Epidemiology of recurrent traumatic brain injury in the general population

A systematic review

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ABSTRACT

Objective: To comprehensively assess recurrent traumatic brain injury (rTBI) risk and risk factors in the general population.

Methods: We systematically searched MEDLINE, EMBASE, and the references of included studies until January 16, 2017, for general population observational studies reporting rTBI risk or risk factors. Estimates were not meta-analyzed due to significant methodologic heterogeneity between studies, which was evaluated using meta-regression.

Results: Twenty-two studies reported recurrence risk and 11 reported on 27 potential risk factors. rTBI risk was heterogeneous and varied from 0.43% (95% confidence interval [CI] 0.19%–0.67%) to 41.92% (95% CI 34.43%–49.40%), with varying follow-up periods (3 days–55 years). Median time to recurrence ranged from 0.5 to 3.8 years. In studies where cases were ascertained from multiple points of care, at least 5.50% (95% CI 4.80%–6.30%) of patients experienced a recurrence after a 1-year follow-up. Studies that used administrative data/self-report surveys to ascertain cases tended to report higher risk. Risk factors measured at time of index traumatic brain injury (TBI) that were significantly associated with rTBI in more than one study were male sex, prior TBI before index case, moderate or severe TBI, and alcohol intoxication. Risk factors reported in a single study that were significantly associated with rTBI were epilepsy, not seeking medical care, and multiple factors indicative of low socioeconomic status.

Conclusions: rTBI is an important contributor to the general population TBI burden. Certain risk factors can help identify individuals at higher risk of these repeated injuries. However, higher quality research that improves on rTBI surveillance methodology is needed. ***Neurology*®** **2017;89:2198–2209**

GLOSSARY

CI = confidence interval; **ICD** = International Classification of Diseases; **MORE** = Methodological Evaluation of Observational Research; **RF** = risk factor; **rTBI** = recurrent traumatic brain injury; **TBI** = traumatic brain injury.

Traumatic brain injury (TBI) causes considerable long-term disability and mortality, creating an important economic burden for society.[1–3] Epidemiologic investigations have demonstrated that TBI is a heterogeneous public health problem because of varying injury determinants and differing ways to define TBI since there is no gold standard to diagnose the condition.[4] Another level of heterogeneity arises from the injury burden being composed of both incident and recurrent TBI (rTBI) cases, which are distinct entities.[5] However, the epidemiologic characteristics of rTBI in the general population have not been comprehensively investigated, as most studies on the topic have focused on athletes.[6–9]

Patients with rTBI are known to have poorer outcomes even when a repeated injury is mild.[10–12] In the acute phase, individuals with rTBI have greater disability for a longer duration when compared to individuals with a single TBI.[9] This disability is mainly manifested as more severe postconcussive symptoms and psychiatric comorbidities.[9,13] In the long term, there is growing evidence that repetitive head trauma leads to an increased risk of suicide and chronic traumatic encephalopathy.[10,14–16]

Supplemental data at Neurology.org

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As such, preventing rTBI is important for controlling the overall general population TBI burden.[17] To achieve the latter, a comprehensive assessment of its epidemiologic characteristics in the general population is required. One aim of this systematic review was to estimate rTBI risk in the general population across all disease severities and age groups. A second aim was to identify rTBI risk factors (RFs) and assess their strength of association with rTBI. We also planned to assess factors that explain heterogeneity in estimates reported across studies.

METHODS

This systematic review was conducted following a prespecified protocol, which is available on PROSPERO (CRD42017055597), and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18]

Search strategy and selection criteria. We performed a systematic search of MEDLINE and EMBASE between database inception (1946 and 1947, respectively) and October 15, 2016 (updated on January 16, 2017) for studies that reported rTBI risk or RFs. In consultation with a librarian experienced in conducting systematic review searches, we developed a broad search strategy consisting of 2 concepts using keywords and MeSH/EMTREE indexing terms (e-Methods at Neurology.org). Briefly, concept 1 was for TBI (keywords: "brain injur*," "concussion," "head injur*") and concept 2 was for recurrence (keywords: "recur*," "recidivis*," "repeat*," "repetit*," "multiple"). The "and" Boolean operator was used to combine these 2 concepts. We restricted our search to studies published in English or French and excluded conference abstracts. O.L. reviewed all titles/abstracts and full text and 1 of 3 other authors independently reviewed a subset of the same studies (E.Y.L., G.A.P., J.R.-L.). All selected titles/abstracts went on to full-text review. Adjudication was used to resolve any disagreement between reviewers during full-text review.

The inclusion criteria for this systematic review were studies that reported on the proportion of rTBI cases (individuals experiencing a repeated TBI after an initial injury) among a cohort of index TBI cases with a defined follow-up period or studies that reported on RFs and their association measure for a cohort of index TBI cases. We assessed all baseline characteristics of the index TBI cohort that were potential RFs. Since our objective was to estimate rTBI risk, we excluded studies that reported rTBI prevalence. As this review focused on rTBI in the general population, we excluded studies that reported estimates on specific population subgroups (e.g., athletes, veterans). We also excluded case reports and reviews. The bibliographies of all included studies were hand searched to identify additional studies that met the review's inclusion criteria. If 2 publications used the same study population, we included the study with the larger sample size.

Two reviewers (O.L. reviewed all studies) independently completed data extraction and quality assessment using a pilot-tested data extraction and quality assessment form. The following variables were extracted: total number of recurrent events, size of index TBI cohort, follow-up period (total time followed since index TBI or average follow-up period for studies recruiting index cases over many years), crude and adjusted association measures of all RFs (or individual counts of rTBI cases/noncases that are exposed/unexposed to the RFs), covariates used to adjust RF association measures, age groups included in the study, mean age, sex proportions, TBI severity distribution, data source (administrative health data/survey vs registry/medical charts), inclusion criteria for patients with TBI, and TBI/rTBI case definitions. Authors of included studies were contacted if data on the counts of rTBI or index TBI cases were missing.

Quality assessment was completed using the Methodological Evaluation of Observational Research (MORE), which evaluates the quality of incidence and RF studies based on internal and external validity domains.[19] With this quality assessment tool, each domain is scored as "OK," "minor flaw," "major flaw," or "poor reporting." This quality assessment checklist has been used in systematic reviews that adapt the tool to their research question.[20,21] The quality assessment was conducted while assessing the studies' ability to validly estimate rTBI risk and the association between RFs and rTBI. For the quality assessment of RFs, only the internal validity was assessed since the external validity criteria were identical to those evaluated for the rTBI risk quality assessment. The quality of studies was summarized by the proportion of items that were scored as OK, minor flaw, major flaw, or poorly reported.

Statistical analysis. We reported the rTBI risk (incidence of repeat TBI among a cohort of patients with an initial TBI over a defined follow-up period) and the association measures for rTBI RFs. Crude estimates were reported as risk ratios or odds ratios and adjusted estimates as hazard ratios or odds ratios (depending on how studies reported them). It was decided a priori that if study methods and characteristics were too heterogeneous, a meta-analysis would not be completed.

We planned to use meta-regression analysis for both rTBI risk and association measures of the RFs if at least 10 studies reported on a given RF. This constraint was to ensure that the meta-regression analysis was sufficiently powered.[22] The following factors were assessed as heterogeneity factors: age groups included (children vs adults or entire population), follow-up period (half of study period for studies recruiting TBI cases longitudinally), study quality (number of OK criteria), data source to ascertain rTBI cases (administrative/survey data vs registry/clinical assessment), and comprehensiveness of cases ascertained (at one vs multiple points of care: emergency department, hospitalization, or outpatient). Data sources were categorized as such because administrative data and self-report surveys have been shown to be less accurate than clinical assessment or registries to ascertain TBI cases.[23] The amount of between-study heterogeneity explained by these covariates was estimated with the R^2 statistic.[22]

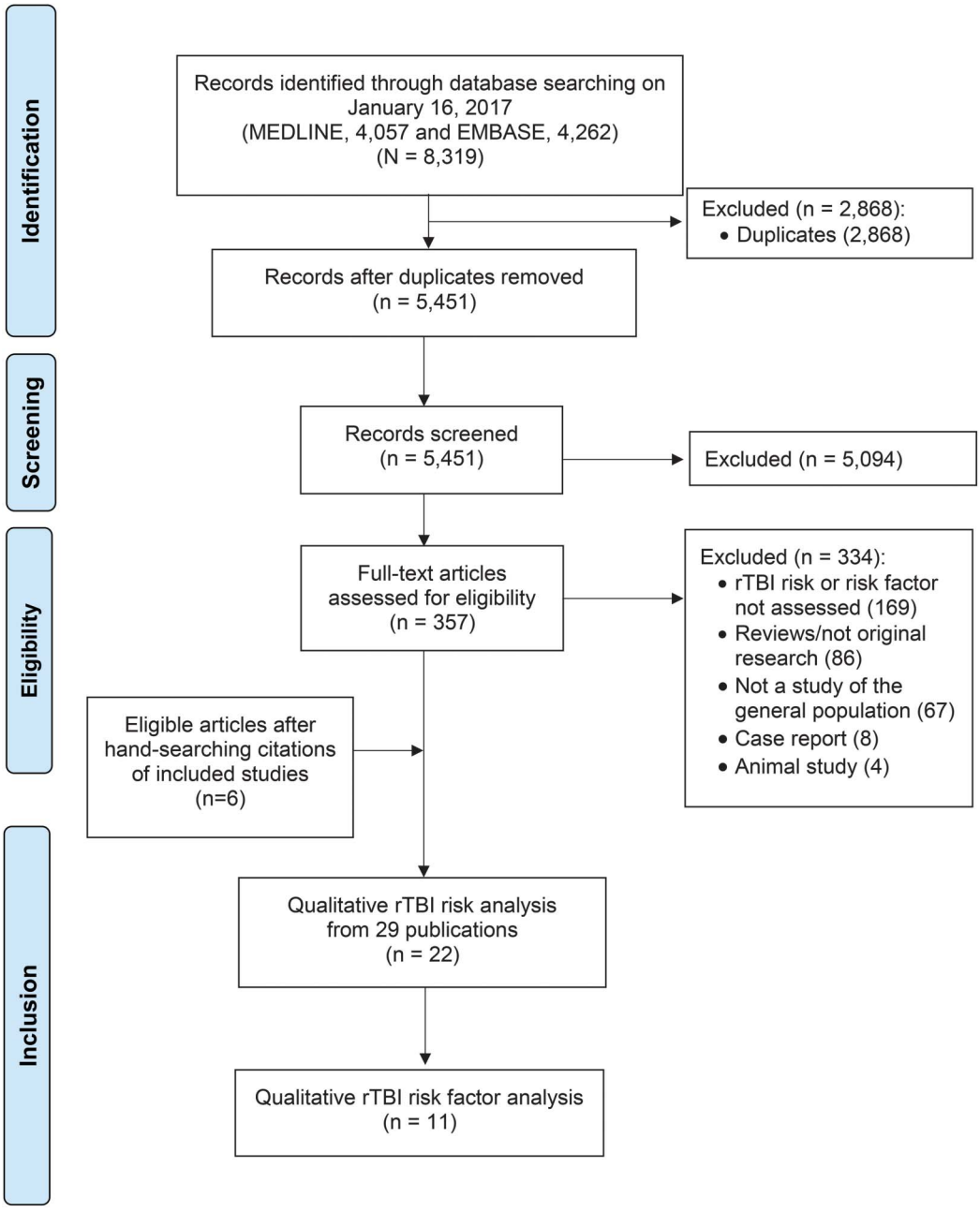
All analyses were conducted in STATA 14 and forest plots were produced using R (Metafor package).

RESULTS

Our search identified 8,319 potentially relevant citations and 357 publications were retained for full-text review. A total of 29 publications met the inclusion criteria for rTBI risk assessment. Seven of these publications were studies completed on the same population as another publication that met the inclusion criteria but that had a smaller sample size. As such, 22 studies[24–45] were retained for rTBI risk analysis and 11 studies[26,30–32,35–37,40,43,46,47] were retained for the analysis of rTBI RFs (figure 1). A meta-analysis was not completed because of significant methodologic heterogeneity between included studies.

Recurrent TBI risk. The included studies contained 406,982 TBI cases, 38,981 of which went on to have

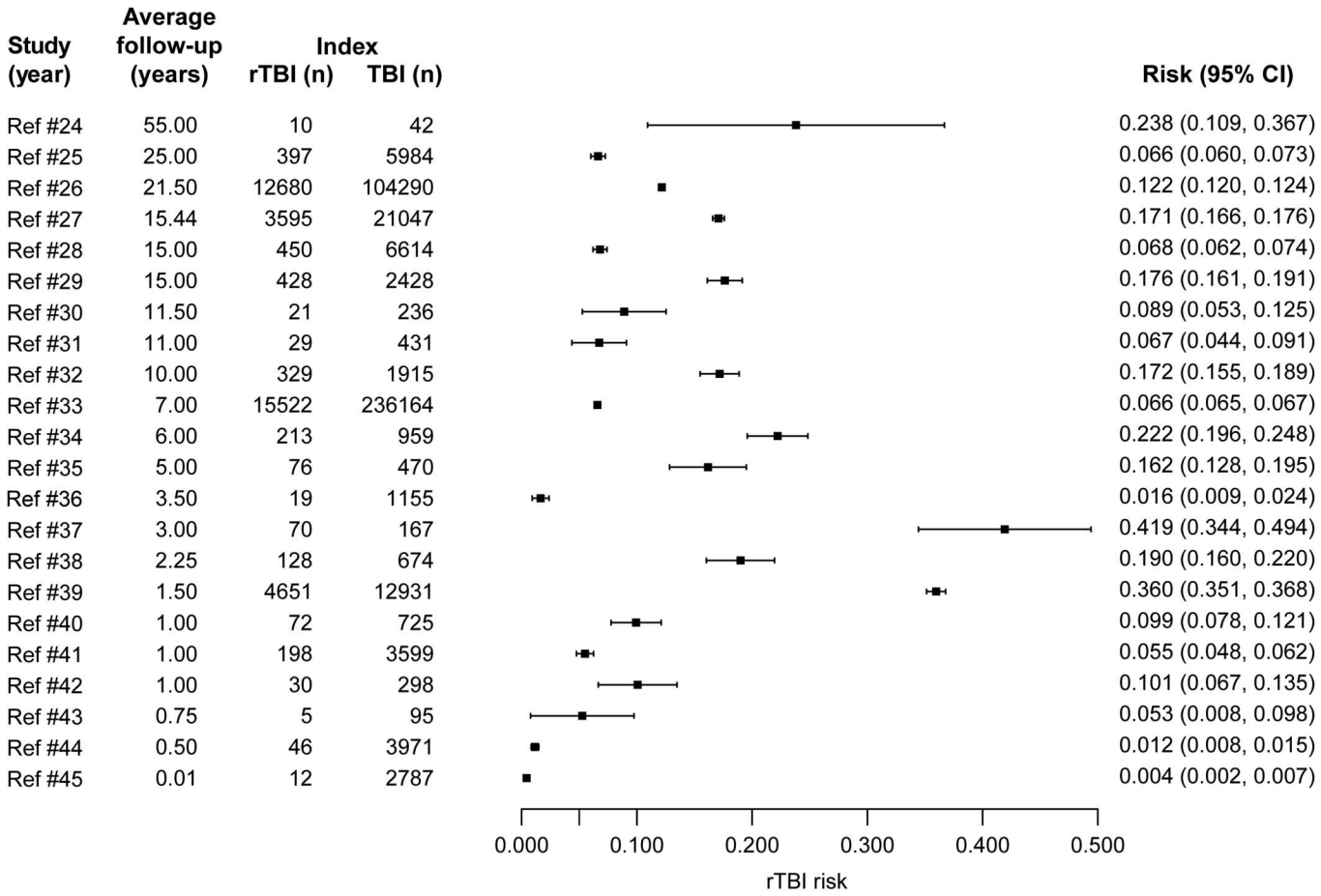
Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of included and excluded studies



Flow diagram of search results for the systematic review. The detailed search strategy is available in the e-Methods. The e-Results provide a list of all included studies for the recurrent traumatic brain injury (rTBI) risk and risk factor analysis. The e-Results also provide a list of the 7 publications that were excluded from the analysis because they had the same population as 1 of the 22 included studies.

an rTBI. The risk of rTBI varied from 0.43% (95% confidence interval [CI] 0.19%–0.67%) to 41.92% (95% CI 34.43%–49.40%) (figure 2). After at least 1-year follow-up, 5.50% (95% CI 4.80%–6.30%) of individuals had a recurrent event when rTBI cases were ascertained at multiple points of care. Follow-up time ranged from 3 days to 55 years. Study methods and characteristics were heterogeneous (table 1 and further details in table e-1) and only 50% of the studies had a primary aim related to rTBI. Cases were mainly ascertained from administrative data (41%),[25–30,34,39,44] but some studies used surveys (18.1%),[24,32,35,37] medical charts (31.8%),[31,36,38,40,42,43,45] and trauma registries (9%).[33,41] Index and rTBI case definitions varied significantly across studies. In 4 studies,[25,31,33,40] all age groups were included, whereas all other studies limited the population to specific age groups. One study restricted TBI and rTBI cases to sports-related injuries

Figure 2 Recurrent traumatic brain injury (rTBI) risk estimates



rTBI risks reported in the 22 included studies. The forest plot is ordered from studies with the longest to shortest average follow-up period. CI = confidence interval; TBI = traumatic brain injury.

in the general population.[34] Five studies reported the risk of rTBI at different follow-up time after index TBI.[28,33,34,40,41] Many recurrent events occurred early after the index case; the median time to rTBI was under 6 months in 1-year-long studies that used a comprehensive rTBI case ascertainment definition.[40,41] In contrast, the median time to recurrence was 3.8 years for a study with a 15-year follow-up period that only included rTBI cases hospitalized for less than 2 days (figure e-1).[28]

MORE-defined study quality revealed that internal validity had more flaws and poor reporting than external validity. Regarding internal validity criteria, all studies poorly reported on at least 1 item and 21 studies had at least 1 minor flaw. In contrast, 6 studies did not have any flaws or poor reporting for external validity criteria (figure 3 and table e-2). For internal validity, the most common major flaw, minor flaw, and poorly reported criteria were not using a validated method to measure rTBI occurrence, using a data source intended for health care purposes to measure incidence, and not reporting the precision of rTBI estimates, respectively. For external validity, the most common major flaw, minor flaw, and poorly reported criteria were using a nongeneral population sampling frame, not adjusting for sampling bias, and not providing a flow diagram of participants included/excluded from the study, respectively.

We explained the heterogeneity of estimates between studies through meta-regression analysis. The data source used to ascertain cases explained 25%–29% of the between-study variance, with studies using administrative data or surveys reporting higher risks. Studies ascertaining cases at more than 1 point of care (emergency department, hospital, clinic) tended to report higher risks, but this only explained 9% of the between-study variance. Other study-level factors, including study follow-up time, did not explain significant heterogeneity (table e-3).

Risk factors for rTBI. Eleven studies reported on 27 different potential RFs. The RFs at the time of initial injury that were significantly associated with a higher risk of rTBI in more than a single study were male sex (3/8 studies), prior TBI (3/5 studies), moderate/severe TBI (2/4 studies), and alcohol intoxication

Table 1 Description of 22 included studies that assess recurrent traumatic brain injury (rTBI) risk/incidence

Authors	Country	Study period	Study design (rTBI as primary aim)	Follow-up, y	Inclusion criteria for index TBI	Data source	rTBI definition	Age group, y	Time to rTBI	rTBI/index TBI, n	rTBI risk
Chen et al.[24]	USA	1993–1996	Case-control (no)	30–80	Self-report of any TBI from controls in New England matched to ALS cases on age, sex, and area code from 1993 to 1996	Survey	Patient self-report of TBI requiring medical care during lifetime	30–80	NA	10/42	0.24
Annegers et al.[25]	USA	1935–1984	Cohort (no)	0–50	Inpatient, ED, or outpatient visits for TBI	Administrative: Medical record linkage system of the Rochester Epidemiology Project	Clinical definition	All	NA	397/5,984	0.07
Sariaslan et al.[26]	Sweden	1973–2013	Cohort (no)	3–40	Inpatient, ED, and outpatient visits for TBI of individuals born from 1973 to 1985 occurring before age 25 y	Administrative: National Patient Register	ICD 8/9/10 TBI code 15 days after index TBI	0–25	NA	12,680/10,4290	0.12
Richard et al.[27]	Canada	1987–2008	Cohort (no)	0–22	Inpatient, ED, and outpatient visits for TBI	Administrative: Régie de l'Assurance Maladie du Québec medical services database	ICD-9 TBI code 90 days after index	0–17	NA	3,595/21,047	0.17[a]
Teasdale et al.[28]	Denmark	1979–2009	Cohort (yes)	0–30	Inpatient visits for men with concussion for less than 2 days and who were assessed by the Draft Board after age 18 between 2006 and 2010	Administrative: Ministry of Health database (Landspatientregister)	ICD 9/10 TBI code 3 days after index TBI	0–35	Median: 3.8 y	450/6,614	0.068
McMillan et al.[29]	UK	1995–2011	Case-control (no)	15	Inpatient visits in Glasgow with mild head injury (GCS ≥ 13)	Administrative: Information Services Division of the National Health Survey of Scotland	ICD 9/10 code	>14	NA	428/2,428	0.176
Winqvist et al.[30]	Finland	1978–2000	Cohort (yes)	0–23	Inpatient or ED visits lasting >24 h for TBI	Administrative: Finnish Hospital discharge register	ICD 8/9/10 codes for TBI	12–34	NA	21/236	0.09
Vaaramo et al.[31]	Finland	1999–2009	Cohort (yes)	11	ED visits for TBI at a single hospital	Discharge register and ED checklist (index TBI)/ administrative data of hospitalizations and hospital charts (rTBI)	ICD-10 TBI code from National Hospital Discharge Register and hospital charts from Oulu Hospital	All	NA	29/431	0.067
Bijur et al.[32]	UK	1970–1980	Case-control (yes)	10	Parent self-report of any TBI for community children in the UK	National survey	Parent self-report	0–10	NA	329/1,915	0.17
Wilson and Selassie[33]	USA	1998–2011	Case-control (yes)	0–14	Inpatient/ED visits for TBI	South Carolina TBI Surveillance System	ICD-9 TBI code 1 week after index	All	11.6% at 1 mo and 23.1% at 6 mo[b]	15,522/236,164	0.066
Harris et al.[34]	Canada	1997–2008	Cohort (yes)	0–12	ED visits for sports injuries within 5 hospitals' catchment areas of Edmonton's metropolitan area	Administrative: Ambulatory Care Classification System	ICD 9/10 TBI code 14 days after index TBI	1–35	Median: 613 days	213/959	0.222
Edna and Cappelen[35]	Norway	1979–1984	Cohort (no)	5	Inpatient visits at 4 surgical departments	Survey	Patient self-report	15–64	NA	76/470	0.16
Partington[36]	UK	1952–1958	Cohort (no)	0–7	Inpatient visits for head injury at a single children's hospital 1952–1958	Medical chart	Clinical diagnosis	0–13	NA	19/1,155	0.016
Liu and Li[37]	China	2004–2005	Cohort (yes)	0–6	Community sample of 6-y-old schoolchildren in Jintan	Parent self-report survey	Parent self-report	0–6	NA	70/167	0.42

Continued

Table 1 Continued

Authors	Country	Study period	Study design (rTBI as primary aim)	Follow-up, y	Inclusion criteria for index TBI	Data source	rTBI definition	Age group, y	Time to rTBI	rTBI/index TBI, n	rTBI risk
Lee and Fine[38]	USA	2004–2008	Cohort (no)	0–4.5	All concussion patients referred to an outpatient practice	Medical chart	Clinical	11–19	NA	128/674	0.19
Chu et al.[39]	Taiwan	2004–2006	Cohort (no)	0–3	All medical claims for TBI in 2004/2005	Administrative: Longitudinal Health Insurance Database of Taiwan	ICD-9 TBI code	>18	NA	4,651/12,931	0.359
Theadom et al.[40]	New Zealand	2010–2011	Cohort/case-control for risk factor analyses (yes)	1	Inpatient/outpatient visits and self-reported cases in Hamilton, New Zealand	Clinical interview, medical chart, self-report, administrative health data	Clinical: diagnostic committee established diagnosis	All	61.1% at 6 mo	72/725	0.1
Swaine et al.[41]	Canada	2000–2003	Cohort (yes)	1	ED visits for TBI to 2 pediatric provincial neurotrauma centers	ED trauma registry (index TBI) and parent self-report (rTBI)	Parent self-report of TBI requiring medical attention	1–18	58.2% 6 mo	198/3,599	0.055
Klonoff[42]	Canada	1968–1970	Case-control (no)	1	Inpatient and ED visits for TBI presenting to a single pediatric hospital	Medical chart and parent self-report survey	Parent self-report	0–16	NA	30/298	0.10
Taubman et al.[43]	USA	2011–2013	Case-control (yes)	0–1.5	Outpatient primary care visits for concussion without intracranial lesions on imaging, occurring within 7 days of TBI and for patients not hospitalized greater than 24 h	Medical chart	Clinical definition	11–19	NA	5/95	0.053
Collins et al.[44]	USA	2010–2011	Cohort (no)	0–1	Inpatient, ED, and outpatient visits at a single pediatric hospital	Administrative: local hospital database	ICD-9 TBI code 90 days after index	0–20	NA	46/3,971	0.01
Ganti et al.[45]	USA	2008–2011	Cohort (yes)	72 h	ED visits at single level 1 trauma centre (GCS ≥13)	Administrative: local hospital database and medical chart for severity and rTBI assessment	Patients presenting back to the same ED with a new TBI	>18	NA	12/2,787	0.004

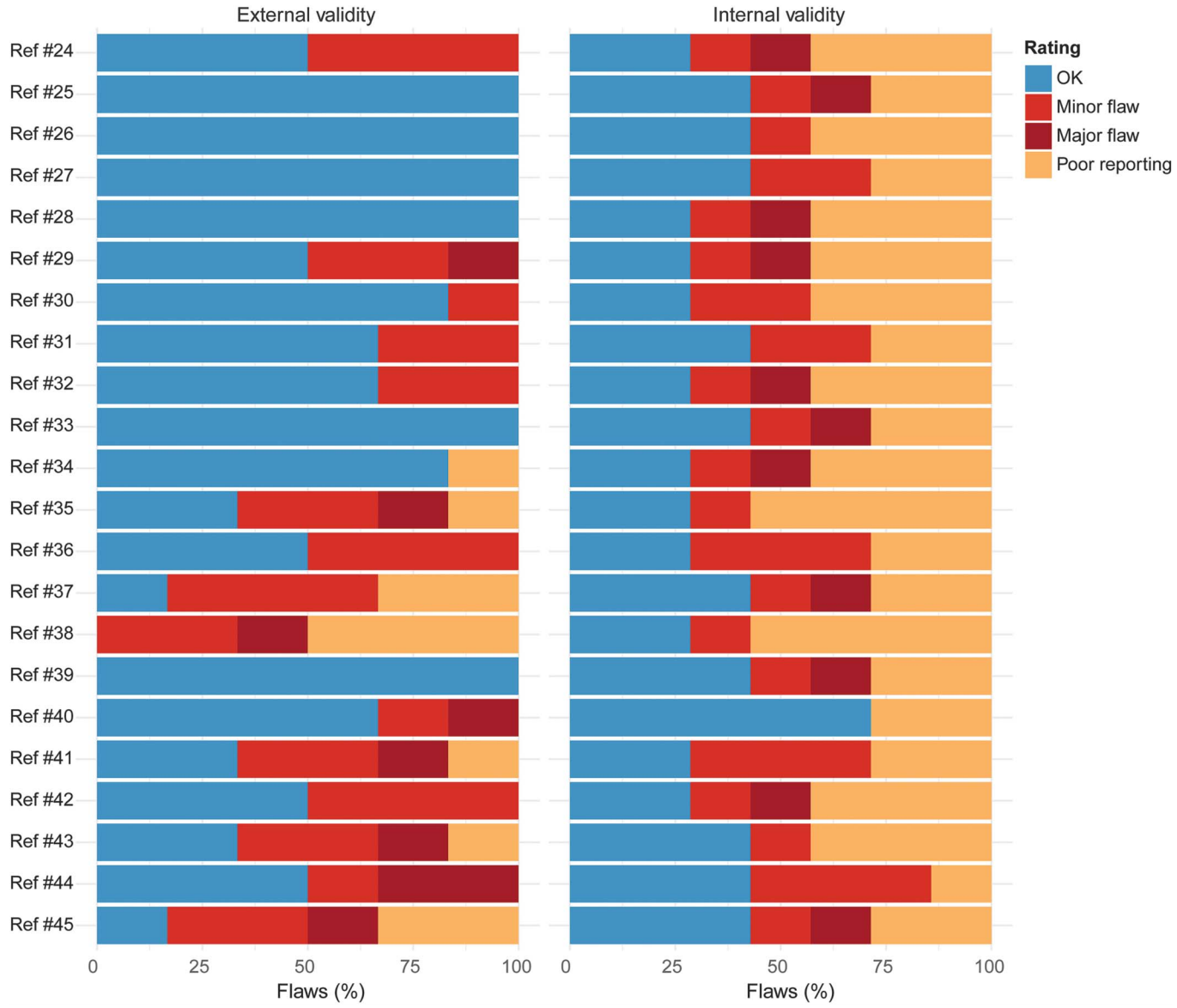
Abbreviations: ALS = amyotrophic lateral sclerosis; ED = emergency department; GCS = Glasgow Coma Scale score; ICD = *International Classification of Diseases*; NA = not available/reported; rTBI = recurrent traumatic brain injury; TBI = traumatic brain injury.

Further details on the characteristics of the studies are available in table e-1.

[a] Authors were contacted to obtain the number of rTBI events and the average follow-up period (15.4 years) of the index TBI cases.

[b] Median time to injury was taken from Saunders et al.,[47] which was conducted on the same population as Wilson and Selassie.[33]

Figure 3 Quality assessment for recurrent traumatic brain injury (rTBI) risk



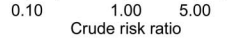
Quality assessment of rTBI risk stratified by internal and external validity. The proportion of each type of response to the 6 external validity criteria and 7 internal validity criteria is shown. Table e-2 provides a summary of the criteria used in the quality assessment.

(3/4 studies). Other studies measuring these RFs generally reported estimates in the same qualitative direction but with less precision. RFs significantly associated with a higher risk of rTBI but where estimates were only reported in a single study were epilepsy disorder[46] and not seeking medical care.[40] Moreover, several factors related to low socioeconomic status (lowest decile income level,[26] uninsured status,[46] low education level,[47] parental criminal history[26]) were associated with higher rTBI risk. In contrast, rural residence and nonwhite race was associated with a decrease in rTBI risk, although these estimates were imprecise. Multiple studies reported other RFs (age, education level of parents, and mechanism of injury) but their association with rTBI occurrence was less conclusive because of conflicting results or imprecise estimates (figure 4). When reported, adjusted RF association measures generally showed the same qualitative association as the crude association measures but were often imprecise. Meta-regression analysis was not completed for RF association measures since no RF was reported by at least 10 studies (lack of power to conduct the analysis).

RF quality assessment was variable across different RFs and the 10 studies that reported on them (figure e-3). Poor reporting and minor flaws were identified across all RFs. Major flaws were common and affected all risk factors, except for not seeking medical care within 24 hours. Many of the same quality assessment criteria were affected across different risk factors

Figure 4 Association measures for all identified risk factors

Risk factor	Study	RF+/ rTBI+	RF+/ rTBI−	RF−/ rTBI+	RF−/ rTBI−	Crude RR	Adjusted HR/OR
Sex (male)	Ref #26	9154	58027	3526	33583	1.43 (1.38–1.49)	
	Ref #30	14	154	7	61	0.85 (0.34–1.92)	0.86 (0.33–2.28)
	Ref #31	36	528	16	247	1.05 (0.59–1.86)	0.88 (0.47–1.64)
	Ref #32	232	904	97	682	1.64 (1.32–2.04)	
	Ref #35	60	283	16	111	1.39 (0.83–2.32)	
	Ref #36	15	810	4	351	1.61 (0.54–4.83)[a]	
	Ref #37	39	57	31	40	0.93 (0.65–1.33)	
	Ref #46	214	2607	89	1447	1.31 (1.03–1.66)	1.28 (1.00–1.65)
Prior TBI	Ref #31	6	28	46	747	3.04 (1.40–6.63)	3.39 (1.32–8.72)
	Ref #35	14	49	62	345	1.46 (0.87–2.44)	
	Ref #40	43	31	28	38		1.88 (0.96–3.69)[b]
	Ref #43	24	10	66	80	2.91 (1.30–6.52)[c]	
	Ref #46	24	158	279	3896	1.97 (1.34–2.91)	1.62 (1.08–2.42)
Severity (moderate/ severe vs. mild)	Ref #26	2427	21187	7346	73330	1.13 (1.08–1.18)	
	Ref #30	2	28	19	187	0.72 (0.18–2.95)	1.43 (0.28–7.22)
	Ref #31	10	101	19	301	1.52 (0.73–3.16)	
	Ref #46	160	1800	142	2254	1.37 (1.11–1.71)[d]	1.24 (1.00–1.54)[d]
Alcohol intoxication	Ref #30	9	27	12	188	4.17 (1.89–9.16)	4.41 (1.53–12.70)
	Ref #31	28	268	24	507	2.09 (1.24–3.54)	2.51 (1.38–4.56)
	Ref #40	13	13	57	56		0.98 (0.42–2.30)[b]
	Ref #47	46	435	101	1517	1.53 (1.10–2.14)	
Rural	Ref #30	7	150	14	65	0.25 (0.11–0.60)	0.23 (0.09–0.59)
	Ref #37	10	19	60	78	0.79 (0.46–1.36)	
	Ref #40	17	19	55	53		0.86 (0.41–1.83)[b]
	Ref #46	70	1042	233	3012	0.88 (0.68–1.14)	
Mechanism (fall vs. other)	Ref #30	2	36	19	179	0.55 (0.13–2.26)	
	Ref #40	29	24	43	48		1.35 (0.68–2.66)[b]
	Ref #46	109	1212	194	2842	1.29 (1.03–1.62)	
Single parent	Ref #26	4807	30765	7873	60845	1.18 (1.14–1.22)	
	Ref #30	3	15	18	200	2.02 (0.66–6.21)	1.64 (0.45–6.02)
	Ref #37	1	5	67	89	0.39 (0.06–2.34)	
Age (10−year increase)[e]	Ref #31					1.22 (1.00–1.34)	1.11 (1.00–1.34)
	Ref #46					1.03 (0.98–1.07)	0.96 (0.82–1.05)
Drug use	Ref #40	7	3	62	65		2.45 (0.61–9.89)[b]
	Ref #47	13	111	134	1941	1.62 (0.95–2.79)	
Race (nonwhite)	Ref #40	56	55	16	17		1.08 (0.50–2.35)[b]
	Ref #46	77	1196	226	2858	0.83 (0.64–1.06)	0.65 (0.50–0.84)
Polytrauma	Ref #40	42	42	24	28		1.17 (0.58–2.33)[b]
	Ref #46	203	2931	100	1123	0.79 (0.63–1.00)	
Lifetime psychiatric comorbidity in parent	Ref #26	4187	26461	8493	65149	1.18 (1.14–1.23)	
	Ref #37	6	4	64	93	1.47 (0.86–2.53)	
Parent's education (<high school)	Ref #26	2563	16696	10117	74914	1.12 (1.07–1.17)	
	Ref #37	18	45	52	52	0.57 (0.37–0.88)[f]	
Education (<college)	Ref #47	111	1294	36	658	1.52 (1.06–2.19	
Medical comorbidities	Ref #46	146	1914	157	2140	1.04 (0.84–1.29)	
Insurance (uninsured)	Ref #46	108	1026	195	3028	1.57 (1.26–1.97)	
Epilepsy	Ref #46	40	316	263	3738	1.71 (1.25–2.34)	
Father's occupation (unemployed)	Ref #37	1	7	69	90	0.29 (0.05–1.82)	
Mother's occupation (unemployed)	Ref #37	2	9	68	88	0.42 (0.12–1.48)	
Father's smoking status (nonsmoker)	Ref #37	15	16	52	78	1.21 (0.80–1.84)	
Mother's age at child's birth (<25 years)	Ref #37	14	24	56	73	0.85 (0.54–1.35)	
Lead (≥10ug/dL in blood)	Ref #37	5	7	65	90	0.99 (0.50–1.99)	
Parent with a criminal history	Ref #26	6722	42365	5958	49245	1.27 (1.23–1.31)	
Income (lowest decile)	Ref #26	1531	9797	11149	81813	1.13 (1.07–1.18)	
Comorbid psychiatric condition	Ref #31	4	26	48	749	2.21 (0.85–5.74)	
Not seeking medical care within 24 hours	Ref #40	19	8	53	64		2.87 (1.16–7.09)[b]
Skull fracture	Ref #35	14	60	62	334	1.21 (0.72–2.04)	



Forest plot of association measures for the 27 risk factors identified in the systematic search and measured at baseline (incident traumatic brain injury [TBI]). Covariates used for adjustment and matching are provided in table e-5. [a]Risk ratio (RR) was calculated using all occurrences of recurrent TBI (rTBI) and not for individual patients (data were not available; there were 44 repeat injuries in 25 patients). [b]All studies reported by Theadom et al.[40] are adjusted odds ratios (ORs)

Continued

for a given study. The most common major flaw was not validating the method used to measure rTBI occurrence, and the most common minor flaw was that many studies' data sources were primarily intended for medical purposes. Poor reporting was most frequently the result of not providing any justification for the sample size used (table e-4).

DISCUSSION The epidemiologic characteristics of rTBI in the general population were previously uncharacterized. This systematic review has comprehensively described the important contribution that rTBI has to the overall TBI burden. After 1 year of follow-up from the time of an index TBI, at least 5.5% of individuals will have a recurrence that requires medical attention. As such, these recurrent events play an important role in amplifying the TBI burden since they are known to be associated with increased disability.[14–16] Furthermore, we have shown that many recurrent events occur in the first 6 months after index TBI. Previous evidence demonstrates that shorter intervals between index TBI and rTBI are associated with greater disability since the injured brain is still recovering from the initial injury.[48,49] Thus, these early recurrences, which are common, are particularly burdensome to the general population.

Our study demonstrates that many RFs for rTBI are similar to those for incident TBI. Males have a higher incidence of TBI across all populations and age groups, which is similar to the association we found for rTBI.[21,50] In addition, we described an increasing risk of rTBI among younger children in one study,[26] which resembles the pattern seen for first-time injuries.[51] Older age has also been shown to be a risk factor for incident TBI, although this characteristic was inconclusive for rTBI in our study.[52] Given this evidence, rTBI may also have a bimodal distribution where younger children and older adults are at higher risk, but further investigation is warranted. Also, alcohol intoxication is known to increase the risk of TBI and appears to be an important factor in predicting rTBI.[53] In fact, one study demonstrated that brief alcohol interventions at the time of index trauma reduce the risk of trauma recurrence.[54] Moreover, patients with an epilepsy disorder seem to be at higher risk of rTBI, which supports the idea that patients with epilepsy have a higher risk of injuries.[55] Finally, our study demonstrates that lower socioeconomic status is associated with an increased risk of rTBI, which is substantiated by other studies that have provided similar findings.[56,57]

We also identified RFs for rTBI that differ from those for index injuries or are unique for rTBI. Patients with a moderate or severe index TBI are more likely to endure rTBI than cases with a mild index TBI, suggesting that more disabling injuries are associated with a greater risk of recurrence.[58] Similarly, prior TBI before the initial injury under study also predicted a higher risk of recurrence, which indicates that rTBI risk in the general population increases as more injuries occur. Similar evidence in athlete populations supports this association.[8] Furthermore, nonwhite race and rural residence tended to demonstrate a protective, yet imprecise, association for rTBI. Similarly, some RFs related to lower socioeconomic status (unemployed parents, low parental education) are also associated with a decreased rTBI risk. These RFs are typically associated with an increased risk for incident TBI.[59] Such discrepancies may be explained by the fact that individuals in these social settings may have poorer access to health care, which would lead to an underestimation of their rTBI risk. Clearly, further investigations on these RF associations are required. In short, knowledge of these RFs provides stakeholders in TBI prevention with a means to identify patients at higher risk of recurrence, such that prevention efforts geared towards these individuals may be prioritized.

As this review confirms, there has only been limited research on rTBI epidemiology in the general population. In contrast, there has been substantial research dedicated to this topic in athletes.[8] For example, interventions to reduce the risk of rTBI in athletes, such as delaying return to play, have been shown to be effective.[8] Analogous interventions that mitigate the risk of rTBI in the general population have not been investigated, perhaps because there had never been a comprehensive description of its frequent occurrence. Despite the extensive review we completed, we must highlight that many studies we included have important validity flaws, since half of them did not have a primary aim related to rTBI. Therefore, research that primarily focuses on rTBI is required to produce higher-quality evidence on the topic. In such studies, it would be important to develop and use uniform methods to measure rTBI and baseline RFs, which is similar to what has been suggested to improve the quality of incident TBI

Figure 4 legend, continued:
because cases and controls were matched. [c]Crude estimate is an OR. [d]Comparison is severe vs moderate/mild. [e]Crude estimate is a hazard ratio (HR) and standardized mean differences are not shown but reported in figure e-2. [f]Data are shown for father's education only, but similar estimates were also reported for mother's education (not shown). Saunders et al.[46] and Saunders et al.[47] were used to assess risk factors (RFs) instead of Wilson and Selassie,[33] which did not report RFs but had a larger sample size for the same study population.

surveillance.[23] In addition, the timing of injuries after the index case should be reported so that the high-risk period of recurrence can be thoroughly assessed. By following such recommendations there would be less methodologic heterogeneity between studies, which would allow for better comparisons of rTBI epidemiologic characteristics across jurisdictions and time.

An important contributor to the aforementioned heterogeneity of rTBI risk and RF associations is the variability of case definitions for rTBI across different data sources. This heterogeneity similarly affects surveillance studies for incident TBI where comparing estimates across jurisdictions is challenging.[21,23] However, when studying rTBI, varying follow-up times used to assess the outcome as well as the unknown validity of case definitions further complicate this problem. Regarding incident TBI, administrative data have been shown to be inaccurate at identifying cases (sensitivity of 45%–70% and specificity of >97%), but such information is not available for rTBI.[60] We demonstrated that studies using administrative health data or surveys report higher rTBI risk, which suggests that these data sources may lack specificity for detecting rTBI cases. For example, participants in studies using surveys to assess rTBI may overreport the occurrence of events. In studies using administrative data, this lack of specificity may result from ICD-coded claims being identified as rTBI when they are in fact follow-up visits for the index TBI. This problem is particularly apparent in Chu et al.,[39] where a high rTBI risk of 36% over a follow-up period of up to 3 years was reported. These authors did not exclude medical claims with a TBI diagnosis for a certain period after the index TBI, as was done in other studies to ensure that follow-up visits for the index case were not counted as rTBI cases.[26,27,29,34] Since administrative health data provide a feasible and timely approach to conduct surveillance and epidemiologic research, studies evaluating the accuracy of case-detection algorithms for rTBI in these data sources are required.

Our systematic review has several limitations. First, publication bias may have occurred since we only included the peer-reviewed literature and public health reports on rTBI may be available in the gray literature. We decided to omit these studies since an important component of this review was to focus on the quality assessment of included studies and the MORE checklist was not designed to evaluate the gray literature. Second, there was significant heterogeneity in the methods and populations used to assess rTBI risk and RFs across studies. This limited our ability to meta-analyze the risk and RF association measure estimates even when studies had similar follow-up periods. Although we were unable to estimate the risk of rTBI over time, we still demonstrated that there is a tendency for the risk to be the highest in the first months to years after the index case. Finally, many RFs only had crude association measures reported. Confounding of the association between the RFs and the rTBI outcome is thus possible. Conclusions on association measures did not change when comparing crude and adjusted estimates, but we must still cautiously interpret them.

rTBI affects a significant proportion of individuals with TBI, oftentimes early after a first injury, amplifying the overall TBI burden in the general population. Several factors can help identify patients at a higher risk of recurrence. However, there is significant heterogeneity of estimates between studies and methodologic flaws compromise the quality of the literature on the topic. As such, further high-quality research is needed to validate approaches for measuring rTBI occurrence so that it is possible to accurately conduct surveillance, assess risk factors, and evaluate potential rTBI-mitigating interventions in the general population.

AUTHOR CONTRIBUTIONS

Study concept and design: Dr. Lasry, Dr. Marcoux, and Dr. Buckeridge. Acquisition, analysis, or interpretation of data: Dr. Lasry, E.Y. Liu, G.A. Powell, and J. Ruel-Laliberté. Drafting of manuscript: Dr. Lasry. Critical revision of manuscript for important intellectual content: All authors. Administrative, technical, or material support: Dr. Lasry and G.A. Powell. Study supervision: Drs. Marcoux and Buckeridge.

ACKNOWLEDGMENT

The authors thank Genevieve C. Gore (MLIS, McGill University, Schulich Library of Science and Engineering) for assistance in developing the search strategy used in this review.

STUDY FUNDING

Dr. Lasry reports having been supported by a Canadian Institutes of Health Research Vanier Canada Graduate Scholarship to support his doctoral studies. Erin Yiran Liu reports having received a Richard H. Tomlinson Fellowship from McGill University to support her doctoral studies. Dr Buckeridge reports receiving a salary award from the Canadian Institutes of Health Research.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received May 12, 2017. Accepted in final form September 5, 2017.

REFERENCES

1. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil 2006;21:375–378.
2. Scholten AC, Haagsma JA, Panneman MJM, van Beeck EF, Polinder S. Traumatic brain injury in the Netherlands: incidence, costs and disability-adjusted life years. PLoS One 2014;9:e110905.
3. Te Ao B, Brown P, Tobias M, et al. Cost of traumatic brain injury in New Zealand evidence from a population-based study. Neurology 2014;83:1645–1652.
4. Menon DK, Schwab K, Wright DW, et al. Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil 2010;91:1637–1640.

5. Salcido R, Costich JF. Recurrent traumatic brain injury. Brain Inj 1992;6:293–298.
6. McCrea M, Hammeke T, Olsen G, Leo P, Guskiewicz K. Unreported concussion in high school football players: implications for prevention. Clin J Sport Med 2004;14:13–17.
7. Centers for Disease Control and Prevention (CDC). Sports-related recurrent brain injuries: United States. MMWR Morb Mortal Wkly Rep 1997;46:224–227.
8. Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013;80:2250–2257.
9. Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA concussion study. JAMA 2003;290:2549–2555.
10. Guskiewicz KM, Marshall SW, Bailes J, et al. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. Neurosurgery 2005;57:719–726.
11. Kerr ZY, Evenson KR, Rosamond WD, et al. Association between concussion and mental health in former college atheletes. Inj Epidemiol 2014;1:28.
12. Benson BW, Meeuwisse WH, Rizos J, Kang J, Burke CJ. A prospective study of concussions among National Hockey League players during regular season games: the NHL-NHLPA Concussion Program. CMAJ 2011;183:905–911.
13. Cunningham J, Brison RJ, Pickett W. Concussive symptoms in emergency department patients diagnosed with minor head injury. J Emerg Med 2011;40:262–266.
14. Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. Clin Sports Med 2011;30:179–188.
15. Fralick M, Thiruchelvam D, Tien HC, et al. Risk of suicide after a concussion. CMAJ 2016;188:497–504.
16. Teasdale TW, Engberg AW. Suicide after traumatic brain injury: a population study. J Neurol Neurosurg Psychiatry 2001;71:436–440.
17. Zasler N, Katz D, Zafonte R. Brain Injury Medicine. 2nd ed. New York: Demos Medical Publishing; 2006.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
19. Shamliyan TA, Kane RL, Ansari MT, et al. Development quality criteria to evaluate nontherapeutic studies of incidence, prevalence, or risk factors of chronic diseases: pilot study of new checklists. J Clin Epidemiol 2011;64:637–657.
20. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis 2015;74:65–73.
21. Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of traumatic brain injury in Europe: a living systematic review. J Neurotrauma 2016;30:1–30.
22. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Meta-regression. Chichester, UK: John Wiley & Sons, Ltd.; 2009.
23. Barker-Collo SL, Feigin VL. Capturing the spectrum: suggested standards for conducting population-based traumatic brain injury incidence studies. Neuroepidemiology 2009;32:1–3.
24. Chen H, Richard M, Dandler DP, Umbach DM, Kamel F. Head injury and amyotrophic lateral sclerosis. Am J Epidemiol 2007;166:810–816.
25. Annegers J, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. N Engl J Med 1998;338:20–24.
26. Sariaslan A, Sharp DJ, D'Onofrio BM, Larsson H, Fazel S. Long-term outcomes associated with traumatic brain injury in childhood and adolescence: a nationwide Swedish cohort study of a wide range of medical and social outcomes. PLoS Med 2016;13:e1002103.
27. Richard YF, Swaine BR, Sylvestre MP, Lesage A, Zhang X, Feldman DE. The association between traumatic brain injury and suicide: are kids at risk? Am J Epidemiol 2015;182:177–184.
28. Teasdale TW, Frosig AJ, Engberg A. Adult cognitive ability and educational level in relation to concussions in childhood and adolescence: a population study of young men. Brain Inj 2014;28:1721–1725.
29. McMillan TM, Weir CJ, Wainman-Lefley J. Mortality and morbidity 15 years after hospital admission with mild head injury: a prospective case-controlled population study. J Neurol Neurosurg Psychiatry 2014;85:1214–1220.
30. Winqvist S, Luukinen H, Jokelainen J, Lehtilahti M, Nayha S, Hillbom M. Recurrent traumatic brain injury is predicted by the index injury occurring under the influence of alcohol. Brain Inj 2008;22:780–785.
31. Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M. Head trauma sustained under the influence of alcohol is a predictor for future traumatic brain injury: a long-term follow-up study. Eur J Neurol 2014;21:293–298.
32. Bijur PE, Haslum M, Golding J. Cognitive outcomes of multiple mild head injuries in children. J Dev Behav Pediatr 1996;17:143–148.
33. Wilson DA, Selassie AW. Risk of severe and repetitive traumatic brain injury in persons with epilepsy: a population-based case-control study. Epilepsy Behav 2014;32:42–48.
34. Harris AW, Voaklander DC, Jones CA, Rowe BH. Time-to-subsequent head injury from sports and recreation activities. Clin J Sport Med 2012;22:91–97.
35. Edna TH, Cappelen J. Late post-concussional symptoms in traumatic head injury. An analysis of frequency and risk factors. Acta Neurochir 1987;86:12–17.
36. Partington MW. The importance of accident-proneness in the aetiology of head injuries in childhood. Arch Dis Child 1960;35:215–223.
37. Liu J, Li L. Parent-reported mild head injury history and behavioural performance in children at 6 years. Brain Inj 2013;27:1263–1270.
38. Lee MA, Fine B. Adolescent concussions. Conn Med 2010;74:149–156.
39. Chu S, Chiu W, Lin H, Chiang Y, Liou T. Hazard ratio and repeat injury for dementia in patients with and without a history of traumatic brain injury: a population-based secondary data analysis in Taiwan. Asia Pac J Public Health 2016;28:519–527.
40. Theadom A, Parmar P, Jones K, et al. Frequency and impact of recurrent traumatic brain injury in a population-based sample. J Neurotrauma 2015;32:674–681.
41. Swaine BR, Tremblay C, Platt RW, Grimard G, Zhang X, Pless IB. Previous head injury is a risk factor for

subsequent head injury in children: a longitudinal cohort study. Pediatrics 2007;119:749–758.
42. Klonoff H. Head injuries in children: predisposing factors accident conditions, accident proneness and sequelae. Am J Public Health 1971;61:2405–2417.
43. Taubman B, McHugh J, Rosen F, Elci OU. Repeat concussion and recovery time in a primary care pediatric office. J Child Neurol 2016;31:1607–1610.
44. Collins CL, Yeates KO, Pommering TL, et al. Direct medical charges of pediatric traumatic brain injury in multiple clinical settings. Inj Epidemiol 2014;1:13.
45. Ganti L, Conroy LM, Bodhit A, et al. Understanding why patients return to the emergency department after mild traumatic brain injury within 72 hours. West J Emerg Med 2015;16:481–485.
46. Saunders LL, Selassie AW, Hill EG, et al. A population-based study of repetitive traumatic brain injury among persons with traumatic brain injury. Brain Inj 2009;23:866–872.
47. Saunders LL, Selassie AW, Hill EG, et al. Pre-existing health conditions and repeat traumatic brain injury. Arch Phys Med Rehabil 2009;90:1853–1859.
48. Wall SE, Williams WH, Cartwright-Hatton S, et al. Neuropsychological dysfunction following repeat concussions in jockeys. J Neurol Neurosurg Psychiatry 2006;77:518–520.
49. Iverson GL, Echemendia RJ, LaMarre AK, Brooks BL, Gaetz MB. Possible lingering effects of multiple past concussions. Rehabil Res Pract 2012;2012:316575.
50. Nguyen R, Fiest KM, McChesney J, et al. The international incidence of traumatic brain injury: a systematic review and meta-analysis. Can J Neurol Sci 2016;43:774–785.
51. Thurman DJ. The epidemiology of traumatic brain injury in children and youths: a review of research since 1990. J Child Neurol 2016;31:20–27.
52. Roozenbeek B, Maas AIR, Menon DK. Focus on traumatic brain injury: changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol 2013;9:231–236.
53. McHugo GJ, Krassenbaum S, Donley S, Corrigan JD, Bogner J, Drake RE. The prevalence of traumatic brain injury among people with co-occurring mental health and substance use disorders. J Head Trauma Rehabil 2017;32:E65–E74.
54. Gentilello LM, Rivara FP, Donovan DM, et al. Alcohol interventions in a trauma center as a means of reducing the risk of injury recurrence. Ann Surg 1999;230:473–483.
55. Friedman DE, Chiang S, Tobias RS. Do recurrent seizure-related head injuries affect seizures in people with epilepsy? Epilepsy Behav 2012;23:159–161.
56. Amram O, Schuurman N, Pike I, et al. Socio economic status and traumatic brain injury amongst pediatric populations: a spatial analysis in greater Vancouver. Int J Environ Res Public Health 2015;12:15594–15604.
57. Bruns JJ, Hauser WA. The epidemiology of traumatic brain injury: a review. Epilepsia 2003;44:2–10.
58. Jennett B, Bond M. Assessment of outcome after severe brain damage: a practical scale. Lancet 1975;1:480–484.
59. Feigin VL, Theadom A, Barker-collo S, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. Lancet Neurol 2013;12:53–64.
60. St Germaine-Smith C, Metcalfe A, Pringsheim T, et al. Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. Neurology 2012;79:1049–1055.