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Complete List of Authors:	Arbour, Caroline; Hôpital du Sacré-Coeur de Montréal, Bouferguene, Yasmine; Hôpital du Sacré-Coeur de Montréal Beauregard, Roxanne; Hôpital du Sacré-Coeur de Montréal Lavigne, Gilles; Université de Montréal, Médecine dentaire Herrero Babiloni , Alberto; Hôpital du Sacré-Coeur de Montréal
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TITLE: Update on the prevalence of chronic headache in adult civilian traumatic brain injury: protocol for a systematic review and meta-analysis

Authors' details and affiliations:

Caroline Arbour[1-2], Ph.D., Yasmine Bouferguène[1,3], B.Sc., Roxanne Beauregard[2], RN, Gilles Lavigne[1,3], Ph.D., Alberto Herrero Babiloni[1,3], M.Sc.

1. Hôpital du Sacré-Coeur de Montréal Research Center, Montreal, Quebec, Canada;
2. Faculty of Nursing, Université de Montréal, Montréal, Québec, Canada;
3. Faculty of Dental Medicine, Université de Montréal, Montreal, Québec, Canada.

Corresponding author: Any comments or inquiry about this publication should be addressed to Caroline Arbour, Hôpital du Sacré-Coeur de Montréal, 5400 Boul. Gouin Ouest. Room: E-1381, Montréal (Québec) H4J 1C5. Tel: 338-2222 ext: 3741, Email: caroline.arbour@umontreal.ca

Email addresses:

Caroline Arbour (caroline.arbour@umontreal.ca)

Yasmine Bouferguene (yasmine.bouferguene@umontreal.ca)

Roxanne Beauregard (beauregar_01@hotmail.com)

Gilles Lavigne (gilles.lavigne@umontreal.ca)

Alberto Herrero Babiloni (herre220@umn.edu)

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ABSTRACT

Introduction: Traumatic brain injury (TBI) is a major public health concern as it contributes to more deaths and disability than any other traumatic insult. Chronic headache is a common consequence of TBI affecting productivity and quality of life. The only review providing information about headache prevalence after TBI was published in 2008, combined data from civilian and military TBI, and was strictly derived from Medline database. Due to recent changes in TBI diagnosis and civil trauma epidemiology, the aim of the current study is to carry out a systematic review and meta-analysis to derive updated prevalence estimates of chronic headache in adult civilian TBI.

Methods and analysis: The methods have been defined following PRISMA guidelines. Studies published from 2008 through 2019 will be identified searching the electronic databases Medline, Embase, Cochrane, Google Scholar, Directory of Open Access Journals, and Web of Science. Retrieved records will be independently screened by two authors and relevant data will be extracted from studies reporting data on chronic headache prevalence among civilian TBI individuals (16 years and older). The pooled prevalence estimate of any form of headaches disorders will be computed applying random-effects meta-analysis. Heterogeneity will be assessed using the I2 statistic and explored through subgroup analyses considering TBI severity (mild versus moderate/severe). Quality appraisal of the studies and estimations of risk of bias will be performed using validated checklists.

Ethics and dissemination: The result of this systematic review will be published in a peer-reviewed journal and disseminated at relevant conferences presentations. Formal ethical approval is not required because we will search and evaluate only existing sources of literature. By focusing on studies conducted in the last decade, this review will provide the

most up-to-date information about the global prevalence of chronic headache after TBI. Considering the economical and social burden of chronic headache after TBI, accurate estimates of this problematic is of utmost importance for planning, implementing and evaluating prevention interventions.

Clinical trial registration : CRD42018094138.

Keywords: Traumatic brain injury, headache, prevalence, systematic review protocol

ARTICLE SUMMARY

Strengths and limitations

► This systematic review will yield solid and updated estimates on the prevalence of chronic headache in adult traumatic brain injury populations.

► Unlike previous prevalence estimates on pain after head trauma, data included in this review will be restricted to civilian traumatic brain injury and exclude studies conducted in a military context, as differences between the two groups have been documented in terms of premorbid characteristics and patterns of recovery.

► Data of chronic headache after traumatic brain injury will first be pooled to provide a global prevalence estimate of the problematic, then analyzed separately in mild and moderate/severe cases.

► The increased reliance in TBI research on self-report information to confirm the history of head trauma is likely to reduce the comparability with studies using the classical clinician's assessment approach to TBI diagnostic.

► Regarding the development of chronic headache after TBI, heterogeneity in prevalence estimates might be caused by multiple features including psychiatric disorders comorbidity and time elapsed since injury. Those elements will be thoroughly documented.

BACKGROUND

Traumatic brain injury (TBI) occurs when an external force is applied to the head leading to permanent or temporary disabilities [1]. TBI can be considered mild, moderate or severe depending on changes in cognitive and executive processes [2]. TBI is a major threat to global health as 69 million individuals worldwide are estimated to sustain such injury each year [3]. In the European Union, more than 1.4 million individuals are hospitalized for TBI annually [4]. In the United States, 2.8 million individuals seek medical attention for TBI each year with an estimated annual cost of over $76 billion [5-6]. Incidence of TBI is also on the rise in low and middle-income countries, mainly due to the increased use of motor vehicles [7-9]. While sport and military-related TBI have received considerable media attention in the last decade, the highest combined incidence of TBI-related emergency department visits, hospitalizations, and deaths occurs in civilians [10].

Chronic pain is a common consequence of TBI [11]. To date, headache following TBI has been the focus of several studies and reports on the topic [12-14]. According to the International Headache Society, chronic headache attributed to head trauma is defined as a headache developing in the days/weeks following the impact and persisting more than 3 months after [15-16]. Chronic headache after TBI has no defining clinical features, and it is classified as a secondary headache disorder because of the close temporal relation to another disorder known to cause headache [15]. This remains true even when the headache has the characteristics of a primary headache (migraine, tension-type headache, cluster headache, or one of the other primary headaches). In terms of recovery, chronic headache after TBI as been associated to higher rates of anxiety and depression symptoms and

reduced quality of life [17]. In TBI adults, the odds of returning to work successfully are more than cut in half for each unit increase in chronic headache intensity [18].

The only available estimates of chronic headache in adult TBI date back to 2008 when chronic pain prevalence data were pooled from 23 studies (from 1951 to 2008) yielding a global prevalence of 57.8% for chronic headache, with surprising higher rates in mild TBI (75.3%) when compared to moderate/severe TBI (32.1%) [19]. In the last decade, several factors may have led to significant changes in chronic headache epidemiology after TBI including the revision of mild TBI diagnosis criteria to make it more inclusive and an historic peak of TBI in the elderly attributed to the aging population [20-22]. In addition, the above-mentioned systematic review conducted by Nampiaparampil [19] combined epidemiological data from civilian TBI and military-related TBI, reducing the comparability between eligible studies. Moreover, the review did not account for the presence of psychiatric disorders comorbidity, which would have been important as we now know these elements may contribute to pain chronicity after TBI [23]. For all the aforementioned reasons, updating the prevalence estimate of chronic headache in adult civilian TBI becomes especially relevant.

OBJECTIVES

The aim of the current study is to carry out a systematic review and meta-analysis to derive updated estimates on global and severity-specific prevalence of chronic headache in adult civilian TBI. The proposed review will address two main questions:

1. What is the updated global prevalence of chronic headache in adult civilian TBI?

2. What is the specific prevalence of chronic headache in adult civilians with mild TBI versus moderate/severe TBI?

Considering the increased reliance on self-report and screening measures to validate the occurrence of events leading to TBI in recent years, we expect an increase in chronic headache prevalence in adult civilian TBI [24]. These updated data will inform the planning, implementation and evaluation of chronic pain prevention intervention in trauma care, and potentially, contribute to reduce its morbidity after TBI.

METHODS/DESING

The methods for this systematic review have been defined in advance following the Prepared Items for Systematic Reviews and Meta-Analysis (PRISMA) [25]. The protocol was developed according to the PRISMA-P checklist [26]. (see online supplementary Appendix 1) The study has been registered on PROSPERO (CRD42018094138).

Eligibility criteria

Studies will be selected according to the criteria outlined below.

Study designs:

Studies will be considered for inclusion based on their relevance to answer the review questions. For review question 1, any form of observational studies investigating the prevalence of chronic headache after civilian TBI, or from which prevalence estimates can be derived and that meet the eligibility criteria will be considered. More specifically, prevalence estimates for chronic headache after TBI will be derived from either: (1) The general population (i.e., from population prevalence surveys), (2) Patient registries or

primary care practices' databases, (3) Hospital-based populations, or (4) Screening programmes. For review question 2, studies eligible for question 1, in which prevalence estimates are presented based on TBI severity will be considered. Studies will not be restricted by language. However, all will have to report original data and be peer-reviewed. Expert opinion letters or editorials, conference summaries, or reviews will be excluded. Intervention studies (including randomized control trials) will also be excluded on the basis that they are not deemed appropriate to help answer the review questions.

Population:

The population of interest consists of individuals (18 years or older) from the general population who have sustained a mild, moderate or severe TBI. Considering teenagers aged 16 years and older are often treated in adult trauma units, studies including 16 and 17 years old individuals in their sampling procedures will also be considered for inclusion. Mixed patient population studies will also be considered for inclusion if the analyses of results are stratified according to patients' diagnosis and mechanism of injury, allowing the review team to discern findings specific to the civilian TBI group. Studies about chronic headache following military TBI will not be considered in this study as differences compared to civilian TBI in terms of premorbid characteristics and patterns of recovery have been documented [27-28]. For similar reasons, pain studies using animal models of TBI will be excluded [29-31]. Consistent with Nampiaparampil [19], only studies using a clearly defined operational definition for the diagnosis of TBI will be considered for inclusion. Recognized criteria for the diagnosis of TBI include either: (1) a period of unconsciousness and/or post-traumatic amnesia, (2) clinician's confirmation of the initial Glasgow coma scale score at hospital admission, or (3) a self-professed

experience of transient neuropsychological dysfunction following injury to the head [1, 32-34].

Outcomes:

The primary outcome will be the global prevalence of chronic headache following TBI. The secondary outcome will be a better understanding of the associations between chronic headache and TBI severity. The latest could potentially help to identify which type of TBI patients are most likely to benefit from systematic screening and preventive interventions for headache disorders during acute recovery.

Timing:

Considering the latest estimates of chronic headache prevalence after TBI are based on studies published from 1951 to February 2008, only studies published from March 2008 to 2019 will be considered for inclusion.

Setting:

As TBI is a serious public health problem around the world [35], no geographical limitations will be applied.

Information sources

The following databases will be searched: Medline, Embase, Cochrane Library, Google Scholar, and Directory of Open Access Journals. For search optimization, we will scan the reference lists of included studies. We will also search the authors' personal bibliography on Web of Science to make sure that all relevant material has been captured.

Search strategy

The specific search strategies will be created by a Health Sciences Librarian with expertise in systematic reviews using the Peer Review for Electronic Search Strategies (PRESS) checklist [36]. To date, a first search strategy has been developed by the librarian and peer-reviewed by a member of the review team (YB) in Medline using MeSH subject headings combined with free-text terms around the three search components 'TBI', 'Headaches' and 'Prevalence'. A draft Medline search strategy is included in Appendix 2. The search strategy will eventually be adapted by the librarian for its use in the other databases.

Study records

Data management:

An initial literature searched will be performed by one member of the review team (YB) and reviewed by a second member (AHB). The citation abstract and full text article of all references identified will be uploaded to EndNote (EndNote 2017, Clarative Analytics). The search results from the different electronic databases will be combined in a single EndNote library to facilitate collaboration among the review team members (YB, AHB) during the study selection process. No training in relation to the literature search is planned at this stage as both reviewers are already familiar with Endnote and the content area of the review.

Selection process:

Titles and abstracts of studies generated from the initial search will be screened independently by two members of the review team (YB, AHB). The full-text will be retrieved and independently assessed by both authors for eligibility based on the

inclusion/exclusion criteria mentioned previously. The full-text of remaining articles will be independently examined by the same reviewers to reach a final list of articles. Disagreements at either screening stage will be resolved through discussion with a third reviewer (CA). The reasons for study exclusion will be documented. For duplicated references, and data that has been published more than once, the most complete study will be chosen for inclusion in the library while the others will be removed. A PRISMA flow diagram of the study selection procedure will be prepared to provide an overview of the decisions that are made in the data collection process [25].

Data collection process:

Consistent with Nampiaparampil [19], prevalence in this review is defined as the estimate of the total amount of chronic headache at a time point or period interval in a certain sample of adult civilian TBI. Based on this definition, data will be extracted from the included studies using a standardized data extraction spreadsheet. The data extraction spreadsheet will be pre-tested by two members of the review team (YB, RB) on ten randomly selected publications and modified accordingly. Using the same data extraction spreadsheet, the reviewers (YB, RB) will independently extract and manage the data for each of the included studies. Disagreements will be resolved by discussion between the two authors; if no agreement can be reached, consensus will be sought through discussions with a third author (CA). Authors of the included studies will be contacted in case clarifications or further data are needed (up to three attempts by email over a period of eight weeks). Data will be extracted on the following:

1. Publication details: title, journal, author, year, city and country, in which the study was conducted, type of publication, and source of funding.

2. Design: type of study (cohort, case-control, etc), method of data collection, response rate, recruitment and sampling methods, and eligibility (inclusion and exclusion criteria).
3. Study participant details: number of persons interviewed or surveyed, population characteristics including setting, age, sex, and premorbid characteristics including pre-existing primary headache disorders. Information about TBI severity will be rigorously extracted with respect to the clinical features and classification methods widely used (see Table 1).
4. Data for outcome measures: prevalence of chronic headache after TBI in general or according to TBI severity, characteristics of the headache (migraine, tension-type headache, cluster headache, or one of the other primary headaches), time period referenced in assessment of the condition, and factors (mainly comorbidities) found to be related significantly to the development of headaches after TBI.
5. Missing data: Considering there are no standardized time points for the assessment of chronic headache after TBI, prospective multiple assessments can be expected in some studies. This may potentially result in missing data. Reasons for missing data will be recorded from the original articles. If the original articles did not include this detail, we will try our best to obtain requisite information by contacting the corresponding author of the referenced articles for the missing data. The potential impact of the effect of missing data on the final findings of the review will be addressed in the discussion.

Table 1. TBI severity classification inspired by the Mayo Clinic classification system [37]

Classification	Criteria
Moderate/severe TBI (definite)	-Death
	-Loss of consciousness > 30 minutes
	-Antegrade amnesia > 24 hours
	-Glasgow Coma scale score < 13 in the initial 24 hours
	-Intracerebral, subdural, epidural, or subarachnoid hemorrhages; cerebral or hemorrhagic contusion, penetrating TBI, or brainstem injury
Mild TBI (probable)	- Loss of consciousness – momentarily to < 30 minutes
	-Post-traumatic anterograde amnesia – momentarily to < 2 – 4 hours
	-Depressed basilar or linear skull fracture (dura intact)
Symptomatic (possible mild TBI)	- A history of head trauma is reported by the patient - One or more of the following symptoms are reported: blurred vision, confusion (changes in mental status), dizziness, headache, nausea or focal neurological symptoms

Critical appraisal

Critical appraisal of included studies will be assessed independently by two members of the review team (YB, RB) applying The Joanna Briggs Institute's critical appraisal checklist specifically developed for studies reporting prevalence data to be included in systematic reviews and meta-analysis (see Appendix 3) [38]. Disagreements will be resolved by discussion between the two authors and a third author will be involved if needed (CA). Methodological quality will be considered 'low', 'moderate' and 'high' if three or less, four to six, and seven to nine criteria will be met, respectively [39]. The Joanna Briggs Institute's checklist will be used as a reference when conducting sensitivity analysis restricted to high quality studies.

Risk of bias

Risk of bias of included studies will be independently evaluated by two members of the review team (YB, RB) using the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al* (see Appendix 4) [40]. Individual items will be rated as "Yes" if the criterion is fulfilled. Otherwise, if the design of the study is not applicable or if there is insufficient information in the study to permit a judgment for a particular criterion, it will be noted as "No". In the event that a full consensus cannot be reached between the two reviewers, the opinion of a third reviewer (CA) will be obtained, and the proceeding majority consensus will be taken.

Data analysis and synthesis

We will perform descriptive analysis and report the characteristics of included studies in summary tables and narrative text. Limitations of the studies will be discussed in detail.

As we anticipate variability between included studies (mainly in the time points considered for the screening of headache disorders), the pooled prevalence estimate of chronic headache will be computed applying random-effects meta-analysis models (rather than assuming a single true value in a fixed-effect approach) using the MetaXL (www.epigear.com) add-in for Microsoft Excel. A pooled prevalence figure will be calculated with 95% CI. Meta-analysis will be limited to studies with at least 100 participants. Heterogeneity within included studies will be assessed through the utilization of the I^2 statistics, with I^2 values of 25%, 50% and 75% being considered low, moderate and high respectively [41]. Depending on data availability, we plan to account for heterogeneity

conducting meta-regressions and subgroup analysis considering the following covariates: time elapsed since TBI and TBI severity. Sensitivity analysis will be carried out considering only studies of the highest methodological quality (e.g. meeting seven to nine criteria from The Joanna Briggs Institute's critical appraisal checklist).

Patient and public involvement

As this will be a review of published data, patients will not be primarily involved in any stage of the study. Data will be collected from published studies available in the previously mentioned electronic databases.

DISCUSSION

To date, the only systematic review providing information about chronic headache following TBI was published in 2008 [19], and no new review is underway based on PROSPERO. Considering the recent changes in TBI diagnosis and epidemiology, there is a strong rational for updating current evidence on chronic headache prevalence in adult civilian TBI.

The systematic review and meta-analysis we plan to carry builds on the methodology applied previously [19], but reducing its limitations. Indeed, the previous review on the topic was performed solely through a MEDLINE search even though clinicians and educational outreach is an important goal of TBI research dissemination [42-43]. The exclusion of other databases in which many journals are not indexed and the restriction of publications in other languages than English may have limited the findings and contributed to the confusion about the influence of TBI severity of headache

prevalence. We believe that the use of additional sources of data aside from Medline will provide rigorous and updated estimates on prevalence of chronic headache in TBI. Moreover, differently from Nampiaparampil (2008), we will limit the review to studies about non-military TBI as the highest combined incidence of TBI-related emergency department visits, hospitalizations, and deaths occurs in civilians. In terms of research, pooling of such data is necessary to monitor trends in comorbidities among individuals who sustained TBI and to contribute to the design of further outcome studies. Last but not the least, we will include, in a separate section of the review, data about the prevalence of chronic headache after TBI based on TBI severity.

To our knowledge, this is the first systematic review and meta-analysis protocol addressing the important need to update the prevalence estimates of chronic headache in adult civilian TBI. At a practical level, such data are important to inform the planning, implementation and evaluation of chronic pain prevention intervention in trauma care, and potentially, contribute to reduce its morbidity after TBI.

Contributions: CA and GL conceived the study. YB and AHB performed the preliminary search. YB reviewed the search strategy with the help of Health Sciences librarian. YB and RB will oversee data extraction and analysis. CA and AHB participated in the conception of the protocol and produced the first draft of the manuscript. The definitive protocol was reviewed and approved by all authors (CA, YB, RB, GL, AHB).

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no role in the development of the protocol. GL holds a Canada Research Chair on Pain, Sleep, and Traumatic Injuries.

Competing interests: The authors declare that they have no conflicts of interest in relation to this work.

Patient consent for publication: Not applicable.

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APPENDICES

UPDATE on the PREVALENCE of CHRONIC HEADACHE in ADULT CIVILIAN TRAUMATIC BRAIN INJURY: PROTOCOL for a SYSTEMATIC REVIEW and METE-ANALYSIS

[Caroline Arbour PhD[1-2], Yasmine Bouferguène BSc[1,3], Roxanne Beauregard RN[1-2], Gilles Lavigne PhD[1,3], Alberto Herrero Babiloni MSc[1,3]]

*Corresponding author: caroline.arbour@umontreal.ca

1. Hôpital du Sacré-Coeur de Montréal Research Center, Montreal, Quebec, Canada;
2. Faculty of Nursing, Université de Montréal, Montréal, Québec, Canada;
3. Faculty of Dental Medicine, Université de Montréal, Montreal, Québec, Canada.

APPENDIX 1

PRISMA-P checklist [1]

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title: Identification	1a	UPDATE on the PREVALENCE of CHRONIC HEADACHE in ADULT CIVILIAN TRAUMATIC BRAIN INJURY: PROTOCOL for a SYSTEMATIC REVIEW and METE-ANALYSIS
Update	1b	Updating (with methodological modifications) Nampiaparampil, 2008. [2]
Registration	2	PROSPERO (CRD42018094138)
Authors: Contact	3a	Caroline Arbour PhD[1-2] (CA*), Yasmine Bouferguène BSc[1,3], Roxanne Beauregard RN[1-2], Gilles Lavigne PhD[1,3], Alberto Herrero Babiloni MSc[1,3] * caroline.arbour@umontreal.ca 1) Hôpital du Sacré-Coeur de Montréal Research Center, Montreal, Canada; 2) Faculty of Nursing, Université de Montréal, Montréal, Canada; 3) Faculty of Dental Medicine, Université de Montréal, Montreal, Canada.
Contributions	3b	CA and GL conceived the study. YB and AHB performed the preliminary search. YB reviewed the search strategy. YB and RB will oversee data extraction and analysis. CA and AHB produced the first draft of the manuscript. The definitive protocol was reviewed and approved by all authors. *[page 16 line 16]*
Amendments	4	Significant changes to the protocol will be updated in PROSPERO and reported in the final paper.
Support: Sources	5a	This project is funded by a start up fund provided by the research center of the Hôpital du Sacré-Coeur de Montréal to CA. The Hôpital du Sacré-Coeur de Montréal had no role in the development of the protocol. GL holds a Canada Research Chair on Pain, Sleep, and Traumatic Injuries. *[page 16 line 21]*
Sponsor	5b	None declared. *[page 17 line 3]*
INTRODUCTION		
Rationale	6	Chronic headache is a common consequence of traumatic brain injury. The only review providing information about headache prevalence after brain trauma was published in 2008 and was strictly derived from Medline database and combined data from civilian and military populations. Due to recent changes in brain trauma diagnosis and civil epidemiology, the aim of the current study is to carry out a systematic review and meta-analysis to derive updated prevalence estimates of chronic headache in adult civilian traumatic brain injury. *[page 5-6]*
Objectives	7	To derive updated estimates on global and severity-specific prevalence of chronic headache in adult civilian traumatic brain injury. *[page 6 line 18]*
METHODS		
Eligibility criteria	8	**Study designs:** Observational studies (case-control and Cohort studies) reporting prevalence of chronic headache (or from which prevalence can be derived); Published from March 2008 to this day. RCT, case control, case series, case report as well as duplicate reports will be excluded. **Population**: Representative sample of adult civilian traumatic brain injury patients (16 years and older); No geographic limitations; Patient identification by physician diagnosis, self-reported status, populational trauma registries, other medical/administrative registers. Prevalence data reported based on brain trauma severity (mild, moderate/severe) will be treated separately.

		Outcomes: The primary outcome will be the global prevalence of chronic headache following traumatic brain injury. The secondary outcome will be a better understanding of the associations between chronic headache and brain trauma severity. *[page 7-9]*
Information sources	9	Searching in the electronic databases (Medline, Embase, Cochrane, Google Scholar, and Directory of Open Access Journals), manual references' listing of included studies and authors' personal bibliography on Web of Science. *[page 9 line 17]*
Search strategy	10	See Appendix 2
Study records:		
Data management	11a	Studies retrieved will be grouped and duplicates removed with support of a reference management software package. Studies eligibility will be assessed independently by two authors. Discrepancies between authors will be resolved by discussion and consultation of a third author if needed. The study selection process will be reported in a PRISMA flow diagram. *[page 10 line 11]*
Selection process	11b	Studies will be selected independently by both authors based on pre-established eligibility criteria. Discrepancies between authors will be resolved by discussion and consultation of a third author if needed. Reasons for exclusion will be documented. *[page 10 line 20]*
Data collection process	11c	Data extraction will be performed independently by two authors using a pre-tested spreadsheet. Disagreements will be resolved by discussion between the two authors; if no agreement can be reached, consensus will be sought through discussions with a third author Up to three attempts by mail will be done if additional data or clarification will be required from the included studies. *[page 11 line 9]*
Data items	12	Data extraction will include: studies' title, journal, first author's name and affiliation(s), year and country of publication, design, response rate and sample size, sampling method, participants' sociodemographic and clinical characteristics, TBI severity, time elapsed since TBI, prevalence of chronic headache, characteristics of the headache, psychiatric comorbidities, risk factors, missing data, reasons for missing data. *[page 11 line 22]*
Outcomes and prioritization	13	Every headache lasting for more than 3 months after occurrence of brain trauma independent of its characteristics. [3] *[page 4 line 16]*
Risk of bias in individual studies	14	Critical appraisal of included studies will be assessed independently by two members of the review team applying The Joanna Briggs Institute's critical appraisal checklist. Likewise, risk of bias will be independently evaluated by two reviewers using the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al.* Disagreements will be resolved by discussion between the two authors and a third author will be involved if needed. The Joanna Briggs Institute's checklist will be used as a reference when conducting sensitivity analysis restricted to high quality studies. *[page 13-14]*
Data synthesis	15a	We will estimate chronic headache global prevalence in adult civilian traumatic injury. Whenever possible, chronic headache prevalence estimates in mild cases and moderate/severe cases will be computed. The analysis will only include studies with sample sizes greater than 100 participants. *[page 14-15]*
	15b	Chronic headache prevalence pooled estimates for all pre-specified outcomes will be computed applying random effect meta-analysis models. Heterogeneity within included studies will be assessed using the I 2 statistic and visual inspection of forest plots. *[page 14-15]*
	15c	Sub-group sensitivity analysis will be performed (if possible) and considering studies of highest methodological quality according to time elapsed since injury and head trauma severity (mild versus moderate/severe). *[page 14-15]*
	15d	Descriptive analysis and report the characteristics of included studies. *[page 14-15]*

Meta-bias(es)	16	Considering confirmation of traumatic brain injury diagnosis can vary from one study to another, therefore introducing a selection bias, only studies using a clearly defined operational definition for the diagnosis of TBI will be considered for inclusion. *[page 7 line 18]*
Confidence in cumulative evidence	17	NA

APPENDIX 2

Medline search strategy (from 2008 to Present)

Traumatic brain injury (population)

1. Brain Injuries [MeSH]
2. Craniocerebral Trauma [tiab]
3. Head Injuries, Closed [tiab]
4. Skull Fractures [tiab]
5. mTBI* [tiab]
6. tbi* [tiab]
7. concuss* [tiab]
8. ((head* or cerebr* or crani* or skull* or intracran*) adj2 (injur* or trauma* or damag* or wound* or swell* or oedema* or edema* or fracture* or contusion* or pressur*)) [tiab]
9. ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or bleed*)) [tiab]
10. 1 OR/9

Chronic headache disorders (condition)

11. Headache [MeSH]
12. Head pain [tiab]
13. Hemicrania [tiab]
14. migraine* [tiab]
15. cephalia* [tiab]
16. cephalea* [tiab]
17. cephalgia* [tiab]
18. cephalagia* [tiab]
19. 11 OR/18
20. 10 AND 19

Prevalence

21. prevalen* [tiab]
22. Inciden* [tiab]
23. Percent* [tiab]
24. epidemiol* [tiab]
25. frequenc* [tiab]
26. occurrenc* [tiab]
27. morbidit* [tiab]
28. rate* [tiab]
29. Probabilit* [tiab]
30. Epidemiological studies [MeSH]
31. Population* [tiab]
32. Severit* [tiab]
33. Progress* [tiab]
34. Risk [tiab]
35. 21 OR/34

All combined

36. 20 AND 35

APPENDIX 3

Joanna Briggs Institute's critical appraisal checklist for studies of prevalence data [4]

Criteria	Response
1.Was the sample frame appropriate to address the target population?	*Yes, No, Unclear, Not applicable*
2.Were the study participants sampled in an appropriate way?	*Yes, No, Unclear, Not applicable*
3.Was the sample size adequate?	*Yes, No, Unclear, Not applicable*
4.Were the study subjects and the setting described in detail?	*Yes, No, Unclear, Not applicable*
5.Was the data analysis conducted with sufficient coverage of the identified sample?	*Yes, No, Unclear, Not applicable*
6.Were valid methods used for the identification of the condition?	*Yes, No, Unclear, Not applicable*
7.Was the condition measured in a standard, reliable way for all participants?	*Yes, No, Unclear, Not applicable*
8.Was there appropriate statistical analysis?	*Yes, No, Unclear, Not applicable*
9.Was the response rate adequate, and if not, was the low response rate managed appropriately?	*Yes, No, Unclear, Not applicable*

APPENDIX 4

Quality assessment checklist for prevalence studies adapted from Hoy et al. [5]

Risk of bias items	Risk of bias levels	Points scored
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes (LOW RISK):** The study's target population was a close representation of the national population.	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	**Yes (LOW RISK):** The sampling frame was a true or close representation of the target population.	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes (LOW RISK):** The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders.	0
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes (LOW RISK):** All data were collected directly from the subjects.	0
	No (HIGH RISK): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	**Yes (LOW RISK):** An acceptable case definition was used.	0
	No (HIGH RISK): An acceptable case definition was NOT used.	1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes (LOW RISK):** The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes (LOW RISK):** The same mode of data collection was used for all subjects.	0
	No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	1
9. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	**Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

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BMJ Open

Update on the prevalence of persistent headache in adult civilian traumatic brain injury: protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology
Keywords:	Traumatic brain injury, Headache, Prevalence, Systematic review protocol

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TITLE: Update on the prevalence of persistent headache in adult civilian traumatic brain injury: protocol for a systematic review and meta-analysis

Authors' details and affiliations:

Caroline Arbour[1-2], Ph.D., Yasmine Bouferguène[1,3], B.Sc., Roxanne Beauregard[2], RN, Gilles Lavigne[1,3], Ph.D., Alberto Herrero Babiloni[1,3], M.Sc.

1. Hôpital du Sacré-Coeur de Montréal Research Center, Montreal, Quebec, Canada;
2. Faculty of Nursing, Université de Montréal, Montréal, Québec, Canada;
3. Faculty of Dental Medicine, Université de Montréal, Montreal, Québec, Canada.

Corresponding author: Any comments or inquiry about this publication should be addressed to Caroline Arbour, Hôpital du Sacré-Coeur de Montréal, 5400 Boul. Gouin Ouest. Room: E-1381, Montréal (Québec) H4J 1C5. Tel: 338-2222 ext: 3741, Email: caroline.arbour@umontreal.ca

Email addresses:

Caroline Arbour (caroline.arbour@umontreal.ca)

Yasmine Bouferguene (yasmine.bouferguene@umontreal.ca)

Roxanne Beauregard (beauregar_01@hotmail.com)

Gilles Lavigne (gilles.lavigne@umontreal.ca)

Alberto Herrero Babiloni (herre220@umn.edu)

ABSTRACT

Introduction: Traumatic brain injury (TBI) is a major public health concern. Persistent headache is a common consequence of TBI affecting productivity and quality of life. The only review providing information about headache prevalence after TBI was published in 2008, combined data from civilian and military TBI, and was strictly derived from Medline database. Due to recent changes in TBI diagnosis and civil trauma epidemiology, the aim of the current study is to carry out a systematic review and meta-analysis to derive updated prevalence estimates of persistent headache in adult civilian TBI.

Methods and analysis: The methods have been defined following PRISMA guidelines. Studies published from 2008-2019 will be identified searching the electronic databases Medline, Embase, Cochrane, Google Scholar, Directory of Open Access Journals, and Web of Science. Retrieved records will be independently screened by two authors and relevant data will be extracted from studies reporting data on persistentheadache prevalence among civilian TBI individuals (≥16 years). The pooled prevalence estimates of any form of headache will be computed applying random-effects meta-analysis. Heterogeneity will be assessed using the I2 statistic and explored through subgroup analyses considering TBI severity (mild versus moderate/severe). Estimations of risk of bias will be performed using the Risk of Bias Tool for Prevalence Studies.

Ethics and dissemination: The result of this systematic review will be published in a peer-reviewed journal and disseminated at relevant conferences presentations. Formal ethical approval is not required because we will search and evaluate only existing sources of literature. By focusing on studies conducted in the last decade, this review will provide the most up-to-date information about the global prevalence of persistent headache after TBI. Considering the economical and social burden of persistent headache after TBI, accurate

estimates of this problematic is of utmost importance for planning, implementing and evaluating prevention interventions.

Clinical trial registration : CRD42018094138.

Keywords: Traumatic brain injury, headache, prevalence, systematic review protocol

ARTICLE SUMMARY

Strengths and limitations

► This systematic review will yield solid and updated estimates on the prevalence of persistent headache in adult traumatic brain injury populations.

► Unlike previous prevalence estimates on pain after head trauma, data included in this review will be restricted to civilian traumatic brain injury and exclude studies conducted in a military context, as differences between the two groups have been documented in terms of premorbid characteristics and patterns of recovery.

► Data of persistent headache after traumatic brain injury will first be pooled to provide a global prevalence estimate of the problematic, then analyzed separately in mild and moderate/severe cases.

► The increased reliance in TBI research on self-report information to confirm the history of head trauma is likely to reduce the comparability with studies using the classical clinician's assessment approach to TBI diagnostic.

► Regarding the development of persistent headache after TBI, heterogeneity in prevalence estimates might be caused by multiple features including psychiatric disorders comorbidity and time elapsed since injury. Those elements will be thoroughly documented.

BACKGROUND

Traumatic brain injury (TBI) occurs when an external force is applied to the head leading to permanent or temporary disabilities [1]. TBI can be considered mild, moderate or severe depending on changes in cognitive and executive processes [2]. TBI is a major threat to global health as 69 million individuals worldwide are estimated to sustain such injury each year [3]. In the European Union, more than 1.4 million individuals are hospitalized for TBI annually [4]. In the United States, 2.8 million individuals seek medical attention for TBI each year with an estimated annual cost of over $76 billion [5-6]. Incidence of TBI is also on the rise in low and middle-income countries, mainly due to the increased use of motor vehicles [7-9]. While sport and military-related TBI have received considerable media attention in the last decade, the highest combined incidence of TBI-related emergency department visits, hospitalizations, and deaths occurs in civilians [10].

Chronic pain is a common consequence of TBI [11]. To date, headache following TBI has been the focus of several studies and reports on the topic [12-14]. According to the International Headache Society, persistent headache attributed to head trauma is defined as a headache developing in the days/weeks following the impact and persisting more than 3 months after [15-16]. Persistent headache after TBI has no defining clinical features, and it is classified as a secondary headache disorder because of the close temporal relation to another disorder known to cause headache (in this case TBI) [15]. This remains true even when the headache has the characteristics of a primary headache (migraine, tension-type headache, cluster headache, or one of the other primary headaches). In terms of recovery, persistent headache after TBI has been associated to higher rates of anxiety

and depression symptoms and reduced quality of life [17]. In TBI adults, the odds of returning to work successfully are more than cut in half for each unit increase in posttraumatic headache intensity [18].

The only available estimates of headache in adult TBI date back to 2008 when chronic pain prevalence data were pooled from 23 studies (from 1951 to 2008) yielding a global prevalence of 57.8% for persistent headache, with surprising higher rates in mild TBI (75.3%) when compared to moderate/severe TBI (32.1%) [19]. In the last decade, several factors may have led to significant changes in chronic headache epidemiology after TBI including the revision of mild TBI diagnosis criteria to make it more inclusive and an historic peak of TBI in the elderly attributed to the aging population [20-22]. In addition, the above-mentioned systematic review conducted by Nampiaparampil [19] combined epidemiological data from civilian TBI and military-related TBI, reducing the comparability between eligible studies. Moreover, the review did not account for the presence of psychiatric disorders comorbidity, which would have been important as we now know these elements may contribute to pain chronicity after TBI [23]. For all the aforementioned reasons, updating the prevalence estimate of persistent headache in adult civilian TBI becomes especially relevant.

OBJECTIVES

The aim of the current study is to carry out a systematic review and meta-analysis to derive updated estimates on global and severity-specific prevalence of persistent headache in adult civilian TBI. The proposed review will address two main questions:

1. What is the updated global prevalence of persistent headache in adult civilian TBI?
2. What is the specific prevalence of persistent headache in adult civilians with mild TBI versus moderate/severe TBI?

Considering the increased reliance on self-report and screening measures to validate the occurrence of events leading to TBI in recent years, we expect an increase in persistent headache prevalence in adult civilian TBI [24]. These updated data will inform the planning, implementation and evaluation of chronic pain prevention intervention in trauma care, and potentially, contribute to reduce its morbidity after TBI.

METHODS/DESING

The methods for this systematic review have been defined in advance following the Prepared Items for Systematic Reviews and Meta-Analysis (PRISMA) [25]. The protocol was developed according to the PRISMA-P checklist [26]. (see online supplementary Appendix 1) The study has been registered on PROSPERO (CRD42018094138).

Eligibility criteria

Studies will be selected according to the criteria outlined below.

Study designs:

Studies will be considered for inclusion based on their relevance to answer the review questions. For review question 1, any form of observational studies investigating the prevalence of persistent headache after civilian TBI, or from which prevalence estimates can be derived and that meet the eligibility criteria will be considered. More

specifically, prevalence estimates for persistent headache after TBI will be derived from either: (1) The general population (i.e., from population prevalence surveys), (2) Patient registries or primary care practices' databases, (3) Hospital-based populations, or (4) Screening programmes. For review question 2, studies eligible for question 1, in which prevalence estimates are presented based on TBI severity will be considered. Studies will not be restricted by language. However, all will have to report original data and be peer-reviewed. Expert opinion letters or editorials, conference summaries, or reviews will be excluded. Intervention studies (including randomized control trials) will also be excluded on the basis that they are not deemed appropriate to help answer the review questions.

Population:

The population of interest consists of individuals (18 years or older) from the general population who have sustained a mild, moderate or severe TBI. Considering teenagers aged 16 years and older are often treated in adult trauma units, studies including 16 and 17 years old individuals in their sampling procedures will also be considered for inclusion. Mixed patient population studies will also be considered for inclusion if the analyses of results are stratified according to patients' diagnosis and mechanism of injury, allowing the review team to discern findings specific to the civilian TBI group. Studies about persistent headache following military TBI will not be considered in this study as differences compared to civilian TBI in terms of premorbid characteristics and patterns of recovery have been documented [27-28]. For similar reasons, pain studies using animal models of TBI will be excluded [29-31]. Consistent with Nampiaparampil [19], only studies using a clearly defined operational definition for the diagnosis of TBI will be considered for inclusion. Recognized criteria for the diagnosis of TBI include either: (1) a

period of unconsciousness and/or post-traumatic amnesia, (2) clinician's confirmation of the initial Glasgow coma scale score at hospital admission, or (3) a self-professed experience of transient neuropsychological dysfunction following injury to the head [1, 32-34].

Outcomes:

The primary outcome will be the global prevalence of persistent headache following TBI. In order to be considered 'persistent', headache will have to occur for longer than 3 months after initial onset to fulfil the criteria of the International Classification of Headache Disorders – 3rd edition (ICHD-3) [15]. The secondary outcome will be a better understanding of the associations between persistent headache and TBI severity. The latest could potentially help to identify which type of TBI patients are most likely to benefit from systematic screening and preventive interventions for headache disorders during acute recovery.

Timing:

Considering the latest estimates of persistent headache prevalence after TBI are based on studies published from 1951 to February 2008, only studies published from March 2008 to 2019 will be considered for inclusion.

Setting:

As TBI is a serious public health problem around the world [35], no geographical limitations will be applied.

Information sources

The following databases will be searched: Medline, Embase, Cochrane Library, Google Scholar, and Directory of Open Access Journals. For search optimization, we will scan the reference lists of included studies. We will also search the authors' personal bibliography on Web of Science to make sure that all relevant material has been captured.

Search strategy

The specific search strategies will be created by a Health Sciences Librarian with expertise in systematic reviews using the Peer Review for Electronic Search Strategies (PRESS) checklist [36]. To date, a first search strategy has been developed by the librarian and peer-reviewed by a member of the review team (YB) in Medline using MeSH subject headings combined with free-text terms around the three search components 'TBI', 'Headaches' and 'Prevalence'. A draft Medline search strategy is included in Appendix 2. The search strategy will eventually be adapted by the librarian for its use in the other databases.

Study records

Data management:

An initial literature search will be performed by one member of the review team (YB) and entirely review by a second member (AHB). The citation abstract and full text article of all references identified will be uploaded to EndNote (EndNote 2017, Clarative Analytics). The search results from the different electronic databases will be combined in a single EndNote library to facilitate collaboration among the review team members (YB, AHB) during the study selection process. No training in relation to the literature search is

planned at this stage as both reviewers are already familiar with Endnote and the content area of the review.

Selection process:

Titles and abstracts of studies generated from the initial search will be screened independently by two members of the review team (YB, AHB). The full-text will be retrieved and independently assessed by both authors for eligibility based on the inclusion/exclusion criteria mentioned previously. The full-text of remaining articles will be independently examined by the same reviewers to reach a final list of articles. Disagreements at either screening stage will be resolved through discussion with a third reviewer (CA). The reasons for study exclusion will be documented. For duplicated references, and data that has been published more than once, the most complete study will be chosen for inclusion in the library while the others will be removed. A PRISMA flow diagram of the study selection procedure will be prepared to provide an overview of the decisions that are made in the data collection process [25].

Data collection process:

Consistent with Nampiaparampil [19], prevalence in this review is defined as the estimate of the total amount of persistent headache at a time point or period interval in a certain sample of adult civilian TBI. Based on this definition, data will be extracted from the included studies using a standardized data extraction spreadsheet. The data extraction spreadsheet will be pre-tested by two members of the review team (YB, RB) on ten randomly selected publications and modified accordingly. Using the same data extraction spreadsheet, the reviewers (YB, RB) will independently extract and manage the data for each of the included studies. Disagreements will be resolved by discussion between the

two authors; if no agreement can be reached, consensus will be sought through discussions with a third author (CA). Authors of the included studies will be contacted in case clarifications or further data are needed (up to three attempts by email over a period of eight weeks). Data will be extracted on the following:

1. Publication details: title, journal, author, year, city and country, in which the study was conducted, type of publication, and source of funding.
2. Design: type of study (cohort, case-control, etc), method of data collection, response rate, recruitment and sampling methods, and eligibility (inclusion and exclusion criteria).
3. Study participant details: number of persons interviewed or surveyed, population characteristics including setting, age, sex, and premorbid characteristics including pre-existing primary headache disorders. Information about TBI severity will be rigorously extracted with respect to the clinical features and classification methods widely used (see Table 1) [37].
4. Data for outcome measures: prevalence of persistent headache after TBI in general or according to TBI severity, characteristics of the headache (migraine, tension-type headache, cluster headache, or one of the other primary headaches), time period referenced in assessment of the condition, and factors (mainly comorbidities) found to be related significantly to the development of headaches after TBI.
5. Missing data: Considering there are no standardized time points for the assessment of persistent headache after TBI, prospective multiple assessments can be expected in some studies. This may potentially result in missing data. Reasons for missing

data will be recorded from the original articles. If the original articles did not include this detail, we will try our best to obtain requisite information by contacting the corresponding author of the referenced articles for the missing data. The potential impact of the effect of missing data on the final findings of the review will be addressed in the discussion.

Table 1. TBI severity classification inspired by the Mayo Clinic classification system

Classification	Criteria
Moderate/severe TBI (definite)	-Death
	-Loss of consciousness > 30 minutes
	-Antegrade amnesia > 24 hours
	-Glasgow Coma scale score < 13 in the initial 24 hours
	-Intracerebral, subdural, epidural, or subarachnoid hemorrhages; cerebral or hemorrhagic contusion, penetrating TBI, or brainstem injury
Mild TBI (probable)	- Loss of consciousness – momentarily to < 30 minutes
	-Post-traumatic anterograde amnesia – momentarily to < 2 – 4 hours
	-Depressed basilar or linear skull fracture (dura intact)
Symptomatic (possible mild TBI)	- A history of head trauma is reported by the patient - One or more of the following symptoms are reported: blurred vision, confusion (changes in mental status), dizziness, headache, nausea or focal neurological symptoms

Risk of bias

Risk of bias of included studies will be independently evaluated by two members of the review team (YB, RB) using the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al* (see Appendix 3) [38]. Individual items will be rated as "Yes" if the criterion is fulfilled. Otherwise, if the design of the study is not applicable or if there is insufficient

information in the study to permit a judgment for a particular criterion, it will be noted as "No". In the event that a full consensus cannot be reached between the two reviewers, the opinion of a third reviewer (CA) will be obtained, and the proceeding majority consensus will be taken.

Data analysis and synthesis

We will perform descriptive analysis and report the characteristics of included studies in summary tables and narrative text. Limitations of the studies will be discussed in detail.

As we anticipate variability between included studies (mainly in the time points considered for the screening of headache disorders), the pooled prevalence estimate of persistent headache will be computed applying random-effects meta-analysis models (rather than assuming a single true value in a fixed-effect approach) using the MetaXL (www. epigear.com) add-in for Microsoft Excel. A pooled prevalence figure will be calculated with 95% CI. Meta-analysis will be limited to studies with at least 100 participants allowing an acceptable margin of error of ≤10% in the prevalence estimates of headache [39]. Heterogeneity within included studies will be assessed through the utilization of the I^2 statistics, with I^2 values of 25%, 50% and 75% being considered low, moderate and high respectively [40]. Depending on data availability, we plan to account for heterogeneity conducting meta-regressions and subgroup analysis considering the following covariates: time elapsed since TBI and TBI severity. Sensitivity analysis will be carried out considering only studies of the highest methodological quality using the Risk of Bias Tool for Prevalence Studies checklist.

Ethics and dissemination

As this will be a review of published data, patients will not be primarily involved in any stage of the study. Data will be collected from published studies available in the previously mentioned electronic databases. On completion of the analysis, we will prepare a manuscript for publication in a peer-reviewed journal and present the results at conferences.

Patient and Public Involvement

No patient involved.

DISCUSSION

To date, the only systematic review providing information about chronic headache following TBI was published in 2008 [19], and no new review is underway based on PROSPERO. Considering the recent changes in TBI diagnosis and epidemiology, there is a strong rational for updating current evidence on persistent headache prevalence in adult civilian TBI.

The systematic review and meta-analysis we plan to carry out builds on the methodology applied previously [19], but reducing its limitations. Indeed, the previous review on the topic was performed solely through a MEDLINE search even though clinicians and educational outreach is an important goal of TBI research dissemination [41-42]. The exclusion of other databases in which many journals are not indexed and the restriction of publications in other languages than English may have limited the findings and contributed to the confusion about the influence of TBI severity of headache

prevalence. We believe that the use of additional sources of data aside from Medline will provide rigorous and updated estimates on prevalence of chronic headache in TBI. Moreover, differently from Nampiaparampil (2008), we will limit the review to studies about non-military TBI as the highest combined incidence of TBI-related emergency department visits, hospitalizations, and deaths occurs in civilians. In terms of research, pooling of such data is necessary to monitor trends in comorbidities among individuals who sustained TBI and to contribute to the design of further outcome studies. Another point that will differ from Nampiaparampil's work is the use of ICHD-3 operative criteria for the definition of persistent headache. As shown in a recent systematic review of posttraumatic headache in children [43], use of a standardized definition helps to make distinction between the prevalence of non-specific persistent headache and prevalence of persistent headache as defined by recognized organizations. Last but not the least, we will include, in a separate section of the review, data about the prevalence of persistent headache after TBI based on TBI severity.

To our knowledge, this is the first systematic review and meta-analysis protocol addressing the important need to update the prevalence estimates of persistent headache in adult civilian TBI. Some limitations can be anticipated due to missing data and heterogeneity of the studies. Aside from variations in persistent headache definition, another aspect that could contribute to study heterogeneity is the fact that depressed skull fractures with intact dura have only been recently recognized as mild TBI [37]. Thus, studies performed before 2017 may not have included these cases in their estimates of persistent headache after mild TBI. Despite these limitations, we anticipated our data will still be important to inform the planning, implementation and evaluation of chronic pain

prevention intervention in trauma care, and potentially, contribute to reduce its morbidity after TBI.

Contributions: CA and GL conceived the study. YB and AHB performed the preliminary search. YB reviewed the search strategy with the help of Health Sciences librarian. YB and RB will oversee data extraction and analysis. CA and AHB participated in the conception of the protocol and produced the first draft of the manuscript. The definitive protocol was reviewed and approved by all authors (CA, YB, RB, GL, AHB).

Funding: This project is funded by a start up fund provided by the research center of the Hôpital du Sacré-Coeur de Montréal to CA. The Hôpital du Sacré-Coeur de Montréal had no role in the development of the protocol. GL holds a Canada Research Chair on Pain, Sleep, and Traumatic Injuries.

Competing interests: The authors declare that they have no conflicts of interest in relation to this work.

Patient consent for publication: Not applicable.

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APPENDICES

UPDATE on the PREVALENCE of PERSISTENT HEADACHE in ADULT CIVILIAN TRAUMATIC BRAIN INJURY: PROTOCOL for a SYSTEMATIC REVIEW and METE-ANALYSIS

[Caroline Arbour PhD[1-2], Yasmine Bouferguène BSc[1,3], Roxanne Beauregard RN[1-2], Gilles Lavigne PhD[1,3], Alberto Herrero Babiloni MSc[1,3]]

*Corresponding author: caroline.arbour@umontreal.ca

1. Hôpital du Sacré-Coeur de Montréal Research Center, Montreal, Quebec, Canada;
2. Faculty of Nursing, Université de Montréal, Montréal, Québec, Canada;
3. Faculty of Dental Medicine, Université de Montréal, Montreal, Québec, Canada.

APPENDIX 1

PRISMA-P checklist [1]

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title: Identification	1a	UPDATE on the PREVALENCE of PERSISTENT HEADACHE in ADULT CIVILIAN TRAUMATIC BRAIN INJURY: PROTOCOL for a SYSTEMATIC REVIEW and METE-ANALYSIS
Update	1b	Updating (with methodological modifications) Nampiaparampil, 2008. [2]
Registration	2	PROSPERO (CRD42018094138)
Authors: Contact	3a	Caroline Arbour PhD[1-2] (CA*), Yasmine Bouferguène BSc[1,3], Roxanne Beauregard RN[1-2], Gilles Lavigne PhD[1,3], Alberto Herrero Babiloni MSc[1,3] * caroline.arbour@umontreal.ca 1) Hôpital du Sacré-Coeur de Montréal Research Center, Montreal, Canada; 2) Faculty of Nursing, Université de Montréal, Montréal, Canada; 3) Faculty of Dental Medicine, Université de Montréal, Montreal, Canada.
Contributions	3b	CA and GL conceived the study. YB and AHB performed the preliminary search. YB reviewed the search strategy. YB and RB will oversee data extraction and analysis. CA and AHB produced the first draft of the manuscript. The definitive protocol was reviewed and approved by all authors. *[page 17 line 1]*
Amendments	4	Significant changes to the protocol will be updated in PROSPERO and reported in the final paper.
Support: Sources	5a	This project is funded by a start up fund provided by the research center of the Hôpital du Sacré-Coeur de Montréal to CA. The Hôpital du Sacré-Coeur de Montréal had no role in the development of the protocol. GL holds a Canada Research Chair on Pain, Sleep, and Traumatic Injuries. *[page 17 line 6]*
Sponsor	5b	None declared. *[page 17 line 12]*
INTRODUCTION		
Rationale	6	Persistent headache is a common consequence of traumatic brain injury. The only review providing information about headache prevalence after brain trauma was published in 2008 and was strictly derived from Medline database and combined data from civilian and military populations. Due to recent changes in brain trauma diagnosis and civil epidemiology, the aim of the current study is to carry out a systematic review and meta-analysis to derive updated prevalence estimates of persistent headache in adult civilian traumatic brain injury. *[page 5-6]*
Objectives	7	To derive updated estimates on global and severity-specific prevalence of persistent headache in adult civilian traumatic brain injury. *[page 6 line 19]*
METHODS		
Eligibility criteria	8	**Study designs:** Observational studies (case-control and Cohort studies) reporting prevalence of chronic headache (or from which prevalence can be derived); Published from March 2008 to this day. RCT, case control, case series, case report as well as duplicate reports will be excluded. **Population**: Representative sample of adult civilian traumatic brain injury patients (16 years and older); No geographic limitations; Patient identification by physician diagnosis, self-reported status, populational trauma registries, other medical/administrative registers. Prevalence data reported based on brain trauma severity (mild, moderate/severe) will be treated separately.

		Outcomes: The primary outcome will be the global prevalence of persistent headache following traumatic brain injury. The secondary outcome will be a better understanding of the associations between chronic headache and brain trauma severity. *[page 9]*
Information sources	9	Searching in the electronic databases (Medline, Embase, Cochrane, Google Scholar, and Directory of Open Access Journals), manual references' listing of included studies and authors' personal bibliography on Web of Science. *[page 9 line 22]*
Search strategy	10	See Appendix 2
Study records:		
Data management	11a	Studies retrieved will be grouped and duplicates removed with support of a reference management software package. Studies eligibility will be assessed independently by two authors. Discrepancies between authors will be resolved by discussion and consultation of a third author if needed. The study selection process will be reported in a PRISMA flow diagram. *[page 10 line 17]*
Selection process	11b	Studies will be selected independently by both authors based on pre-established eligibility criteria. Discrepancies between authors will be resolved by discussion and consultation of a third author if needed. Reasons for exclusion will be documented. *[page 11 line 3]*
Data collection process	11c	Data extraction will be performed independently by two authors using a pre-tested spreadsheet. Disagreements will be resolved by discussion between the two authors; if no agreement can be reached, consensus will be sought through discussions with a third author Up to three attempts by mail will be done if additional data or clarification will be required from the included studies. *[page 11 line 15]*
Data items	12	Data extraction will include: studies' title, journal, first author's name and affiliation(s), year and country of publication, design, response rate and sample size, sampling method, participants' sociodemographic and clinical characteristics, TBI severity, time elapsed since TBI, prevalence of chronic headache, characteristics of the headache, psychiatric comorbidities, risk factors, missing data, reasons for missing data. *[page 12 line 4]*
Outcomes and prioritization	13	Every headache lasting for more than 3 months after occurrence of brain trauma independent of its characteristics. [3] *[page 9 line 7]*
Risk of bias in individual studies	14	Risk of bias will be independently evaluated by two reviewers using the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al.* Disagreements will be resolved by discussion between the two authors and a third author will be involved if needed. Hoy *et al.* checklist will be used as a reference when conducting sensitivity analysis restricted to high quality studies. *[page 13 line 11]*
Data synthesis	15a	We will estimate persistent headache global prevalence in adult civilian traumatic injury. Whenever possible, persistent headache prevalence estimates in mild cases and moderate/severe cases will be computed. The analysis will only include studies with sample sizes greater than 100 participants. *[page 14]*
	15b	Persistent headache prevalence pooled estimates for all pre-specified outcomes will be computed applying random effect meta-analysis models. Heterogeneity within included studies will be assessed using the I 2 statistic and visual inspection of forest plots. *[page 14]*
	15c	Sub-group sensitivity analysis will be performed (if possible) and considering studies of highest methodological quality according to time elapsed since injury and head trauma severity (mild versus moderate/severe). *[page 14]*
	15d	Descriptive analysis and report the characteristics of included studies. *[page 14]*
Meta-bias(es)	16	Considering confirmation of traumatic brain injury diagnosis can vary from one study to another, therefore introducing a selection bias, only studies using a clearly

		defined operational definition for the diagnosis of TBI will be considered for inclusion. *[page 7 line 19]*
Confidence in cumulative evidence	17	NA

APPENDIX 2

Medline search strategy (from 2008 to Present)

Traumatic brain injury (population)

1. Brain Injuries [MeSH]
2. Craniocerebral Trauma [tiab]
3. Head Injuries, Closed [tiab]
4. Skull Fractures [tiab]
5. mTBI* [tiab]
6. tbi* [tiab]
7. concuss* [tiab]
8. ((head* or cerebr* or crani* or skull* or intracran*) adj2 (injur* or trauma* or damag* or wound* or swell* or oedema* or edema* or fracture* or contusion* or pressur*)) [tiab]
9. ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or bleed*)) [tiab]
10. 1 OR/9

Chronic headache disorders (condition)

11. Headache [MeSH]
12. Head pain [tiab]
13. Hemicrania [tiab]
14. migraine* [tiab]
15. cephalia* [tiab]
16. cephalea* [tiab]
17. cephalgia* [tiab]
18. cephalagia* [tiab]
19. 11 OR/18
20. 10 AND 19

Prevalence

21. prevalen* [tiab]
22. Inciden* [tiab]
23. Percent* [tiab]
24. epidemiol* [tiab]
25. frequenc* [tiab]
26. occurrenc* [tiab]
27. morbidit* [tiab]
28. rate* [tiab]
29. Probabilit* [tiab]
30. Epidemiological studies [MeSH]
31. Population* [tiab]
32. Severit* [tiab]
33. Progress* [tiab]
34. Risk [tiab]
35. 21 OR/34

All combined

36. 20 AND 35

APPENDIX 3

Quality assessment checklist for prevalence studies adapted from Hoy et al. [4]

Risk of bias items	Risk of bias levels	Points scored
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes (LOW RISK):** The study's target population was a close representation of the national population.	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	**Yes (LOW RISK):** The sampling frame was a true or close representation of the target population.	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes (LOW RISK):** The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders.	0
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes (LOW RISK):** All data were collected directly from the subjects.	0
	No (HIGH RISK): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	**Yes (LOW RISK):** An acceptable case definition was used.	0
	No (HIGH RISK): An acceptable case definition was NOT used.	1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes (LOW RISK):** The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes (LOW RISK):** The same mode of data collection was used for all subjects.	0
	No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	1
9. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	**Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

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BMJ Open

Update on the prevalence of persistent posttraumatic headache in adult civilian traumatic brain injury: protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology
Keywords:	Traumatic brain injury, Headache, Prevalence, Systematic review protocol

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TITLE: Update on the prevalence of persistent posttraumatic headache in adult civilian traumatic brain injury: protocol for a systematic review and meta-analysis

Authors' details and affiliations:

Caroline Arbour[1-2], Ph.D., Yasmine Bouferguène[1,3], B.Sc., Roxanne Beauregard[2], RN, Gilles Lavigne[1,3], Ph.D., Alberto Herrero Babiloni[1,3], M.Sc.

1. Hôpital du Sacré-Coeur de Montréal Research Center, Montreal, Quebec, Canada;
2. Faculty of Nursing, Université de Montréal, Montréal, Québec, Canada;
3. Faculty of Dental Medicine, Université de Montréal, Montreal, Québec, Canada.

Corresponding author: Any comments or inquiry about this publication should be addressed to Caroline Arbour, Hôpital du Sacré-Coeur de Montréal, 5400 Boul. Gouin Ouest. Room: E-1381, Montréal (Québec) H4J 1C5. Tel: 338-2222 ext: 3741, Email: caroline.arbour@umontreal.ca

Email addresses:

Caroline Arbour (caroline.arbour@umontreal.ca)

Yasmine Bouferguene (yasmine.bouferguene@umontreal.ca)

Roxanne Beauregard (beauregar_01@hotmail.com)

Gilles Lavigne (gilles.lavigne@umontreal.ca)

Alberto Herrero Babiloni (herre220@umn.edu)

ABSTRACT

Introduction: Traumatic brain injury (TBI) is a major public health concern. Persistent posttraumatic headache (PTH) is a common consequence of TBI affecting productivity and quality of life. The only review providing information about headache prevalence after TBI was published in 2008, combined data from civilian and military TBI, and was strictly derived from Medline database. Due to recent changes in TBI diagnosis and trauma epidemiology, the aim of the current study is to perform a systematic review and meta-analysis to derive updated prevalence estimates of persistent PTH in adult civilian TBI.

Methods and analysis: The methods have been defined following PRISMA guidelines. Studies published from 2008-2019 will be identified searching the electronic databases Medline, Embase, Cochrane, Google Scholar, Directory of Open Access Journals, and Web of Science. Retrieved records will be independently screened by two authors and relevant data will be extracted from studies reporting data on persistent PTH prevalence among civilian TBI individuals (≥16 years). The pooled prevalence estimates of any form of headache will be computed applying random-effects meta-analysis. Heterogeneity will be assessed using the I2 statistic and explored through subgroup analyses considering TBI severity (mild versus moderate/severe). Estimations of risk of bias will be performed using the Risk of Bias Tool for Prevalence Studies.

Ethics and dissemination: The result of this systematic review will be published in a peer-reviewed journal and disseminated at relevant conferences presentations. Formal ethical approval is not required because we will search and evaluate only existing sources of literature. By focusing on studies conducted in the last decade, this review will provide the most up-to-date information about the global prevalence of persistent PTH after TBI. Considering the economical and social burden of persistent PTH after TBI, accurate

estimates of this problematic disorder is of utmost importance for planning, implementing and evaluating prevention interventions.

Clinical trial registration : CRD42018094138.

Keywords: Traumatic brain injury, headache, prevalence, systematic review protocol

ARTICLE SUMMARY

Strengths and limitations

► This systematic review will yield solid and updated estimates on the prevalence of persistent posttraumatic headache in adult traumatic brain injury populations.

► Unlike previous prevalence estimates on pain after head trauma, data included in this review will be restricted to civilian traumatic brain injury and exclude studies conducted in a military context, as differences between the two groups have been documented in terms of premorbid characteristics and patterns of recovery.

► Data of persistent posttraumatic headache after traumatic brain injury will first be pooled to provide a global prevalence estimate of this problematic disorder, then analyzed separately in mild and moderate/severe cases.

► The increased reliance in TBI research on self-report information to confirm the history of head trauma is likely to reduce the comparability with studies using the classical clinician's assessment approach to TBI diagnostic.

► Regarding the development of persistent posttraumatic headache after TBI, heterogeneity in prevalence estimates might be caused by multiple features including psychiatric disorders comorbidity and time elapsed since injury. Those elements will be thoroughly documented.

BACKGROUND

Traumatic brain injury (TBI) occurs when an external force is applied to the head leading to permanent or temporary disabilities [1]. TBI can be considered mild, moderate or severe depending on changes in cognitive and executive processes [2]. TBI is a major threat to global health as 69 million individuals worldwide are estimated to sustain such injury each year [3]. In the European Union, more than 1.4 million individuals are hospitalized for TBI annually [4]. In the United States, 2.8 million individuals seek medical attention for TBI each year with an estimated annual cost of over $76 billion [5-6]. Incidence of TBI is also on the rise in low and middle-income countries, mainly due to the increased use of motor vehicles [7-9]. While sport and military-related TBI have received considerable media attention in the last decade, the highest combined incidence of TBI-related emergency department visits, hospitalizations, and deaths occurs in civilians [10].

Chronic pain is a common consequence of TBI [11]. To date, posttraumatic headache (PTH) following TBI has been the focus of several studies and reports on the topic [12-14]. According to the International Headache Society, persistent PTH attributed to head trauma is defined as a headache developing within 7 days following the impact and persisting more than 3 months after [15-16]. Persistent PTH after TBI has no defining clinical features, and it is classified as a secondary headache disorder because of the close temporal relation to another disorder known to cause headache (in this case TBI) [15]. This remains true even when the headache has the characteristics of a primary headache (migraine, tension-type headache, cluster headache, or one of the other primary headaches). In terms of recovery, persistent PTH after TBI has been associated to higher rates of anxiety

and depression symptoms and reduced quality of life [17]. In TBI adults, the odds of returning to work successfully are more than cut in half for each unit increase in posttraumatic headache intensity [18].

The only available estimates of headache in adult TBI date back to 2008 when chronic pain prevalence data were pooled from 23 studies (from 1951 to 2008) yielding a global prevalence of 57.8% for persistent PTH, with surprising higher rates in mild TBI (75.3%) when compared to moderate/severe TBI (32.1%) [19]. In the last decade, several factors may have led to significant changes in chronic headache epidemiology after TBI including the revision of mild TBI diagnosis criteria to make it more inclusive and an historic peak of TBI in the elderly attributed to the aging population [20-22]. In addition, the above-mentioned systematic review conducted by Nampiaparampil [19] combined epidemiological data from civilian TBI and military-related TBI, reducing the comparability between eligible studies. Moreover, the review did not account for the presence of psychiatric disorders comorbidity, which would have been important as we now know these elements may contribute to pain chronicity after TBI [23]. For all the aforementioned reasons, updating the prevalence estimate of persistent PTH in adult civilian TBI becomes especially relevant.

OBJECTIVES

The aim of the current study is to carry out a systematic review and meta-analysis to derive updated estimates on global and severity-specific prevalence of persistent PTH in adult civilian TBI. The proposed review will address two main questions:

1. What is the updated global prevalence of persistent PTH in adult civilian TBI?

2. What is the specific prevalence of persistent PTH in adult civilians with mild TBI versus moderate/severe TBI?

Considering the increased reliance on self-report and screening measures to validate the occurrence of events leading to TBI in recent years, we expect an increase in persistent PTH prevalence in adult civilian TBI [24]. These updated data will inform the planning, implementation and evaluation of chronic pain prevention intervention in trauma care, and potentially, contribute to reduce its morbidity after TBI.

METHODS/DESING

The methods for this systematic review have been defined in advance following the Prepared Items for Systematic Reviews and Meta-Analysis (PRISMA) [25]. The protocol was developed according to the PRISMA-P checklist [26]. (see online supplementary Appendix 1) The study has been registered on PROSPERO (CRD42018094138).

Eligibility criteria

Studies will be selected according to the criteria outlined below.

Study designs:

Studies will be considered for inclusion based on their relevance to answer the review questions. For review question 1, any form of observational studies investigating the prevalence of persistent PTH after civilian TBI, or from which prevalence estimates can be derived and that meet the eligibility criteria will be considered. More specifically, prevalence estimates for persistent PTH occurring within 7 days after TBI will be derived from either: (1) The general population (i.e., from population prevalence surveys), (2)

Patient registries or primary care practices' databases, (3) Hospital-based populations, or (4) Screening programmes. For review question 2, studies eligible for question 1, in which prevalence estimates are presented based on TBI severity will be considered. Studies will not be restricted by language. However, all will have to report original data and be peer-reviewed. Expert opinion letters or editorials, conference summaries, or reviews will be excluded. Intervention studies (including randomized control trials) will also be excluded on the basis that they are not deemed appropriate to help answer the review questions.

Population:

The population of interest consists of individuals (18 years or older) from the general population who have sustained a mild, moderate or severe TBI. Considering teenagers aged 16 years and older are often treated in adult trauma units, studies including 16 and 17 years old individuals in their sampling procedures will also be considered for inclusion. Mixed patient population studies will also be considered for inclusion if the analyses of results are stratified according to patients' diagnosis and mechanism of injury, allowing the review team to discern findings specific to the civilian TBI group. Studies about persistent PTH following military TBI will not be considered in this study as differences compared to civilian TBI in terms of premorbid characteristics and patterns of recovery have been documented [27-28]. For similar reasons, pain studies using animal models of TBI will be excluded [29-31]. Consistent with Nampiaparampil [19], only studies using a clearly defined operational definition for the diagnosis of TBI will be considered for inclusion. Recognized criteria for the diagnosis of TBI include either: (1) a period of unconsciousness and/or post-traumatic amnesia, (2) clinician's confirmation of the initial Glasgow coma scale score at hospital admission, or (3) a self-professed

experience of transient neuropsychological dysfunction following injury to the head [1, 32-34].

Outcomes:

The primary outcome will be the global prevalence of persistent PTH following TBI. In order to be considered 'persistent', headache will have to occur for longer than 3 months after initial onset to fulfil the criteria of the International Classification of Headache Disorders – 3rd edition (ICHD-3) [15]. The secondary outcome will be a better understanding of the associations between persistent PTH and TBI severity. The latest could potentially help to identify which type of TBI patients are most likely to benefit from systematic screening and preventive interventions for headache disorders during acute recovery.

Timing:

Considering the latest estimates of persistent PTH prevalence after TBI are based on studies published from 1951 to February 2008, only studies published from March 2008 to 2019 will be considered for inclusion.

Setting:

As TBI is a serious public health problem around the world [35], no geographical limitations will be applied.

Information sources

The following databases will be searched: Medline, Embase, Cochrane Library, Google Scholar, and Directory of Open Access Journals. For search optimization, we will

scan the reference lists of included studies. We will also search the authors' personal bibliography on Web of Science to make sure that all relevant material has been captured.

Search strategy

The specific search strategies will be created by a Health Sciences Librarian with expertise in systematic reviews using the Peer Review for Electronic Search Strategies (PRESS) checklist [36]. To date, a first search strategy has been developed by the librarian and peer-reviewed by a member of the review team (YB) in Medline using MeSH subject headings combined with free-text terms around the three search components 'TBI', 'Headaches' and 'Prevalence'. A draft Medline search strategy is included in Appendix 2. The search strategy will eventually be adapted by the librarian for its use in the other databases.

Study records

Data management:

An initial literature search will be performed by one member of the review team (YB) and entirely reviewed by a second member (AHB). The citation abstract and full text article of all references identified will be uploaded to EndNote (EndNote 2017, Clarative Analytics). The search results from the different electronic databases will be combined in a single EndNote library to facilitate collaboration among the review team members (YB, AHB) during the study selection process. No training in relation to the literature search is planned at this stage as both reviewers are already familiar with Endnote and the content area of the review.

Selection process:

Titles and abstracts of studies generated from the initial search will be screened independently by two members of the review team (YB, AHB). The full-text will be retrieved and independently assessed by both authors for eligibility based on the inclusion/exclusion criteria mentioned previously. The full-text of remaining articles will be independently examined by the same reviewers to reach a final list of articles. Disagreements at either screening stage will be resolved through discussion with a third reviewer (CA). The reasons for study exclusion will be documented. For duplicated references, and data that has been published more than once, the most complete study will be chosen for inclusion in the library while the others will be removed. A PRISMA flow diagram of the study selection procedure will be prepared to provide an overview of the decisions that are made in the data collection process [25].

Data collection process:

Consistent with Nampiaparampil [19], prevalence in this review is defined as the estimate of the total amount of persistent PTH at a time point or period interval in a certain sample of adult civilian TBI. Based on this definition, data will be extracted from the included studies using a standardized data extraction spreadsheet. The data extraction spreadsheet will be pre-tested by two members of the review team (YB, RB) on ten randomly selected publications and modified accordingly. Using the same data extraction spreadsheet, the reviewers (YB, RB) will independently extract and manage the data for each of the included studies. Disagreements will be resolved by discussion between the two authors; if no agreement can be reached, consensus will be sought through discussions with a third author (CA). Authors of the included studies will be contacted in case

clarifications or further data are needed (up to three attempts by email over a period of eight weeks). Data will be extracted on the following:

1. Publication details: title, journal, author, year, city and country, in which the study was conducted, type of publication, and source of funding.
2. Design: type of study (cohort, case-control, etc), method of data collection, response rate, recruitment and sampling methods, and eligibility (inclusion and exclusion criteria).
3. Study participant details: number of persons interviewed or surveyed, population characteristics including setting, age, sex, and premorbid characteristics including pre-existing primary headache disorders. Information about TBI severity will be rigorously extracted with respect to the clinical features and classification methods widely used (see Table 1) [37].
4. Data for outcome measures: prevalence of persistent PTH after TBI in general or according to TBI severity, characteristics of the headache (migraine, tension-type headache, cluster headache, or one of the other primary headaches), time period referenced in assessment of the condition, and factors (mainly comorbidities) found to be related significantly to the development of headaches after TBI.
5. Missing data: Considering there are no standardized time points for the assessment of persistent PTH after TBI, prospective multiple assessments can be expected in some studies. This may potentially result in missing data. Reasons for missing data will be recorded from the original articles. If the original articles did not include this detail, we will try our best to obtain requisite information by contacting the corresponding author of the referenced articles for the missing data. The potential

impact of the effect of missing data on the final findings of the review will be addressed in the discussion.

Table 1. TBI severity classification inspired by the Mayo Clinic classification system

Classification	Criteria
Moderate/severe TBI (definite)	-Death
	-Loss of consciousness > 30 minutes
	-Antegrade amnesia > 24 hours
	-Glasgow Coma scale score < 13 in the initial 24 hours
	-Intracerebral, subdural, epidural, or subarachnoid hemorrhages; cerebral or hemorrhagic contusion, penetrating TBI, or brainstem injury
Mild TBI (probable)	- Loss of consciousness – momentarily to < 30 minutes
	-Post-traumatic anterograde amnesia – momentarily to < 2 – 4 hours
	-Depressed basilar or linear skull fracture (dura intact)
Symptomatic (possible mild TBI)	- A history of head trauma is reported by the patient - One or more of the following symptoms are reported: blurred vision, confusion (changes in mental status), dizziness, headache, nausea or focal neurological symptoms

Risk of bias

Risk of bias of included studies will be independently evaluated by two members of the review team (YB, RB) using the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al* (see Appendix 3) [38]. Individual items will be rated as "Yes" if the criterion is fulfilled. Otherwise, if the design of the study is not applicable or if there is insufficient information in the study to permit a judgment for a particular criterion, it will be noted as "No". In the event that a full consensus cannot be reached between the two reviewers, the

opinion of a third reviewer (CA) will be obtained, and the proceeding majority consensus will be taken.

Data analysis and synthesis

We will perform descriptive analysis and report the characteristics of included studies in summary tables and narrative text. Limitations of the studies will be discussed in detail.

As we anticipate variability between included studies (mainly in the time points considered for the screening of headache disorders), the pooled prevalence estimate of persistent PTH will be computed applying random-effects meta-analysis models (rather than assuming a single true value in a fixed-effect approach) using the MetaXL (www.epigear.com) add-in for Microsoft Excel. A pooled prevalence figure will be calculated with 95% CI. Meta-analysis will be limited to studies with at least 100 participants allowing an acceptable margin of error of ≤10% in the prevalence estimates of headache [39]. Heterogeneity within included studies will be assessed through the utilization of the I^2 statistics, with I^2 values of 25%, 50% and 75% being considered low, moderate and high respectively [40]. Depending on data availability, we plan to account for heterogeneity conducting meta-regressions and subgroup analysis considering the following covariates: time elapsed since TBI and TBI severity. Sensitivity analysis will be carried out considering only studies of the highest methodological quality using the Risk of Bias Tool for Prevalence Studies checklist.

Ethics and dissemination

As this will be a review of published data, patients will not be primarily involved in any stage of the study. Data will be collected from published studies available in the previously mentioned electronic databases. On completion of the analysis, we will prepare a manuscript for publication in a peer-reviewed journal and present the results at conferences.

Patient and Public Involvement

No patient involved.

DISCUSSION

To date, the only systematic review providing information about chronic headache following TBI was published in 2008 [19], and no new review is underway based on PROSPERO. Considering the recent changes in TBI diagnosis and epidemiology, there is a strong rational for updating current evidence on persistent PTH prevalence in adult civilian TBI.

The systematic review and meta-analysis we plan to carry out builds on the methodology applied previously [19], but reducing its limitations. Indeed, the previous review on the topic was performed solely through a MEDLINE search [41-42]. The exclusion of other databases in which many journals are not indexed and the restriction of publications in other languages than English may have limited the findings and contributed to the confusion about the influence of TBI severity of headache prevalence. We believe that the use of additional sources of data aside from Medline will provide rigorous and updated estimates on prevalence of chronic headache in TBI. Moreover, differently from Nampiaparampil (2008), we will limit the review to studies about non-military TBI as the

highest combined incidence of TBI-related emergency department visits, hospitalizations, and deaths occurs in civilians. In terms of research, pooling of such data is necessary to monitor trends in comorbidities among individuals who sustained TBI and to contribute to the design of further outcome studies. Another point that will differ from Nampiaparampil's work is the use of ICHD-3 operative criteria for the definition of persistent PTH. As shown in a recent systematic review of posttraumatic headache in children [43], use of a standardized definition helps to make distinction between the prevalence of non-specific persistent PTH and prevalence of persistent PTH as defined by recognized organizations. Last but not the least, we will include, in a separate section of the review, data about the prevalence of persistent PTH after TBI based on TBI severity.

To our knowledge, this is the first systematic review and meta-analysis protocol addressing the important need to update the prevalence estimates of persistent PTH in adult civilian TBI. Some limitations can be anticipated due to missing data and heterogeneity of the studies. Aside from variations in persistent PTH definition, another aspect that could contribute to study heterogeneity is the fact that depressed skull fractures with intact dura have only been recently recognized as mild TBI [37]. Thus, studies performed before 2017 may not have included these cases in their estimates of persistent PTH after mild TBI. Despite these limitations, we anticipated our data will still be important to inform the planning, implementation and evaluation of chronic pain prevention intervention in trauma care, and potentially, contribute to reduce its morbidity after TBI.

Contributions: CA and GL conceived the study. YB and AHB performed the preliminary search. YB reviewed the search strategy with the help of Health Sciences librarian. YB and RB will oversee data extraction and analysis. CA and AHB participated in the conception

of the protocol and produced the first draft of the manuscript. The definitive protocol was reviewed and approved by all authors (CA, YB, RB, GL, AHB).

Funding: This project is funded by a start up fund provided by the research center of the Hôpital du Sacré-Coeur de Montréal to CA. The Hôpital du Sacré-Coeur de Montréal had no role in the development of the protocol. GL holds a Canada Research Chair on Pain, Sleep, and Traumatic Injuries.

Competing interests: The authors declare that they have no conflicts of interest in relation to this work.

Patient consent for publication: Not applicable.

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APPENDICES

UPDATE on the PREVALENCE of PERSISTENT POSTTRAUMATIC HEADACHE in ADULT CIVILIAN TRAUMATIC BRAIN INJURY: PROTOCOL for a SYSTEMATIC REVIEW and METE-ANALYSIS

[Caroline Arbour PhD[1-2], Yasmine Bouferguène BSc[1,3], Roxanne Beauregard RN[1-2], Gilles Lavigne PhD[1,3], Alberto Herrero Babiloni MSc[1,3]]

*Corresponding author: caroline.arbour@umontreal.ca

1. Hôpital du Sacré-Coeur de Montréal Research Center, Montreal, Quebec, Canada;
2. Faculty of Nursing, Université de Montréal, Montréal, Québec, Canada;
3. Faculty of Dental Medicine, Université de Montréal, Montreal, Québec, Canada.

APPENDIX 1

PRISMA-P checklist [1]

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	UPDATE on the PREVALENCE of PERSISTENT POSTTRAUMATIC HEADACHE in ADULT CIVILIAN TRAUMATIC BRAIN INJURY: PROTOCOL for a SYSTEMATIC REVIEW and METE-ANALYSIS
Update	1b	Updating (with methodological modifications) Nampiaparampil, 2008. [2]
Registration	2	PROSPERO (CRD42018094138)
Authors:		
Contact	3a	Caroline Arbour PhD[1-2] (CA*), Yasmine Bouferguène BSc[1,3], Roxanne Beauregard RN[1-2], Gilles Lavigne PhD[1,3], Alberto Herrero Babiloni MSc[1,3] * caroline.arbour@umontreal.ca 1) Hôpital du Sacré-Coeur de Montréal Research Center, Montreal, Canada; 2) Faculty of Nursing, Université de Montréal, Montréal, Canada; 3) Faculty of Dental Medicine, Université de Montréal, Montreal, Canada.
Contributions	3b	CA and GL conceived the study. YB and AHB performed the preliminary search. YB reviewed the search strategy. YB and RB will oversee data extraction and analysis. CA and AHB produced the first draft of the manuscript. The definitive protocol was reviewed and approved by all authors. *[page 17 line 1]*
Amendments	4	Significant changes to the protocol will be updated in PROSPERO and reported in the final paper.
Support:		
Sources	5a	This project is funded by a start up fund provided by the research center of the Hôpital du Sacré-Coeur de Montréal to CA. The Hôpital du Sacré-Coeur de Montréal had no role in the development of the protocol. GL holds a Canada Research Chair on Pain, Sleep, and Traumatic Injuries. *[page 17 line 6]*
Sponsor	5b	None declared. *[page 17 line 12]*
INTRODUCTION		
Rationale	6	Persistent posttraumatic headache (PTH) is a common consequence of traumatic brain injury. The only review providing information about headache prevalence after brain trauma was published in 2008 and was strictly derived from Medline database and combined data from civilian and military populations. Due to recent changes in brain trauma diagnosis and civil epidemiology, the aim of the current study is to carry out a systematic review and meta-analysis to derive updated prevalence estimates of persistent PTH in adult civilian traumatic brain injury. *[page 5-6]*
Objectives	7	To derive updated estimates on global and severity-specific prevalence of persistent PTH in adult civilian traumatic brain injury. *[page 6 line 19]*
METHODS		
Eligibility criteria	8	**Study designs:** Observational studies (case-control and Cohort studies) reporting prevalence of chronic headache (or from which prevalence can be derived); Published from March 2008 to this day. RCT, case control, case series, case report as well as duplicate reports will be excluded. **Population**: Representative sample of adult civilian traumatic brain injury patients (16 years and older); No geographic limitations; Patient identification by physician diagnosis, self-reported status, populational trauma registries, other

		medical/administrative registers. Prevalence data reported based on brain trauma severity (mild, moderate/severe) will be treated separately. **Outcomes**: The primary outcome will be the global prevalence of persistent PTH following traumatic brain injury. The secondary outcome will be a better understanding of the associations between chronic headache and brain trauma severity. *[page 9]*
Information sources	9	Searching in the electronic databases (Medline, Embase, Cochrane, Google Scholar, and Directory of Open Access Journals), manual references' listing of included studies and authors' personal bibliography on Web of Science. *[page 9 line 22]*
Search strategy	10	See Appendix 2
Study records:		
Data management	11a	Studies retrieved will be grouped and duplicates removed with support of a reference management software package. Studies eligibility will be assessed independently by two authors. Discrepancies between authors will be resolved by discussion and consultation of a third author if needed. The study selection process will be reported in a PRISMA flow diagram. *[page 10 line 17]*
Selection process	11b	Studies will be selected independently by both authors based on pre-established eligibility criteria. Discrepancies between authors will be resolved by discussion and consultation of a third author if needed. Reasons for exclusion will be documented. *[page 11 line 3]*
Data collection process	11c	Data extraction will be performed independently by two authors using a pre-tested spreadsheet. Disagreements will be resolved by discussion between the two authors; if no agreement can be reached, consensus will be sought through discussions with a third author Up to three attempts by mail will be done if additional data or clarification will be required from the included studies. *[page 11 line 15]*
Data items	12	Data extraction will include: studies' title, journal, first author's name and affiliation(s), year and country of publication, design, response rate and sample size, sampling method, participants' sociodemographic and clinical characteristics, TBI severity, time elapsed since TBI, prevalence of chronic headache, characteristics of the headache, psychiatric comorbidities, risk factors, missing data, reasons for missing data. *[page 12 line 4]*
Outcomes and prioritization	13	Every headache lasting for more than 3 months after occurrence of brain trauma independent of its characteristics. [3] *[page 9 line 7]*
Risk of bias in individual studies	14	Risk of bias will be independently evaluated by two reviewers using the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al.* Disagreements will be resolved by discussion between the two authors and a third author will be involved if needed. Hoy *et al.* checklist will be used as a reference when conducting sensitivity analysis restricted to high quality studies. *[page 13 line 11]*
Data synthesis	15a	We will estimate persistent PTH global prevalence in adult civilian traumatic injury. Whenever possible, persistent PTH prevalence estimates in mild cases and moderate/severe cases will be computed. The analysis will only include studies with sample sizes greater than 100 participants. *[page 14]*
	15b	Persistent PTH prevalence pooled estimates for all pre-specified outcomes will be computed applying random effect meta-analysis models. Heterogeneity within included studies will be assessed using the I 2 statistic and visual inspection of forest plots. *[page 14]*
	15c	Sub-group sensitivity analysis will be performed (if possible) and considering studies of highest methodological quality according to time elapsed since injury and head trauma severity (mild versus moderate/severe). *[page 14]*
	15d	Descriptive analysis and report the characteristics of included studies. *[page 14]*

Meta-bias(es)	16	Considering confirmation of traumatic brain injury diagnosis can vary from one study to another, therefore introducing a selection bias, only studies using a clearly defined operational definition for the diagnosis of TBI will be considered for inclusion. *[page 7 line 19]*
Confidence in cumulative evidence	17	NA

APPENDIX 2

Medline search strategy (from 2008 to Present)

Traumatic brain injury (population)

1. Brain Injuries [MeSH]
2. Craniocerebral Trauma [tiab]
3. Head Injuries, Closed [tiab]
4. Skull Fractures [tiab]
5. mTBI* [tiab]
6. tbi* [tiab]
7. concuss* [tiab]
8. ((head* or cerebr* or crani* or skull* or intracran*) adj2 (injur* or trauma* or damag* or wound* or swell* or oedema* or edema* or fracture* or contusion* or pressur*)) [tiab]
9. ((brain* or cerebr* or intracerebr* or crani* or intracran* or head* or subdural* or epidural* or extradural*) adj (haematoma* or hematoma* or hemorrhag* or haemorrhag* or bleed*)) [tiab]
10. 1 OR/9

Chronic headache disorders (condition)

11. Headache [MeSH]
12. Head pain [tiab]
13. Hemicrania [tiab]
14. migraine* [tiab]
15. cephalia* [tiab]
16. cephalea* [tiab]
17. cephalgia* [tiab]
18. cephalagia* [tiab]
19. 11 OR/18
20. 10 AND 19

Prevalence

21. prevalen* [tiab]
22. Inciden* [tiab]
23. Percent* [tiab]
24. epidemiol* [tiab]
25. frequenc* [tiab]
26. occurrenc* [tiab]
27. morbidit* [tiab]
28. rate* [tiab]
29. Probabilit* [tiab]
30. Epidemiological studies [MeSH]
31. Population* [tiab]
32. Severit* [tiab]
33. Progress* [tiab]
34. Risk [tiab]
35. 21 OR/34

All combined

36. 20 AND 35

APPENDIX 3

Quality assessment checklist for prevalence studies adapted from Hoy et al. [4]

Risk of bias items	Risk of bias levels	Points scored
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes (LOW RISK):** The study's target population was a close representation of the national population.	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	**Yes (LOW RISK):** The sampling frame was a true or close representation of the target population.	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes (LOW RISK):** The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders.	0
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes (LOW RISK):** All data were collected directly from the subjects.	0
	No (HIGH RISK): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	**Yes (LOW RISK):** An acceptable case definition was used.	0
	No (HIGH RISK): An acceptable case definition was NOT used.	1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes (LOW RISK):** The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes (LOW RISK):** The same mode of data collection was used for all subjects.	0
	No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	1
9. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	**Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

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4. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol.* 2012; 65: 934-9.