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Incidence of post-traumatic epilepsy following pediatric traumatic brain injury: protocol for systematic review and meta-analysis

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ABSTRACT

Introduction: Post-traumatic epilepsy (PTE) is a recognized complication of traumatic brain injury (TBI), and is associated with higher rates of mortality and morbidity when compared to TBI patients without PTE. Most of the literature on PTE has focused on adult populations, and consequently there is a paucity of information regarding pediatric cohorts. Additionally, there is considerable heterogeneity surrounding the reported incidence of PTE following childhood TBI in the literature. The primary aim of our study is to summarize reported PTE incidences in pediatric populations to derive an accurate estimate of the global incidence of PTE following childhood TBI. Our secondary aim will be to explore factors that may increase the likelihood of developing PTE, such as age, injury severity, and clinical findings.

Methods and analysis: A systematic literature search of three electronic databases will be conducted, and publications that report the incidence of PTE in populations under 18 years of age will be included. Two independent investigators will identify relevant publications, and discrepancies will be adjudicated by a third independent investigator. Data extracted will include incidence of PTE, time intervals between TBI and PTE, seizure characteristics, injury characteristics, patient demographics, and clinical data (treatments, diagnostic findings). Data extraction will be performed by two independent investigators and will be cross-checked by a third investigator. A descriptive analysis of PTE incidence will be conducted and a weighted mean calculated. If sufficient data is available, stratified meta-analysis of subgroups will also be conducted.

Ethics and dissemination: Ethics approval was not required for this study. We intend to publish the findings of our study and disseminate our results in relevant conferences and presentations. Together, this study will provide an accurate estimate of PTE incidence in pediatric-aged cohorts; information of great importance for identifying those at greatest risk and understanding potential age-dependent differences in PTE.

Registration details: CRD42021245802 (PROSPERO)

Keywords: Traumatic brain injury, epilepsy, post-traumatic epilepsy, pediatric, childhood, seizure, neurotrauma, incidence

Strengths and limitations

- This study will be the first to provide a comprehensive estimate of the incidence of PTE in pediatric patient cohorts.
- Our protocol was written in accordance with the PRISMA-P guidelines, describing our intentions to conduct a high-quality systematic review and subsequent meta-analysis, if possible.
- Publishing this protocol ensures that we are transparent with the methods and systems we will be using for this study, to reduce the likelihood of duplication as well as minimize the effects of bias on our study.
- Inclusion and exclusion criteria have been defined to cast a wide net, capturing a broad range of published literature regarding the incidence of PTE in the pediatric population.

INTRODUCTION

Traumatic brain injury (TBI) refers to an acquired brain injury that occurs subsequent to sudden trauma. The worldwide incidence of TBI is estimated to be 939 cases per 100,000 person-years affecting approximately 69 million individuals annually[1]. For survivors, TBI is associated with a broad range of physical, cognitive and psychiatric morbidity, including an increased risk of epilepsy[2,3]. Post-traumatic epilepsy (PTE) is defined as the occurrence of unprovoked seizures at least seven days after the initial injury[4-6], and is a widely acknowledged complication of TBI in both adults and children[7,8]. Individuals with a TBI who develop PTE are reported to have a higher mortality rate when compared to patients with a TBI who do not develop PTE[9]. Furthermore, PTE is associated with poorer chronic outcomes including neurological, intellectual and psychological co-morbidities[10-12]. Given the serious nature of PTE, it is vital to gain a complete understanding of its features and characteristics in order to ultimately improve management and outcomes for patients. Within the current literature, there is no uniform reflection of the incidence of PTE specifically following TBI sustained during childhood, as most available data has been concentrated on adult populations, both civilian and military. Making this distinction from adult TBI is important, as developmental age at the time of injury is increasingly recognized as a critical determinant of secondary neuropathology and functional outcomes after TBI[13-15]. In addition, the causes and mechanisms of TBI may differ in a pediatric population compared to adult cohorts, with a greater proportion attributed to falls and non-accidental injuries[16]. Against this backdrop, we outline a protocol for conducting a systematic review and meta-analysis to comprehensively investigate the incidence of PTE following pediatric TBI.

The primary outcome measure of this study will be to assess the incidence of epilepsy following childhood (or, pediatric) TBI. Secondary outcome measures will include risk factors such as

injury severity, patient demographics and clinical findings, and their impact on PTE incidence. In adults, several risk factors for the development of PTE have been identified, including higher injury severity (a higher score on the Glasgow outcome scale), skull fracture, and the presence of hematomas[17], while some studies have identified male sex, interventions and procedures such as mechanical ventilation, and acute post-injury seizures, as factors that increase the likelihood of PTE[18,19]. Such risk factors have been poorly defined to date in PTE after childhood TBI.

METHODS AND ANALYSIS

Protocol and registration

This protocol was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols (PRISMA-P) guidelines[20]. The study was designed by discussion with our scientific team with expertise in both TBI and epilepsy research, including translational scientists (SR, AAB, BS) and clinicians (TOB) and a clinical trainee (FM). The protocol is registered in PROSPERO (www.crd.york.ac.uk/prospero/), identification number CRD42021245802.

Ethics and dissemination

Ethics approval was not sought or required for this study as data will be obtained from already published literature. Upon completion of the systematic review, we will publish the findings in a peer-reviewed academic journal, with raw data available upon reasonable request. Additionally, results may also be disseminated in the form of conferences, presentations and seminars.

Disease of interest

Between 4% and 53% of patients have been reported to experience acute post-traumatic seizures following TBI, defined as provoked seizures occurring within the first 7 days post-injury[7,21]. Post-traumatic seizures are a recognized early complication of TBI, which occur as a result of the acute damage sustained by the brain. 'Immediate' seizures are characterized as those occurring within 24 hours of injury), while 'early' seizures refer to those observed within the first week of injury. In contrast, PTE is a distinct phenomenon, and refers to 'late' onset seizures (more than 7 days post-injury), that are recurrent and unprovoked, as a consequence of secondary injury processes that promote hyper-excitable neuronal circuitry[21]. In line with general consensus in the field, this protocol considers the presentation of late post-traumatic seizures to be adequate for the diagnosis of PTE[22].

Intervention assessed

The intervention assessed will be TBI sustained in the context of pediatric or childhood populations.

Control populations

The control group for our study will be individuals with TBI who do not develop PTE.

Outcome measures

The primary outcome measure will be the reported incidence of epilepsy. Secondary outcome measures will include the effects of potential factors that may increase the risk of developing PTE, such as patient characteristics as well as clinical and injury characteristics.

Literature search

A comprehensive literature search will be conducted of three electronic databases: PubMed, Embase, and Web of Science. Key search terms will include variations and synonyms of the following: epilepsy ("epilepsy" or "seizure" or "status epilepticus"), traumatic brain injury ("traumatic brain injury" or "post-traumatic" or "traumatic" or "TBI" or "brain injury"), and pediatric ("paediatric" or "pediatric" or "newborn" or "infan*" or "child*").

Other sources

To ensure that all relevant articles are included in our study, we will review reference lists of all included studies. Additionally, we will also analyze the reference lists of any previously conducted review articles. The results from our three database searches will be combined with an AND link. All articles yielded from our search will be combined into a single file, and Endnote software (v. X8, Clarivate Analytics) will be utilized to remove duplicates.

Selection Criteria

Inclusion Criteria

Publications with primary clinical data that report PTE in patients under the age of 18 years at the time of injury will be included.

Exclusion Criteria

Review publications, grey literature, conference abstracts, and publications in languages other than English, will be excluded from our review. Publications that do not report patient cohorts under the age of 18 years, and publications that evaluate fewer than 10 patients, will not be included. Additionally, patients with an alternative identifiable cause of epilepsy (e.g. epileptogenic lesions unrelated to traumatic insult, or an identified pathogenic genomic abnormality) will be excluded.

The web-based systematic review platform Covidence (www.covidence.org; Veritas Health Innovation, Melbourne, Australia), will be used to facilitate the screening process. All studies will undergo abstract and title screening by two independent investigators (FM and SR), followed by full-text screening by two independent investigators (FM and SR). All conflicts during this process will be resolved by a third investigator (BDS, TOB or AAB).

Data collection

Two independent investigators (FM and SR) will extract data from the included studies. In addition to the primary outcome measure, additional variables to be extracted include the following: patient demographics (including age at injury), severity of injury (admission Glasgow coma score), diagnostic findings (pathology identified by acute computerized tomography), management of TBI (intensive care unit length of stay, intracranial pressure monitoring, interventions such as decompressive craniectomy, and administration of anti-seizure medications), the presence/absence of immediate and/or early seizures, mechanism of injury (falls, non-accidental injury, motor vehicle accidents, etc.), and the time interval between PTE and TBI (months/years).

Risk of bias assessment

Risk of bias will be assessed by utilizing a modified version of the *Newcastle-Ottawa Scale,* a quality assessment scale for cohort studies which encompasses the domains of selection, comparability, and outcome[23]. Each study will be scored and evaluated by two independent investigators (FM and SR).

Data analysis

For each study we will calculate the proportion of patients with PTE. We will then use Der Simonian and Laird random effect meta-analysis to calculate summary estimate of effect size. The data will be presented as percentage incidence of PTE and its 95% confidence intervals. Statistical heterogeneity of include studies will be measured with I^2. If sufficient data are available, from a minimum of 5 publications, we will perform stratified meta-analysis and meta-regression to investigate the influence of subgroups on our primary outcome, as well as the impact of study design characteristics on results. The effects of subgroups will be determined by utilizing multivariate logistic regression analysis using STATA, with statistical significance set to $p < 0.05$. The subgroups for primary outcome (incidence of PTE following TBI in pediatric population) will be based on additional variables described above in 'Data Collection', e.g. patient demographics (age, sex), age of initial TBI, time of follow up, time of seizure onset and severity of injury. To assess the effects of publication bias we will perform funnel plot, Egger regression and trim and fill[24].

DISCUSSION

Our study aims to evaluate and summarize all available published data on the incidence of PTE following pediatric TBI. Seizures in individuals with PTE are often medically intractable, and the promise of new treatments to prevent epileptogenesis after TBI has not yet been realized[25]. The purpose of our study is to generate improved understanding of PTE in the pediatric population, which will assist clinicians in their approach to the management of both TBI and PTE. Additionally, we hope that this review will identify knowledge gaps and define unanswered research questions, which will provide direction for future research and investigation on this topic, driving towards new strategies to prevent and treat PTE.

To the best of our knowledge, there are currently no other systematic reviews that uniformly consider PTE incidence after childhood TBI. However, our study will complement previous systematic reviews which have investigated the incidence of TBI[26] and epilepsy[27] separately, as well as risk factors of PTE in adult populations[28]. The specific patient population that we are targeting is the key strength of our review when compared to other studies, as we will obtain an accurate representation of the risk of PTE in a pediatric setting. Focusing exclusively on the pediatric population is important, as it is increasingly recognized that the consequences of TBI are dependent upon the developmental age at the time of injury[14,29]. Findings from PTE research in the adult brain may not necessarily apply equally to PTE in the pediatric context, where epileptogenesis after a TBI may be influenced by ongoing brain maturation. By further exploring the risk factors that contribute to PTE in this cohort, this study will also provide valuable information for clinical management.

Authors' contributions

FM, BDS and AAB conceived and designed the review. FM developed the first draft of the protocol manuscript, then SR, TOB, BDS and AAB edited the manuscript. FM, TOB, BDS and AAB designed the search strategies. All authors read and approved the final manuscript prior to submission for publication.

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Competing interests statement

The authors declare that they do not have any competing interests.

Patient and Public Involvement Statement

No patients were involved in the development of this protocol.

Data Availability Statement

Data sharing not applicable, as no datasets were generated and/or analyzed for this protocol.

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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	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	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	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	10
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
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	7
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	7
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	7

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
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)	8
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	8
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	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	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)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	

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Methods and analysis: A systematic literature search of Embase (1947–2021), PubMed (1996–2021) and Web of Science (1900–2021) will be conducted. Publications in English that report the incidence of PTE in populations under 18 years of age will be included. Publications that evaluate fewer than 10 patients, report an alternative cause of epilepsy, or in which a pediatric cohort is not discernable will be excluded. Independent investigators will identify relevant publications, and discrepancies will be adjudicated by a third independent investigator. Data extracted will include incidence of PTE, time intervals between TBI and PTE, seizure characteristics, injury characteristics, patient demographics, and clinical data. Data extraction will be performed by two independent investigators and cross-checked by a third investigator. A descriptive analysis of PTE incidence will be conducted and a weighted mean calculated. If sufficient data is available, stratified meta-analysis of subgroups will also be conducted.

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- Heterogeneity in reporting of clinical characteristics and outcomes may limit the scope of our analysis.
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- The exclusion of non-English publications which may mean we miss some relevant data.

INTRODUCTION

Traumatic brain injury (TBI) refers to an acquired brain injury that occurs subsequent to sudden trauma. The worldwide incidence of TBI is estimated to be 939 cases per 100,000 person-years affecting approximately 69 million individuals annually[1]. For survivors, TBI is associated with a broad range of physical, cognitive and psychiatric morbidity, including an increased risk of epilepsy[2,3]. Post-traumatic epilepsy (PTE) is defined as the occurrence of unprovoked seizures at least seven days after the initial injury[4-6], and is a widely acknowledged complication of TBI in both adults and children[7,8]. Individuals with a TBI who develop PTE are reported to have a higher mortality rate when compared to patients with a TBI who do not develop PTE[9]. Furthermore, PTE is associated with poorer chronic outcomes including neurological, intellectual and psychological co-morbidities[10-12]. Given the serious nature of PTE, it is vital to gain a complete understanding of its features and characteristics in order to ultimately improve management and outcomes for patients. Within the current literature, there is no uniform reflection of the incidence of PTE specifically following TBI sustained during childhood, as most available data has been concentrated on adult populations, both civilian and military. Making this distinction from adult TBI is important, as developmental age at the time of injury is increasingly recognized as a critical determinant of secondary neuropathology and functional outcomes after TBI[13-15]. In addition, the causes and mechanisms of TBI may differ in a pediatric population compared to adult cohorts, with a greater proportion attributed to falls and non-accidental injuries[16]. Against this backdrop, we outline a protocol for conducting a systematic review and meta-analysis to comprehensively investigate the incidence of PTE following pediatric TBI.

The primary outcome measure of this study will be to assess the incidence of epilepsy following childhood (or, pediatric) TBI. Secondary outcome measures will include risk factors such as injury

severity, patient demographics and clinical findings, and their impact on PTE incidence. In adults, several risk factors for the development of PTE have been identified, including higher injury severity (a higher score on the Glasgow outcome scale), skull fracture, and the presence of hematomas[17], while some studies have identified male sex, interventions and procedures such as mechanical ventilation, and acute post-injury seizures, as factors that increase the likelihood of PTE[18,19]. Such risk factors have been poorly defined to date in PTE after childhood TBI.

METHODS AND ANALYSIS

Protocol and registration

This protocol was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols (PRISMA-P) guidelines[20]. The study was designed by discussion with our scientific team with expertise in both TBI and epilepsy research, including translational scientists (SR, AAB, BS) and clinicians (TOB) and a clinical trainee (FM). The protocol is registered in PROSPERO (www.crd.york.ac.uk/prospero/), identification number CRD42021245802.

Disease of interest

Between 4% and 53% of patients have been reported to experience acute post-traumatic seizures following TBI, defined as provoked seizures occurring within the first 7 days post-injury[7,21]. Post-traumatic seizures are a recognized early complication of TBI, which occur as a result of the acute damage sustained by the brain. 'Immediate' seizures are characterized as those occurring within 24 hours of injury), while 'early' seizures refer to those observed within the first week of injury. In contrast, PTE is a distinct phenomenon, and refers to 'late' onset seizures (more than 7 days post-injury), that are recurrent and unprovoked, as a consequence of secondary injury processes that promote hyper-excitable neuronal circuitry[21]. In line with general consensus in the field, this protocol considers the presentation of late post-traumatic seizures to be adequate for the diagnosis of PTE[22].

Intervention assessed

The intervention assessed will be TBI sustained in the context of pediatric or childhood populations.

Control populations

The control group for our study will be individuals with TBI who do not develop PTE.

Outcome measures

The primary outcome measure will be the reported incidence of epilepsy. Secondary outcome measures will include the effects of potential factors that may increase the risk of developing PTE, such as patient characteristics as well as clinical and injury characteristics.

Literature search

A comprehensive literature search will be conducted of three electronic databases: PubMed (1996–2021), Embase (1947–2021), and Web of Science (1900–2021). Key search terms will include variations and synonyms of the following: epilepsy ("epilepsy" or "seizure" or "status epilepticus"), traumatic brain injury ("traumatic brain injury" or "post-traumatic" or "traumatic" or "TBI" or "brain injury"), and pediatric ("paediatric" or "pediatric" or "newborn" or "infan*" or "child*"). For the full list of search terms please refer to the Supplementary file. Our search strategy will not include any language filters.

Other sources

To ensure that all relevant articles are included in our study, we will review reference lists of all included studies. Additionally, we will also analyze the reference lists of any previously conducted

review articles. The results from our three database searches will be combined with an AND link. All articles yielded from our search will be combined into a single file, and Endnote software (v. X8, Clarivate Analytics) will be utilized to remove duplicates.

Selection Criteria

Inclusion Criteria

Publications with primary clinical data that report PTE in patients under the age of 18 years at the time of injury will be included.

Exclusion Criteria

Review publications, grey literature, conference abstracts, and publications in languages other than English, will be excluded from our review. Publications that do not report patient cohorts under the age of 18 years, or from which it is not possible to ascertain pediatric cases will not be included. Additionally, publications that evaluate fewer than 10 patients, will be excluded. Patients with an alternative identifiable cause of epilepsy (e.g. epileptogenic lesions unrelated to traumatic insult, or an identified pathogenic genomic abnormality) will be excluded.

The web-based systematic review platform Covidence (www.covidence.org; Veritas Health Innovation, Melbourne, Australia), will be used to facilitate the screening process. All studies will undergo abstract and title screening by two independent investigators (FM and SR), followed by full-text screening by two independent investigators (FM and SR). All conflicts during this process will be resolved by a third investigator (BDS, TOB or AAB).

Data collection

Two independent investigators (FM and SR) will extract data from the included studies. In addition to the primary outcome measure, additional variables to be extracted include the following: patient demographics (including age at injury), severity of injury (admission Glasgow coma score), diagnostic findings (pathology identified by acute computerized tomography), management of TBI (intensive care unit length of stay, intracranial pressure monitoring, interventions such as decompressive craniectomy, and administration of anti-seizure medications), the presence/absence of immediate and/or early seizures, mechanism of injury (falls, non-accidental injury, motor vehicle accidents, etc.), and the time interval between PTE and TBI (months/years). Pathology identified on CT imaging will be classified according to anatomical location, as well as the presence of hemorrhagic contusion, although this classification system is not final and may be revised to better represent the reporting styles of included publication.

Risk of bias assessment

Risk of bias will be assessed by utilizing a modified version of the *Newcastle-Ottawa Scale,* a quality assessment scale for cohort studies which encompasses the domains of selection, comparability, and outcome[23]. Each study will be scored and evaluated by two independent investigators (FM and SR).

Data analysis

For each study we will calculate the proportion of patients with PTE. We will then use Der Simonian and Laird random effect meta-analysis to calculate summary estimate of effect size. The data will be presented as percentage incidence of PTE and its 95% confidence intervals. Statistical

heterogeneity of include studies will be measured with I^2. If sufficient data are available, from a minimum of 5 publications, we will perform stratified meta-analysis and meta-regression to investigate the influence of subgroups on our primary outcome, as well as the impact of study design characteristics on results. The effects of subgroups will be determined by utilizing multivariate logistic regression analysis using STATA, with statistical significance set to $p < 0.05$. The subgroups for primary outcome (incidence of PTE following TBI in pediatric population) will be based on additional variables described above in 'Data Collection', e.g. patient demographics (age, sex), age of initial TBI, time of follow up, time of seizure onset and severity of injury. To assess the effects of publication bias we will perform funnel plot, Egger regression and trim and fill[24].

ETHICS AND DISSEMINATION

Ethics approval was not sought or required for this study as data will be obtained from already published literature. Upon completion of the systematic review, we will publish the findings in a peer-reviewed academic journal, with raw data available upon reasonable request. Additionally, results may also be disseminated in the form of conferences, presentations and seminars.

DISCUSSION

Our study aims to evaluate and summarize all available published data on the incidence of PTE following pediatric TBI. Seizures in individuals with PTE are often medically intractable, and the promise of new treatments to prevent epileptogenesis after TBI has not yet been realized[25]. The purpose of our study is to generate improved understanding of PTE in the pediatric population, which will assist clinicians in their approach to the management of both TBI and PTE. Additionally, we hope that this review will identify knowledge gaps and define unanswered research questions, which will provide direction for future research and investigation on this topic, driving towards new strategies to prevent and treat PTE.

To the best of our knowledge, there are currently no other systematic reviews that uniformly consider PTE incidence after childhood TBI. However, our study will complement previous systematic reviews which have investigated the incidence of TBI[26] and epilepsy[27] separately, as well as risk factors of PTE in adult populations[28]. The specific patient population that we are targeting is the key strength of our review when compared to other studies, as we will obtain an accurate representation of the risk of PTE in a pediatric setting. Focusing exclusively on the pediatric population is important, as it is increasingly recognized that the consequences of TBI are dependent upon the developmental age at the time of injury[14,29]. Findings from PTE research in the adult brain may not necessarily apply equally to PTE in the pediatric context, where epileptogenesis after a TBI may be influenced by ongoing brain maturation. By further exploring the risk factors that contribute to PTE in this cohort, this study will also provide valuable information for clinical management.

Our study has a number of potential limitations. Firstly, we are not including non-English publications in our analysis, which may exclude some relevant data. Additionally, we are not setting a limit on the study design of publications, which may affect the quality of studies included. Our analysis may be limited by the heterogeneity in the reporting of patient characteristics and clinical outcomes. Finally, studies that report a mixed population of both adult and pediatric patients will be considered for inclusion, but their contribution to our analysis may be challenging if these two age groups were integrated.

Authors' contributions

FM, BDS and AAB conceived and designed the review. FM developed the first draft of the protocol manuscript, then SR, TOB, BDS and AAB edited the manuscript. FM, TOB, BDS and AAB designed the search strategies. All authors read and approved the final manuscript prior to submission for publication.

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Competing interests statement

The authors declare that they do not have any competing interests.

Patient and Public Involvement Statement

No patients were involved in the development of this protocol.

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SEARCH STRATEGY

EMBASE

1. ((Post-traumatic or traumatic or traumatic brain injury or TBI or brain injury) adj5 (Epilepsy or Seizure or Status Epilepticus)).mp.
2. (Paediatric or Pediatric or Childhood or Newborn or Infant or Child*).mp.
3. 1 AND 2

PUBMED

1. ((Post-traumatic or traumatic or traumatic brain injury or TBI or brain injury) adj5 (Epilepsy or Seizure or Status Epilepticus)).mp.
2. (Paediatric or Pediatric or Childhood or Newborn or Infant or Child*).mp.
3. 1 AND 2

WEB OF SCIENCE

1. TS=((Post-traumatic or traumatic or “traumatic brain injury” or TBI or “brain injury”) near/5 (Epilepsy or Seizure or “Status Epilepticus”)).
2. TS=(Paediatric or Pediatric or Childhood or Newborn or Infant or Child*)
3. 1 AND 2

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	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	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	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	10
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
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	7
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	7
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	7

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
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)	8
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	8
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	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	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)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	

*** 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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