the variety of symptomatic outcomes a patient may experience. A greater understanding of this can aid in clinical discussion with patients at the time of injury over expected recovery,

inform when to follow up with patients with ongoing symptoms, and help identify patient groups and time periods for further therapeutic studies.

The aims of systematic review and meta-analysis are

1. to explore the scope of outcome measures used in mTBI research and
2. to build a picture of the temporal recovery profile of patients who have sustained a mTBI

Methods

The review will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study has been registered on the Prospero database (CRD42023462797).

Eligibility criteria

The eligibility criteria for the Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) are detailed in Table 1. Eligibility criteria for inclusion will include observational and interventional studies, enrolling adults (age equal to or greater than 16) with mTBI and assessing patient recovery. To reduce the risk of chronological and selection bias associated with later recruitment, only studies recruiting patients within eight weeks of injury or studies that assessed participants prior to sustaining an injury will be included. A wide range of mTBI definitions will be included:

- Presentation with a history of a head injury, GCS 13 to 15.[2] [23]
- American Congress of Rehabilitation Medicine, revised by the World Health Organisation (WHO) definition published in 1993[24] and revised in 2023[25]: Glasgow coma score 13-15 at 30 minutes post-injury or later upon presentation to health care, and one or more of the following symptoms: up to 30 minutes loss of consciousness, up to 24 hours post-traumatic amnesia (PTA), impaired mental state after and temporally congruent with injury (confusion or disorientation) and/or transient neurological deficit.[25] [26]
- Clinical records data definition (CDC): a documented Abbreviated Injury Severity Scale score of 2 for the head region.[27]
- An administrative data definition for surveillance or research: cases of mTBI were recognised if the patients were assigned certain diagnostic codes chosen by the authors to be consistent with the diagnosis of mTBI. These include the International Classification of Diseases' ninth and tenth editions.[28]

All reported outcomes and outcome measures, including functional recovery, mental health, physical health symptoms, and health-related quality of life, will be included. The reference list of review articles in the search will be screened for further references that meet the inclusion criteria.

The exclusion criteria for study type will be case-control studies, case series, case reports, qualitative studies, review articles and cross-sectional studies. Other exclusion criteria include paediatric studies or mixed populations where no separated results are reported for adults or children respectively, no follow up data, and no specification of TBI severity or separate results for mTBI patients specifically.

Where multiple articles report on the same outcome measure at the same time point for the same patient cohort or overlapping patient cohorts, only one article will be included, prioritising larger sample sizes and more recent publication dates.

Information sources

A planned literature search for articles in the English language will be conducted from inception to the search date using Cochrane, MEDLINE and EMBASE. A trial search was conducted on 05/10/2023 with refinement of the search criteria following this.

Search strategy

The search strategy will use MeSH terms and text words to capture studies relating to mTBI, concussion, and outcomes. The search strategy can be found in Table 2.

Study records

Study selection will be performed using the online tool Rayyan (https://www.rayyan.ai) to allow for the removal of duplicate articles and the initial screening of titles and abstracts. Each title and abstract will be reviewed independently by two reviewers.[29] Two votes will be required to exclude a paper with disagreements solved through discussion or consultations with a third reviewer (principal investigator). For abstracts meeting inclusion criteria, full texts will be retrieved, and each full text will again be independently reviewed against the inclusion and exclusion criteria by two reviewers and an adjudicating third reviewer if required. The reason for study exclusion will be recorded during the full-text screening.

The review will be undertaken in two stages to establish the landscape of outcome measures used and to facilitate appropriate categorisation of outcome measures. The first stage will identify the outcome measures and study cohort characteristics reported across the studies. The second stage will synthesise the results of the outcome measures. A standardised data abstraction form will be created for each data extraction stage, piloted on at least five articles by at least two reviewers each, and the forms will be adjusted as required. Data will be extracted by two independent reviewers for each selected paper. The following data items will be extracted in stage one:

1. Study design
2. Study setting
3. Sample size
4. Definition of mTBI
5. Patient demographics (age, gender, population type (military, sport, community etc.), education level, employment status)
6. Mechanism of injury, including intentional violence
7. Premorbid conditions (mental health (including post-traumatic stress disorder, depression and anxiety), sleep disorders, substance/alcohol use disorder, migraine, attention deficit disorder, dementia, other neurological conditions and other medical co-morbidities)
8. Other factors that may influence outcome: workers compensation, medico-legal action.
9. Location of recruitment (emergency department, primary care, hospital admission, sporting field etc)
10. Glasgow Coma Score
11. Presence of abnormal CT head (percentage attributable to TBI)
12. Presence (number, severity) of subjects with a prior history of TBI
13. Time of recruitment relative to time of injury
14. Timing(s) of outcome measured
15. Outcome measures collected
16. Whether symptom or neurocognitive validity measures were collected and the result of such measures.

The exact data items recorded for stage two will depend on the range of outcome measures found in stage one. This will include:

1. Method of recording outcome measure (i.e. total score, binary thresholds, clinical diagnosis)
2. Definition of complete recovery
3. Proportion of patients with complete symptom resolution at each measured time point and for each outcome measure
4. Loss to follow-up at each time point
5. Definition of complete recovery

The authors will be contacted directly when information from the published manuscripts is unavailable.

Outcomes and prioritisation

The primary outcome of this systematic review and meta-analysis is the time to resolution of symptoms following mTBI. For mTBI patients who do not recover, this review will also explore the time to the plateau of symptoms and sequelae of these symptoms.

Data will be synthesised following PRISMA guidelines.[30]

Assessment of bias and heterogeneity

Studies will be assessed clinically and methodologically (study design, comparability, outcome ascertainment, and risk of bias). The risk of bias will be evaluated using the Cochrane risk of bias tool 2.0 (ROB 2.0) for clinical trials and the Newcastle Ottawa score for cohort studies.[31] [32] This will include an assessment of the impact of missing data on effect estimates.[33] [34] Two reviewers will independently assess each included study for bias. Publication bias and small-study effects will be assessed using funnel plots for the most commonly recorded outcomes for included RCTs. As funnel plots are challenging to interpret for observational studies, they will not be used in this case. However, the potential for bias, including reporting, will be included in the discussion.[24] The Egger method to assess asymmetry will be used for outcomes with more than ten individual studies.

For studies reporting on the same outcome, the magnitude of variation or heterogeneity between studies will be measured by the index of heterogeneity (I^2 and its confidence intervals).[35] I^2 values of 25%, 50% and 75% are assumed to represent low, medium and high heterogeneity, respectively. The significance of the heterogeneity will be determined by χ^2 for Q statistics.

Data synthesis

Data extracted from included studies will be presented in evidence tables or as a narrative summary. We will analyse studies with one and multiple outcome time points separately and then pool this data if appropriate. For statistical analyses, a p-value less than 0.05 will be considered significant.

If data are too heterogeneous to pool, then narrative synthesis of elements will be performed. This will focus on the time to resolution of symptoms in patients who have a full recovery and time to the plateau of symptoms and sequelae in patients who do not recover. Tables of data extracted from each study will be presented.

Data analysis

A descriptive analysis will be performed. If studies have sufficiently homogenous populations, exposures and outcomes data will be pooled and meta-analysis performed to calculate summary measures of effect. To allow for expected differences between studies a random-effects model will be used.

For single-outcome time point data, a series of exploratory multivariate regression models will be used to understand the effects of participant demographics and premorbid/postmorbid factors on outcome. If the relationship is not parametric, other non-parametric methods of curve fitting will be used.

For studies with more than one outcome timepoint, the recovery curve for each study will be presented graphically. If the data is parametric, the equation will be reported, and splines will be used for non-parametric data.

Subgroup analyses

Where possible, prespecified subgroup analysis will be undertaken for key groups where differential extent and rate of recovery may be expected. These groups have been chosen due to either prior literature supporting this (e.g. older age,[36] female sex,[24] repetitive TBI[11] [12] [37]) and/or them being discrete populations which have special characteristics (e.g. military/blast injuries and sports concussion).[2] The planned sub-analyses will therefore be patient age (65 years or over compared to younger adults), sex, patients who have sustained more than one head injury, military and/or blast injuries, and sports concussion, including sub-concussive injuries. Where appropriate sensitivity analyses will be performed using studies which have collected validity measures.

Sensitivity analysis

If there is significant heterogeneity, sensitivity analyses will be performed, with outlying studies removed. Studies at a high risk of bias will also be excluded, and the main conclusions will be based on studies at a low risk of bias.

Patient and public involvement

This review has been discussed with a Patient and Public Involvement and Engagement (PPIE) focus group run in conjunction with the NIHR Brain Injury MedTech Co-operative, which informed its content, including ensuring that different outcome measures were included. A PPIE panel will be involved with the interpretation and dissemination of results.

Ethics and Dissemination

Ethical review is not required, as no original data will be collected. Results will be disseminated through peer-reviewed publications and academic conferences.

Contributorship statement

AN, OH, HH, DW, SR, and VN all contributed to the protocol's conceptualisation, design, data interpretation, critical revision, and final approval. VN is responsible for the overall content as guarantor.

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Tables

Table 1. Population, Exposure, Comparison, Outcomes, and Study Design (PECOS) Strategy for Inclusion and Exclusion

PICOS Strategy	Inclusion Criteria	Exclusion Criteria
P – Population	Aged 16 years or over Sustained an injury consistent with mild traumatic brain injury (mTBI) within 8 weeks of recruitment or had assessment prior to sustaining a mTBI.	No follow up data available Severity of traumatic brain injury is not specified No mild TBI specific data can be extracted < 30 cases of mTBI
E – Exposure	Mechanism of injury consistent with mTBI	
C – Comparator	No specific comparator Not limited to studies with a control group	N/A
O – Outcome	Any study that follows up the patient beyond the time of recruitment at least once, and reports on one or more outcome measures.	Outcome(s) not clearly stated
S – Study design	Systematic reviews and meta-analyses Randomised controlled trials Cohort studies	Cross-sectional studies Case-control studies Case series Case reports Qualitative studies Review articles

Table 2. Search strategy for a systematic review and meta-analysis exploring the time to recovery for adult patients with mild traumatic brain injury

	Medline	Embase
#1	exp post-concussion syndrome/ OR exp brain concussion/ OR exp brain injuries/ OR exp craniocerebral trauma/ OR exp brain injuries, traumatic/	exp concussion/ OR exp brain injuries/ OR exp head injury/ OR exp traumatic brain injury/
#2	("MTBI" OR "mild TBI" OR "TBI" OR "traumatic brain inj*" OR "mild traumatic brain injur*").ab,ti.	("MTBI" OR "mild TBI" OR "TBI" OR "traumatic brain inj*" OR "mild traumatic brain injur*").ab,ti.
#3	exp symptom assessment/ OR exp post-concussion syndrome OR exp mental disorders/ OR exp neurologic manifestations/ OR exp depression/ OR exp dizziness/ OR exp vertigo/ OR exp sleep wake disorders/ OR exp headache/ OR exp post-traumatic headache/	exp symptom assessment/ OR exp postconcussion syndrome/ OR exp behaviour disorder/ OR exp neurologic disease/ OR exp depression/ OR exp mood disorder/ OR exp dizziness/ OR

	OR exp headache disorders, secondary/ OR exp fatigue/ OR exp mental fatigue/ OR exp memory/ OR exp memory disorders/ OR exp irritable mood/ OR exp anxiety/ OR exp anxiety disorders/ OR exp patient health questionnaire/ OR exp Glasgow outcome scale/ OR exp dissociative disorders/ OR exp stress disorders, post-traumatic/ OR exp return to work/ OR exp "Memory and Learning Tests"/ OR exp functional status/ OR exp "Recovery of Function"/ OR exp cognition/ OR exp mental health/ OR exp social status/ OR exp disease progression/ OR exp "Quality of Life"/ OR exp prognosis/ OR exp treatment outcome/ OR exp patient reported outcome measures/	exp vertigo/ OR exp sleep disorder/ OR exp headache/ OR exp posttraumatic headache/ OR exp secondary headache/ OR exp fatigue/ OR exp mental fatigue/ OR exp memory/ OR exp cognition/ OR exp memory disorders/ OR exp irritability/ OR exp anxiety/ OR exp patient health questionnaire/ OR exp Glasgow outcome scale/ OR exp dissociative disorder/ OR exp mental disease/ OR exp posttraumatic stress disorder/ OR exp return to work/ OR exp cognitive function test/ OR exp functional status/ OR exp cognition/ OR exp mental health/ OR exp social status/ OR exp disease exacerbation OR exp "quality of life"/ OR exp prognosis/ OR exp treatment outcome/ OR exp patient-reported outcome/
#4	("symptom*" or "prognos*" or "quality of life" or "functional" or "mortality" or "GOSE" or "Rivermead" or "outcome*").ab,ti.	("symptom*" or "prognos*" or "quality of life" or "functional" or "mortality" or "GOSE" or "Rivermead" or "outcome*").ab,ti.
#5	exp time factors/ OR exp chronology as topic/ OR exp follow up studies/	exp time factor/ OR exp chronology/ OR exp follow up/
#6	("chronology" OR "time course" OR "recovery" OR "resolution" OR "rehabilitation").ab,ti.	("chronology" OR "time course" OR "recovery" OR "resolution" OR "rehabilitation").ab,ti.
#7	exp pediatrics/ OR exp child/ OR exp infant/ OR exp schools/	exp pediatrics/ OR exp child/ OR exp infant/ OR exp school/
#8	("p?ediatric*" OR "child*" OR "infant*").ab,ti.	("p?ediatric*" OR "child*" OR "infant*").ab,ti.

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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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review **Page 1**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **N/A**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number **Page 1**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **Page 1**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review **Page 8**
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 **Page 1**
Sponsor	5b	Provide name for the review funder and/or sponsor **Page 1**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **Page 1**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known **Page 3**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **Page 3**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review **Page 4**
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 **Page 5**
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 **Page 5**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **Page 5**

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) **Page 5**
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 **Page 5**
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 **Page 5**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **Page 6**
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 **Page 6**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **Page 7**
	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) **Page 7**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **Page 7**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **Page 7**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) **Page 7**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **Page 7**

*** 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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