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History of concussion and risk of subsequent injury in athletes and service members: A systematic review and meta-analysis

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ABSTRACT

Risk of secondary injury after a primary concussion in sports and military contexts is an emerging area of interest in research. The purpose of this review was to provide an evidence synthesis describing risk of injury in athletic and military populations with and without a history of concussion.

Electronic database searches were completed through September 7, 2018 in PubMed, EMBASE, CINAHL and SCOPUS. Peer-reviewed observational studies of any design with participants who were athletes or service members; measured the outcome of any type of injury; and compared injury between those with and without a history of concussion were included. Risk of bias was assessed using the Q-Coh II. Twenty-seven articles were included. Seventeen meta-analyses were completed for risk of any injury, risk of concussion, and risk of extremity injury using odds, hazard, and rate ratios. The results indicate significantly increased odds of all injuries (OR = 2.55; 95%CI 1.85,3.52); concussion (OR = 3.73; 95%CI 2.41,5.78); and lower extremity injuries (OR = 1.60; 95%CI 1.32,1.94) in those with a history of concussion compared to those without. Additional analyses reveal this increased risk is apparent when looking at time to event data and rate of injury based on number of exposures. While the reasons for the increased incidence of secondary injury associated with a concussion are not yet understood, there are potentially behavioral attributes and motor control deficits that contribute. It is suggested that research is needed to determine if active therapeutic treatment for disturbances in sensorimotor and neuromotor control after concussion could attenuate the increased risk for injury.

1. Introduction

In sports and military contexts, physical injuries are often sustained which limit participation and decrease performance. Concussion has emerged as one of the most concerning sports injuries with upwards of 3.8 million traumatic brain injuries (TBI), predominantly mild TBI/concussion, occurring annually in the United States (US) (Langlois, 2006). In the US military, annual concussion incidence is variable, depending on engagement in combat, branch of the military, and specific duties (Armistead-Jehle et al., 2017). Mechanisms of injury in military environments for concussion comprise very different types of etiologies, including those from blunt forces and high-explosive blast forces (Greer et al., 2016). According to data from the National Collegiate Athletic Association Injury Surveillance Program in the US (NCAA-ISP), aside from concussion, ankle sprains and anterior-cruciate ligament injuries are the most common orthopedic conditions occurring each year as a result of sports participation (Hootman et al., 2007). Musculoskeletal injuries also commonly befall US service members, significantly contributing to the 1.6 million injuries occurring each year (Hauret et al., 2010). Foot and ankle, knee, and low back injuries are the most commonly reported musculoskeletal injuries in service members (Teyhen et al., 2018).

When a concussion or musculoskeletal injury occurs in athletes or service members, a primary goal is to return to play or military activity, respectively. Generally speaking for concussion, recovery is established once there is dissipation of self-reported symptoms (including headaches, dizziness, noise and light sensitivity, emotional concerns, sleep disturbances, etc.) at rest and with activity (McCrory et al., 2017). For other injuries, the absence of pain and return of normalized movement patterns needed for function are key indicators of recovery. In order for musculoskeletal injuries to be appropriately yet safely challenged, physical therapy intervention is routinely utilized to provide treatment as well as guidance related to return to activity. Research evidence only recently emerged to support physical therapy utilizing multi-modal (i.e. cervical, vestibular, and oculomotor interventions) as a treatment directly following concussion (Reneker et al., 2017). At this time, physical therapy is not routinely utilized after a concussion to establish fitness for return to play or duty.

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A key concern with return to activity is the risk of re-injury. In sports, it is believed that athletes who have suffered one concussion are at a higher risk for another concussion (McCrory et al., 2017). The risk of this phenomenon has not been quantified across studies in athletes and there is little research describing secondary concussion risk in military contexts. Subsequent musculoskeletal injuries are also common after experiencing a primary musculoskeletal injury for both athletic and military populations (Wiggins et al., 2016; Schneider et al., 2000; Fulton et al., 2014). It has been reported that military personal who have experienced a traumatic injury, as opposed to an overuse or unspecified injury, have an 83% increased likelihood of experiencing a subsequent injury (Schneider et al., 2000). One systematic review reported that among professional soccer players, those who have experienced an ankle sprain were 50% more likely to experience a repeated ankle sprain than those who had not experienced a previous injury (Fulton et al., 2014).

Recently there has been an emergence of research reporting risk of musculoskeletal injury after a concussion. It is hypothesized that despite clinical recovery after a concussion, residual deficits in motor control remain, which increases risk of musculoskeletal injury (Brooks et al., 2016; Kardouni et al., 2018). A recent systematic review and meta-analysis was published on the risk of musculoskeletal injury in athletes after a sport-related concussion (McPherson et al., 2018), but the overall phenomenon describing the association between history of any concussion/mild TBI (not just sport-related concussion) and any type of subsequent injury, including estimates for secondary concussion, and using additional metrics of risk has not been reported in athletes. In addition, we are not aware of any previously reported meta-analyses to approximate risk of injury in service members after a concussion.

The purpose of this systematic review and meta-analysis was to provide an evidence synthesis describing risk of injury in athletic and military populations with and without a history of concussion. The objective was to provide summary estimates, utilizing any type of risk data (i.e. odds ratio, hazard ratio, and rate ratio), for overall risk of any type of injury followed by the subsets of concussion risk; extremity injury risk; and lower extremity risk.

2. Methods

2.1. Protocol and registration

This systematic review and meta-analysis was written with reference to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) (Moher et al., 2009). The PRISMA guidelines include a 27-item checklist to increase transparency of reporting. This project was registered prospectively on PROSPERO (2018 CRD42018081298).

2.2. Eligibility criteria

Peer-reviewed observational studies of any design and length of observation were included in this review if they met the following criteria: 1) Participants were athletes/sports-participants at any level of competition or service members. 2) The exposure was concussion of any etiology (including sport or non-sport; blast or blunt force) or no concussion. 3) The outcome of interest was any type of injury. For those exposed to concussion, this was an injury sustained at some point after sustaining a primary concussion. For those without a concussion, this was any injury. 4) The statistical methods reported injury between participants (athletes or service members) with and without a history of concussion. If risk was not calculated within the statistical methods but the data was reported to permit calculation of risk, this was also acceptable. All manuscripts must have been written in English with full-text available. No Limits were placed on date of publication.

2.3. Information sources and search

The computerized search was completed by the study investigators and a University librarian. Identical computer-based search strategies were performed between November 16, 2017 and September 7, 2018 using the following search terms (MeSH terms) from the PubMed database: (“brain concussion”[MeSH Terms] OR (“brain”[All Fields] AND “concussion”[All Fields]) OR “brain concussion”[All Fields]) AND ((“athletic injuries”[MeSH Terms] OR (“athletic”[All Fields] AND “injuries”[All Fields]) OR “athletic injuries”[All Fields] OR (“athletic”[All Fields] AND “injury”[All Fields]) OR “athletic injury”[All Fields]) OR (“military personnel”[MeSH Terms] OR (“military”[All Fields] AND “personnel”[All Fields]) OR “military personnel”[All Fields])) AND (“risk”[MeSH Terms] OR “risk”[All Fields]). The same search strategy was applied to EMBASE. A similar search strategy was used for CINAHL and SCOPUS. There were no limits placed on this search. Additionally, a hand search of the bibliographies of the included studies was completed to identify all relevant studies.

2.4. Study selection

A stepwise, stratified review was performed by the authorship team. Two authors independently reviewed titles, abstracts, and full text articles. At each stage, when disagreement between authors regarding inclusion occurred, a third author reviewed the title/abstract/article in question. At the stage of titles and abstracts, the decision was made by the tie-breaking vote (agreement between 2 of the 3 reviewers). At the stage of full text, the final decision regarding inclusion was determined based on discussion and consensus among the three authors. All studies which met the inclusion criteria were included in this review.

2.5. Data items and extraction

Data extraction included the study design; description of participants; exposure status of previous concussion, including the methods used in the each included study to determine concussion diagnosis; timeframe of observation from concussion to a secondary injury; type of injury; statistical results for estimates of risk of injury (e.g. odds ratio; risk ratios; etc.) or raw data to calculate risk. Any methods of controlling for other confounding factors were also recorded (matching techniques and/or statistical methods).

2.6. Risk of bias in individual studies

The Quality of Cohort Studies, version II (Q-Coh II) was used to assess the methodological quality of the observational studies included in this review. This tool (updated from the Quality of Cohort Studies) (Jarde et al., 2013) has been utilized in previously published reviews (Brown et al., 2015; Cavanaugh et al., 2018). The items within the tool assess the following domains: representativeness of the sample and comparability of the groups at the onset of the study (selection bias), quality of the exposure measure (information bias), comparability of the groups during the study (performance bias), outcome measure quality (information bias), and participant attrition (attrition bias). Previous research on the psychometric properties of this tool reveal good to very good kappa values (ranging from 0.59 to 0.94) for each item (Jarde et al., 2013). The Q-Coh II was utilized without penalizing cross-sectional studies in the scoring for the questions which were longitudinal in nature (Brown et al., 2015). Two authors independently scored each included study. Decisions for the final score of each article were determined through discussion and consensus of the two scorers. Based on the final total score received, a qualitative rating of good (10–12 points), acceptable (7–9 points), or low quality (< 7 points) was given to each study (Brown et al., 2015).

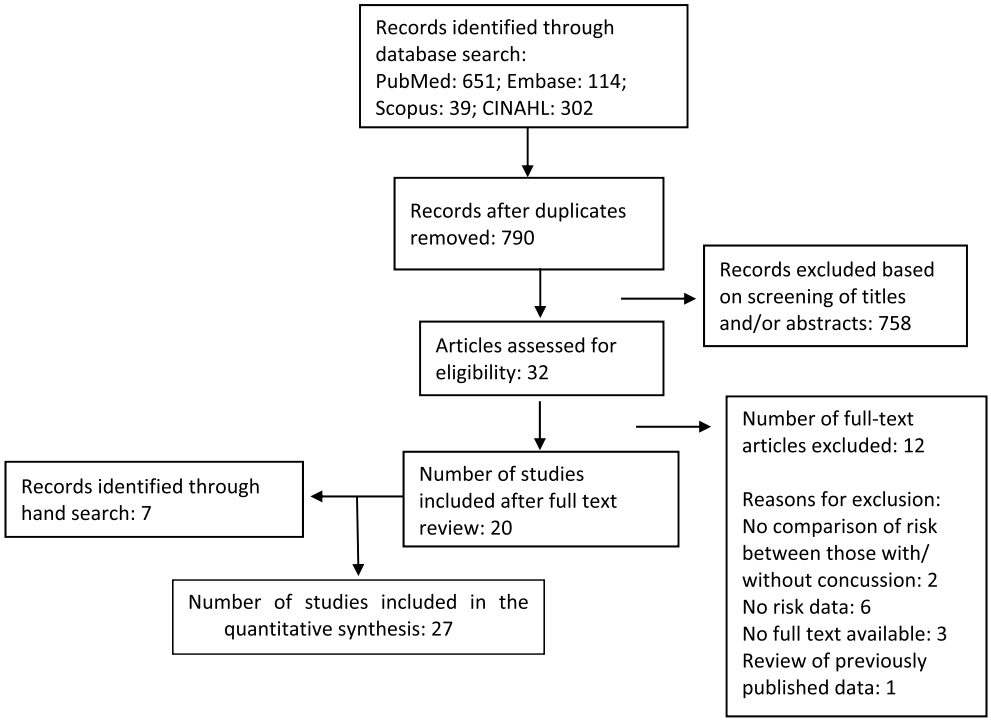

Fig. 1. PRISMA flow-diagram.

2.7. Summary measures and subgroup analyses

The first group of meta-analyses was completed to determine the association between one or more concussions and any type of injury. Secondarily, analyses were completed to approximate risk of subsequent concussion after a primary concussion and separately to approximate risk of an extremity injury after a concussion. All analyses were completed initially by combining results from studies on service members and studies on athletes to develop an overall summary estimate of risk. Analyses were also completed to approximate risk in service members and athletes separately. Lastly, because of differences in the type of risk estimate reported among the various studies which could not be combined into one summary measure, meta-analyses of hazard ratio, rate ratio, and odds ratio were completed as necessary.

2.8. Synthesis of results

Meta-analyses were completed using Comprehensive Meta-Analysis version 3.0. For all analyses completed, if a study reported on multiple sub-groups of participants (i.e. football players and soccer players), the sub-group within the study was used as the unit of analysis (meaning that football players and soccer players were treated as separate groups in the analysis). For each outcome of interest, if the study reported multiple outcomes or the same outcome at multiple timeframes, the mean of the selected outcomes was used in the analysis (meaning that the outcomes in the same participants were not treated as independent observations).

To determine the degree of heterogeneity within the results from the included studies in each meta-analysis, the I^2 statistic was used. The I^2 statistic has more usefulness than the Q-test because it quantifies the degree of between-studies variability, rather than just identifying the presence or absence of heterogeneity (Higgins and Thompson, 2002). To determine which model would be used, if I^2 was less than 50% (indicating less than medium heterogeneity), a fixed effects model was used to describe the typical effect observed across studies. If the I^2 was greater than 50% (indicating greater than medium heterogeneity), the forest plot was visually inspected to determine if a random effects model was appropriate. If all point estimates from the included studies fell on one side of the null, it was determined that a random effects model could be used to adequately represent the mean effect of the included studies; if the point estimate of the effects fell on both sides of the null, it was determined that a meta-analysis was not appropriate (Higgins and Thompson, 2002).

2.9. Risk of bias across studies

Separate funnel plots were obtained for each meta-analysis for the outcome of any injury for odds ratio, hazard ratio, and rate ratio. This was done to include all studies for each type of summary effect measure so that observation of asymmetry could be observed, if present. The classic Begg and Mazumdar's rank correlation (reporting Kendall's tau and p-value) and the fail-safe N were also utilized to determine if statistically, there is likely to be a difference between the results of the published and non-published studies which could lead to biased summary estimates (Soeken and Sripusanapan, 2003; Begg and Mazumdar, 1994).

3. Results

3.1. Study selection and risk of bias within studies

The combined systematic searches of the literature yielded a total of 790 potential articles (with duplicates removed). After review of titles and abstracts, 32 full-text articles were identified and with full text-review, 20 articles were included. Seven additional articles were identified by searching bibliographies of included studies for a total of 27 studies included in the qualitative and quantitative analyses (Fig. 1). The Q-Coh II scores are outlined in Table 1. Fifteen studies had good methodological quality, eleven studies had acceptable methodological quality, and one was determined to be of low methodological quality.

3.2. Individual study characteristics and results

Detailed individual study characteristics are presented in Table 2. Of the included studies, 4 explored risk in service members,

Table 1
Q-Coh Quality Assessment.

Author, year	Selection Bias	Exposure Measures	Performance Bias	Outcome Measures	Attrition Bias	Total Score, Possible 12/12	Quality
Brooks et al., 2016	2	2	2	3	2	11/12	Good
Bryan, 2013	1	1	1	4	2	9/12	Acceptable
Burman et al., 2016	1	1	1	3	2	8/12	Acceptable
Cross et al., 2016	1	2	1	3	2	9/12	Acceptable
Delaney et al., 2000	2	2	2	4	2	12/12	Good
Delaney et al., 2001	2	2	2	4	2	12/12	Good
Delaney et al., 2002	2	2	2	4	2	12/12	Good
Fino et al., 2017	2	2	2	4	2	12/12	Good
Gilbert et al., 2016	1	2	1	4	2	10/12	Good
Guskiewicz et al., 2000	2	1	1	3	2	9/12	Acceptable
Guskiewicz et al., 2003	1	1	2	3	2	9/12	Acceptable
Herman et al., 2017	2	1	2	4	2	11/12	Good
Hollis et al., 2009	1	2	1	4	0	8/12	Acceptable
Houston et al., 2018	1	2	1	4	2	10/12	Good
Kardouni et al., 2018	2	1	2	3	2	10/12	Good
Krill et al., 2018	2	2	2	4	0	10/12	Good
Lynall et al., 2015	2	2	1	4	2	11/12	Good
Lynall et al., 2017	1	1	1	3	2	8/12	Acceptable
Makdissi et al., 2009	2	2	2	3	0	9/12	Acceptable
Nordstrom et al., 2014	1	1	1	3	0	6/12	Low
Nyberg et al., 2015	1	2	1	4	0	8/12	Acceptable
Pietrosimone et al., 2015	1	2	2	4	2	11/12	Good
Schulz et al., 2004	2	1	2	3	0	8/12	Acceptable
Selassie et al., 2013	1	1	1	3	2	8/12	Acceptable
Tsao et al., 2017	1	2	1	4	2	10/12	Good
Whitehead et al., 2014	2	2	2	4	2	12/12	Good
Zemper, 2003	2	2	1	3	2	10/12	Good

described as United States Marines (Tsao et al., 2017); Airmen (Whitehead et al., 2014); Soldiers (Kardouni et al., 2018); or military personnel (Bryan, 2013). The studies on risk in athletes included 23 total studies, reporting in collegiate athletes (Brooks et al., 2016; Delaney et al., 2001, 2002; Burman et al., 2016; Fino et al., 2017; Gilbert et al., 2016; Guskiewicz et al., 2003; Herman et al., 2017; Houston et al., 2018; Krill et al., 2018; Lynall et al., 2015; Zemper, 2003); highest level of club rugby (Cross et al., 2016); amateur men's rugby (Hollis et al., 2009); Canadian Professional Football (Delaney et al., 2000); high school athletes (Zemper, 2003; Lynall et al., 2017; Schulz et al., 2004); elite Australian football (Makdissi et al., 2009; Nordstrom et al., 2014); Swedish Ice Hockey Elite players (Nyberg et al., 2015); National Football League players (Pietrosimone et al., 2015); and people with sport traumatic brain injury (Selassie et al., 2013).

The comparisons based on exposure status made in the original research articles included individuals with: concussion to no concussion (Brooks et al., 2016; Kardouni et al., 2018; Tsao et al., 2017; Whitehead et al., 2014; Delaney et al., 2000, 2001, 2002; Fino et al., 2017; Gilbert et al., 2016; Guskiewicz et al., 2000, 2003; Herman et al., 2017; Houston et al., 2018; Krill et al., 2018; Lynall et al., 2015; Zemper, 2003; Cross et al., 2016; Hollis et al., 2009; Schulz et al., 2004; Makdissi et al., 2009; Nordstrom et al., 2014; Pietrosimone et al., 2015), mild traumatic brain injury (mTBI) to no mTBI (Whitehead et al., 2014; Bryan, 2013); sport TBI to none (Selassie et al., 2013); concussion to ankle injury (Burman et al., 2016); concussion to knee injury and > 1 concussion to knee injury (Nyberg et al., 2015); previous concussion in football or soccer to none (Delaney et al., 2000, 2001, 2002); previous loss of consciousness in soccer or football after a head impact compared to no loss of consciousness after a head impact (Delaney et al., 2000, 2001, 2002), previous loss of consciousness not in soccer or football after a head impact compared to no loss of consciousness after a head impact (Delaney et al., 2000, 2001, 2002); > 1 concussion to no concussion (Tsao et al., 2017); 2 concussions to no concussion (Guskiewicz et al., 2003; Hollis et al., 2009; Pietrosimone et al., 2015); 3 + concussions to no concussion (Guskiewicz et al., 2003; Pietrosimone et al., 2015); and each additional concussion to no concussion (Lynall et al., 2017).

Considering the type of injury outcomes reported, eleven reported on the outcome of concussion, and included the following groups (as described by the original studies), concussion (Tsao et al., 2017; Delaney et al., 2000, 2001, 2002; Guskiewicz et al., 2000, 2003; Zemper, 2003; Hollis et al., 2009; Schulz et al., 2004), mTBI (Bryan, 2013), and head and neck injury at > 2 days; > 2 weeks; and > 1 month post the index concussion (Whitehead et al., 2014). Eleven studies reported on lower extremity injury only. For the purposes of this review, the outcome of lower extremity injury included the following groups (as described by the original studies), lower extremity injury (Brooks et al., 2016; Fino et al., 2017; Krill et al., 2018); knee injury (Gilbert et al., 2016; Houston et al., 2018; Pietrosimone et al., 2015); lateral ankle sprain (Gilbert et al., 2016); ankle sprain (Houston et al., 2018); lower extremity muscle strain (Gilbert et al., 2016); lower extremity injury at 90 (Herman et al., 2017), 180, and 365 days after the index concussion (Lynall et al., 2015); time loss and non-time loss lower extremity injuries (Lynall et al., 2017); ankle/foot injuries (Pietrosimone et al., 2015); total number of LE musculoskeletal injuries (Pietrosimone et al., 2015); and acute lower extremity injury within 15 and 24 months (Kardouni et al., 2018). For the outcome of upper and lower extremity injury, one study grouped hand, arm, and lower extremity injury into one group as follows: extremity injury > 2 days; > 2 weeks and > 1 month post the index concussion (Whitehead et al., 2014). Finally, there were six studies that grouped injury outcomes and did not permit clean classification into one of the aforementioned groups. This included (as described by the original studies): time loss injuries (including concussion) (Cross et al., 2016); injury (lower and upper extremity, back and concussion) (Makdissi et al., 2009); sudden onset injuries (lower extremity, other injuries, and concussion) (Nordstrom et al., 2014), severe and subsequent injury in 7, 21, and 42 days (Nyberg et al., 2015); concussion and ankle injuries (one and ≥ two injuries) (Burman et al., 2016); and severe traumatic brain injury (Selassie et al., 2013).

3.3. Synthesis of results

Across the 17 meta-analyses completed, based on the resulting I^2 and inspection of the forest plots, nine utilized random-effects models and eight utilized fixed effects models.

Table 2
Description of included studies (listed alphabetically).

Study	Participants (n, sex, age, specific sport or military)	Exposed Group (How previous concussion was determined & timeframe)	Comparator Group (how no previous concussion was determined)	Outcomes of injury included	Timeframe (period of observation for second injury)
Brooks et al., 2016 Matched Retrospective Cohort Matched on: sport team, sex, exposure in games for 90 day period. Analysis controlled for hx of LE injury	n = 87 with concussion, age = 19.8 ± 1.3 years old n = 182 without concussion, age = 19.9 ± 1.3 y/o NCAA Division I football, soccer, hockey, softball, basketball, wrestling, volleyball	Injury records from the SIMS database according to the American Academy of Neurology criteria for 3 competitive seasons	No history of concussion (no injury records in the SIMS database)	Acute LE musculoskeletal injury; collected through SIMS database	90-day period following return to play
Bryan, 2013 Cross-sectional patient interview Controlled for in analysis: injury mechanism, depression symptoms, and post-traumatic stress symptoms	n = 139 with mTBI n = 22 without mTBI (military personnel, & male civilian contractors), 93.2% m, age not reported	Patient's self-report during clinical interview at outpatient TBI clinic; Number of previous head injuries sustained during & prior to deployment	No concussion/head injury reported during patient's self-report during clinical interview at outpatient TBI clinic	Repetitive mTBI diagnosed by licensed clinical psychologist using the DoD/VA TBI Task Force's criteria	Clinical interview and reporting/ diagnosis of mild TBI or concussion made during same visit to outpatient TBI clinic
Burman et al., 2016 Retrospective Cohort Control group of same age and same 4 sports	n = 281 with, concussion n = 1259 without concussion but with ankle injury, 20.0 ± 4.7 y/o, collegiate soccer, ice hockey, floorball and handball;	Concussion reported in patient data base; diagnosed in ED	No concussion reported in patient database	Repetitive concussion, ankle injuries	Additional injuries collected from an observation time of 24 months before and after initial concussion
Cross et al., 2016 Prospective Cohort No controlling reported	n = 150 with concussion, n = 666 without concussion, male, age not reported, highest level of club rugby	Team doctors diagnosed concussion based on clinical judgement supported by the SCAT V.2 or SCAT V.3	No diagnosis of concussion was made during the 2010/2013 or 2013/2014 seasons	Subsequent time loss injury, including recurrent concussion	Two rugby seasons
Delaney et al., 2000 Cross-Sectional survey Controlled for in analyses: Age, number of games played, total number of years playing, past concussions in and out of sport, past loss of consciousness in and out of sport, alcohol intake and other sports played	n = 69 with concussion, n = 85 without concussion, male, 27.2 ± 2.7 y/o, professional Canadian football players	Self-report questionnaire that inquired about past recognized concussions and symptoms of concussions	No concussion reported on self-report questionnaire	Repetitive concussions	One season of professional football, self-report questionnaire included information about participant's lifetime past medical history
Delaney et al., 2001 Cross-Sectional survey Controlled for in analyses: Age, number of games played, total number of years playing, past concussions in and out of sport, past loss of consciousness in and out of sport, alcohol intake and other sports played	n = 15 with concussion, n = 29 without concussion, male, 20.2 ± 1.9 y/o, university football players n = 25 with concussion, n = 27 without concussion, male & female, 20.6 ± 2.7 y/o, university soccer players	Self-report questionnaire that inquired about past recognized concussions and symptoms of concussions	No concussion reported on self-report questionnaire	Repetitive concussions	One season of university football and soccer, self-report questionnaire included information about participant's lifetime past medical history
Delaney et al., 2002 Cross-Sectional survey Controlled for in analyses: Age, number of games played, total number of years playing, past concussions in and out of sport, past loss of consciousness in and out of sport, alcohol intake and other sports played	n = 231 with concussion, n = 97 without, concussion, male, 21.1 ± 2.1 y/o, Canadian university football players n = 126 with concussion, n = 75 without concussion, male & female, 20.9 ± 2.0 y/o, Canadian university soccer players	Self-report questionnaire that inquired about past recognized concussions and symptoms of concussions	No concussion reported on self-report questionnaire	Repetitive concussions	One full year of football and soccer participation, self-report questionnaire included information about participant's lifetime past medical history

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Table 2 (*continued*)

Study	Participants (n, sex, age, specific sport or military)	Exposed Group (How previous concussion was determined & timeframe)	Comparator Group (how no previous concussion was determined)	Outcomes of injury included	Timeframe (period of observation for second injury)
Fino et al., 2017 Retrospective Matched Cohort Matched based on: sport, position, exposure/skill level, history of LE injury, age/height/weight Controlled for in analysis: previous LE injury	n = 110 with concussion, n = 110 without concussion, male & female, collegiate baseball, basketball, lacrosse, football, soccer, softball, swimming, tennis, wrestling, volleyball	Concussion reported in injury records, diagnoses made by team physician	No concussion reported in injury records in the previous 2 years	Acute LE injuries of hip, thigh, shank, foot, knee, ankle	Record review from August 2008 to February 2014; looked for acute LE injury 365 days pre/post-concussion.
Gilbert et al., 2016 Cross-sectional survey No controlling reported	n = 155 with concussion, n = 180 without concussion, 21.2 ± 1.4 y/o, collegiate sports: male & female, soccer, football, cheerleading, track & field, basketball, softball, women's volleyball, tennis, field hockey, women's lacrosse, women's swim/dive, baseball, golf, not listed.	21-item questionnaire pertaining to injuries experienced during the student athlete's collegiate career	21-item questionnaire pertaining to injuries experienced during the student athlete's collegiate career	Musculoskeletal injury including: lateral ankle sprain, knee injury, muscle strain	All data collected at one time, no period of observation, questionnaire inquired about lifetime past medical history
Guskiewicz et al., 2000 Prospective Cohort No controlling reported	n = 888 with concussion, n = 16,661 without concussion, male, age not reported, collegiate football	Concussion report completed by AT	No concussion report completed by AT	Recurrent concussion	Up to 3 years (1995–1997)
Guskiewicz et al., 2003 Prospective Cohort Controlled for in analysis: body mass index; academic year in school; years of organized football experience; division and playing position	n = 184 with concussion, n = 2721 without concussion, US collegiate football players	Concussion reported based on extensive health questionnaire and/or GSC	No concussion reported based on extensive health questionnaire or GSC	Recurrent concussions identified by AT	3 football seasons (1999–2001); players who sustained incident concussions were followed up for repeat concussions until completion of their collegiate football career or end of the 2001 season
Herman et al., 2017 Retrospective Matched Cohort Matched by sport, starting status, main position played	n = 90 with concussion, n = 52 males, n = 21 female, n = 148 without concussion, collegiate athletes: football, lacrosse, soccer, basketball	In-season concussion diagnosed by university primary care sports medicine certified MD, identified by training room-based surveillance data	No history of concussion based on training room-base injury surveillance data	First time LE MSI (sprain, strain, dislocation, rupture)	2006/2007 to 2012/2013 seasons, each exposed athlete was followed for 90 days following return to play
Hollis et al., 2009 Prospective Cohort Controlled in analyses: age, and exposure time	n = 313 with concussion, n = 2894 without concussion, 22.7 y/o, non-professional rugby players	Self-administered questionnaire	No history of concussion reported in self-administered questionnaire or mTBI identified during study period	Recurrent mTBI	Between 1 and 3 winter playing seasons (playing seasons are 20 weeks each) over a 3-year period
Houston et al., 2018 Cross-sectional No controlling reported	n = 115 with concussion, n = 353 without concussion, n = 200 males, n = 268 females, 19.5 ± 1.3 y/o, NCAA student athletes	Self-report injury history form	No history of concussion on self-report injury history form	Ankle sprains, knee injuries	All data collected at one time, no period of observation, questionnaire inquired about lifetime past medical history
Kardouni et al., 2018 Matched Prospective Cohort Controlled for history of lower extremity injury history by exclusion; controlled with matching on age, sex, rank, length of service, deployment status, and military career field	n = 11,522 concussion, n = 11,522 without concussion, 93.9% male, 6.1% female, 13.5% < 20 years old, 68.5% 20–29 years old, 14.5% 30–39 years old, 3.5% > 40 years old, active-duty Army soldiers	Concussions identified using ICD-9 codes 850.0, 850.1, 850.5, 850.9 (within 2 year timeframe)	No medical encounters for a head injury or concussion during the study period	Acute LE injuries	All soldiers were followed from the time of incident concussion or time of matching until the first of 1) a lower extremity injury, 2) loss to follow-up, or 3) the end of the 2-year follow up period
Krill et al., 2018 Prospective Cohort No controlling reported	n = 12 with concussion, n = 50 without concussion, incoming collegiate athletes	Injury identified based on the NCAA ISS and injury report completed by AT or MD	No concussions identified based on the NCAA Injury Surveillance System or injury report complete by team AT or MD	LE injuries	Fall regular football seasons between 2012 and 2016
Lynall et al., 2015 Matched Retrospective Cohort Controlled with matching on age, sex, sport, competition playing time, height and weight	n = 44 with concussion, n = 28 male, n = 16 female, age = 20 ± 1.2 y/o n = 58 without concussion; n = 39 male, n = 19 female, 20.5 ± 1.3 y/o	Concussions diagnosed by the university's sports medicine staff	Players had not experienced a concussion since arriving at the university, no concussion in EMR	Acute LE MSI	Data collected from Jan 1, 2010 to October 8, 2013, information about all injuries and illnesses was recorded for 365 d before the concussion and 365 d after return to activity from concussion for the

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Table 2 (*continued*)

Study	Participants (n, sex, age, specific sport or military)	Exposed Group (How previous concussion was determined & timeframe)	Comparator Group (how no previous concussion was determined)	Outcomes of injury included	Timeframe (period of observation for second injury)
Lynall et al., 2017 Retrospective Cohort Controlled in analysis: Number of previous concussions, number of previous lower extremity injuries, number of previous upper extremity injuries, total number of previous injuries, sport contact classification	n = 2004 with concussion, n = 16,212 without concussion, age not reported, 27 high school sports	Data collected from NATION; ATs recorded all concussions into EMR	Athlete did not have a concussion injury entered into the NATION database	Any LE injury, time loss LE injury, non-time loss LE injury	Data originated from 2011 to 2012, 2013–2014
Makdissi et al., 2009 Matched Prospective Cohort Controlled in matching on playing position, age and size	n = 138 with concussion, male, age = 24.0–25.3 y/o, Australian football players n = 138 without concussion, male, 24.1–25.2 y/o, Australian football players	Concussion diagnosed by team MD at time of injury	No diagnosis of concussion made during the study time period	Injury to LE, UE, or back and recurrent concussion	Up to 4 seasons (2000–2003)
Nordstrom et al., 2014 Prospective Cohort Controlled in analysis by number of injuries occurring in the previous year	n = 66 with concussion, male, age = 25.3 ± 4.2 y/o, professional European football n = 1599 without concussion, male, 26.2 ± 4.4 y/o, professional European football	Concussion report completed by AT, completed at time of suspected injury	No concussion report generated	Recurrent concussion, LE injuries, and other injuries	1-11 seasons (range, 2001/2002–2011/2012)
Nyberg et al., 2015 Prospective Cohort No controlling reported	n = 144 with concussion, n = 104 without concussion and with knee injury, age not reported, Swedish Ice Hockey Elite League players	Concussion reported in ISIS and diagnosed by team MD	No concussion reported in medical record review or reported in ISIS	Traumatic injuries including concussion and knee injury (MCL tear or knee distortion)	28 seasons (1984/1985 to 2011/2012), injured players followed for 42 days post return to play
Pietrosimone et al., 2015 Cross-Sectional survey Controlled in analysis by number of years in the NFL, BMI during time in NFL, and playing position	n = 1477 with concussion, n = 952 without concussion, male, age not reported, retired NFL players	The Health Survey of Retired NFL Players questionnaire, collected information related to number of concussions sustained during the NFL playing years	No history of concussion reported in the Health Survey of Retired NFL Players questionnaire	LE MSI	Survey mailed to participants between May 2001 and February 2002, players retired between 1930 and 2001, survey collected lifetime health information prior to retirement from the NFL
Schulz et al., 2004 Prospective Cohort Controlled in analyses by sport, body mass index, year and school, calendar time, school size, and highest educational attainment by head coach	n = 206 with concussion, n = 19,697 without concussion, male & female, age not reported, high school athletes in 13 sports	Demographic form completed at beginning of each season including questions related to the lifetime history of concussion	No history of concussion reported on demographic form completed at beginning of each season	Repetitive concussion	1996–1999, teams followed for three years, lifetime medical history reviewed
Selassie et al., 2013 Retrospective Cohort Controlled in analysis by mechanism of injury, age group, race, sex, SES, comorbid conditions, concomitant injuries, trauma facility level	n = 16,642 with sport-TBI, n = 4,707,081 without sport-TBI (estimated referent population of South Carolina at time of study), male & female age 0–65 + y/o, athletes, specific sports not provided	TBI cases identified through use of ICD-9-CM diagnosis codes 800–801, 803–804, 850–854 and 959.01	No history of TBI or concussion entered into the surveillance database	Severe sport-TBI	Data between 1998 and 2011 reviewed from statewide non-military hospital surveillance system
Tsao et al., 2017 Cross-Sectional Survey Controlled in analysis by blast impact score (based on number of blasts that moved the participant)	n = 1022 with concussion, n = 1590 without concussion, male, 19–50 y/o, Marines	14-item questionnaire that asked about number of concussions prior to and during current deployment, questionnaires reviewed by medical officers	No history of concussion reported on 14-item questionnaire	Subsequent concussion	Survey's completed between 2 weeks and 2 months following return from deployment from April 2010–June 2013, questionnaire addressed previous medical history

(*continued on next page*)

Table 2 (*continued*)

Study	Participants (n, sex, age, specific sport or military)	Exposed Group (How previous concussion was determined & timeframe)	Comparator Group (how no previous concussion was determined)	Outcomes of injury included	Timeframe (period of observation for second injury)
Whitehead et al., 2014 Retrospective Cohort Controlled for in analyses by sex, marital status, race, date of birth category, deployment status, education level, rank, career field, previous mishap status, and injury severity	n = 5065 with mTBI, n = 508,828 without mTBI, n = 409,074 male, n = 104,817 female, age < 32 to > 43 y/o, active duty airmen	Electronic personal data obtained from the DMDC for Airmen who had served on active duty for at least 180 days, cases of mTBI were identified using the ICD-9 codes and blinded medical record review by neurologist	No concussion reported in electronic personal data obtained from the DMDC for Airmen who had served on active duty for at least 180 days	Subsequent mTBI or other head injury, or UE or LE injury	Timeframe began on October 1, 2001, the date they entered active duty, or the date of mTBI or injury consistent with the reference category diagnosis, timeframe ended when they left active duty, had a documentable mishap, the day before a subsequent mTBI or other head injury or at the end of the study (September 20, 2008); whichever happened first
Zemper, 2003 Prospective Cohort study No controlling reported	n = 572 with concussion, n = 14,732 without concussion, male, age not reported, high &, college football players	AIMS ATs at each location completed a form indicating players with a history of concussion in the previous 5 years	No concussion reported in the medical history of each player	Subsequent concussion	Two football seasons over a two year period (1997–1998), history of concussion documented for 5 years prior to enrolling in the study

Legend: y/o: years old, SIMS: Sports Injury Monitoring System, LE: lower extremity, MSI: musculoskeletal injury, RTP: return to play, TBI: traumatic brain injury, DoD/VA: Department of Defense/Veterans Affairs, ED: emergency department, SCAT V.2: Sport Concussion Assessment Version 2, SCAT V.3: Sport Concussion Assessment Tool Version 3, AT: athletic trainer, MD: medical doctor, GSC: graded symptom checklist, MTBI: mild traumatic brain injury, ICD-9: International Classification of Diseases, Ninth Revision, ISS: injury surveillance system, NCAA: National Collegiate Athletic Association, d: days, UE: upper extremities, NATION: National Athletic Treatment, Injury, and Outcomes Network; EMR: electronic medical record, ISIS: International Sports Injury System, MCL: medial collateral ligament, NFL: National Football League, LCL: lateral collateral ligament, ACL: anterior cruciate ligament, PCL: posterior cruciate ligament, DMDC: Defense Manpower Data Center, AIMS: Athletic Injury Monitoring System.

3.3.1. Risk of any secondary injury

In service members and athletes, seventeen studies reported an odds ratio (OR) including 4,842,424 participants (Brooks et al., 2016; Kardouni et al., 2018; Tsao et al., 2017; Bryan, 2013; Delaney et al., 2000, 2001, 2002; Burman et al., 2016; Gilbert et al., 2016; Herman et al., 2017; Houston et al., 2018; Zemper, 2003; Lynall et al., 2017; Nyberg et al., 2015; Pietrosimone et al., 2015; Selassie et al., 2013; Guskiewicz et al., 2000). Results are presented in Table 3. The mean OR of those with a previous concussion sustaining a second injury is 2.55 (95%CI 1.85, 3.52) compared to those with no previous concussion (Fig. 2). Four studies reported a hazard ratio including a total of 538,822 participants (Kardouni et al., 2018; Whitehead et al., 2014; Fino et al., 2017; Nordstrom et al., 2014). The pooled hazard ratio (HR) for those with a previous concussion sustaining a secondary injury is 1.40 (95% CI 1.32, 1.48) compared to those with no previous concussion.

In athletes only, fourteen studies reported an OR including a total of 4,803,924 participants (Brooks et al., 2016; Delaney et al., 2000, 2001, 2002; Burman et al., 2016; Gilbert et al., 2016; Herman et al., 2017; Houston et al., 2018; Zemper, 2003; Lynall et al., 2017; Nyberg et al., 2015; Pietrosimone et al., 2015; Selassie et al., 2013; Guskiewicz et al., 2000). Considering the odds of all injury in athletes, the mean OR of those with a previous concussion sustaining a second injury is 2.75 (95%CI 1.90, 3.98) compared to athletes with no history of concussion. Two studies reported a HR including a total of 1885 participants (Fino et al., 2017; Nordstrom et al., 2014). The pooled HR for a second injury is 1.69 (95% CI 1.29, 2.20) in athletes with a history of concussion compared to athletes with no history of concussion. Seven studies reported a rate ratio including a total of 27,271 athletes (Guskiewicz et al., 2003; Krill et al., 2018; Lynall et al., 2015; Cross et al., 2016; Hollis et al., 2009; Schulz et al., 2004; Makdissi et al., 2009). The pooled rate ratio (RR) for athletes with a previous concussion sustaining a secondary injury is 1.72 (95%CI 1.49, 1.98) compared to those with no previous concussion.

In service members only, three studies reported an odds ratio including a total of 25,817 participants (Kardouni et al., 2018; Tsao et al., 2017; Bryan, 2013). The mean OR for service members with a previous concussion sustaining a secondary injury is 1.54 (95%CI 1.07, 2.21) compared to those with no previous concussion. Two studies reported a HR with a total of 536,937 service members (Kardouni et al., 2018; Whitehead et al., 2014). The pooled HR for any injury is 1.39 (95% CI 1.31, 1.47) for those with a previous concussion compared to no previous concussion.

3.3.2. Risk of secondary concussion

For the meta-analysis describing risk of concussion in service members and athletes with and without a history of a concussion, seven studies reported an OR including a total of 36,400 participants (Tsao et al., 2017; Bryan, 2013; Delaney et al., 2000, 2001, 2002; Zemper, 2003; Guskiewicz et al., 2000). Results are presented in Table 4. The summary estimate of those with a previous concussion sustaining a secondary concussion is 3.73 (95%CI 2.41, 5.78) compared to those with no history of concussion.

In athletes only, five studies reported an OR including a total of 33,627 participants (Delaney et al., 2000, 2001, 2002; Zemper, 2003; Guskiewicz et al., 2000). This analysis revealed the mean OR of athletes with a previous concussion sustaining a secondary concussion is 4.44 (95%CI 2.90, 6.79) compared to athletes with no history of concussion. Three studies reported a rate ratio including a total of 26,015 participants (Guskiewicz et al., 2003; Hollis et al., 2009; Schulz et al., 2004). The pooled RR for athletes with a previous concussion sustaining a secondary concussion is 1.97 (95%CI 1.47, 2.63) compared to those with no previous concussion.

In service members only, two studies reported an odds ratio including a total of 2773 participants (Tsao et al., 2017; Bryan, 2013). The pooled OR for service members with a previous concussion

Table 3
Meta-analyses for risk of any injury.

Outcome	Included studies (n)	Participants (n)	I-Square	Summary Estimate (95% CI)
Summary Estimate: Odds Ratio				
Any injury	17, (Brooks et al., 2016; Kardouni et al., 2018; Tsao et al., 2017; Bryan, 2013; Delaney et al., 2000, 2001, 2002; Burman et al., 2016; Gilbert et al., 2016; Herman et al., 2017; Houston et al., 2018; Zemper, 2003; Lynall et al., 2017; Nyberg et al., 2015; Pietrosimone et al., 2015; Selassie et al., 2013; Guskiewicz et al., 2000)	Athletes and Military Concussion = 35,559 No concussion = 4,806,865	95.95	2.55 (1.85, 3.52)
Any injury	14 (Brooks et al., 2016; Delaney et al., 2000, 2001, 2002; Burman et al., 2016; Gilbert et al., 2016; Herman et al., 2017; Houston et al., 2018; Zemper, 2003; Lynall et al., 2017; Nyberg et al., 2015; Pietrosimone et al., 2015; Selassie et al., 2013; Guskiewicz et al., 2000)	Athletes Concussion = 22,876 No concussion = 4,781,048	94.38	2.75 (1.90, 3.98)
Any injury	3 (Kardouni et al., 2018; Tsao et al., 2017; Bryan, 2013)	Military Concussion = 12,683 No concussion = 13,134	74.81	1.54 (1.07, 2.21)
Summary Estimate: Hazard Ratio				
Any injury	4 (Kardouni et al., 2018; Whitehead et al., 2014; Fino et al., 2017; Nordstrom et al., 2014)	Athletes and Military Concussion = 16,763 No concussion = 522,059	2.62	1.40 (1.32, 1.48)
Any injury	2 (Fino et al., 2017; Nordstrom et al., 2014)	Athletes Concussion = 176 No concussion = 1709	0.00	1.69 (1.29, 2.20)
Any injury	2 (Kardouni et al., 2018; Whitehead et al., 2014)	Military Concussion = 16,587 No concussion = 520,350	7.15	1.39 (1.31, 1.47)
Summary Estimate: Rate Ratio				
Any injury	7 (Guskiewicz et al., 2003; Krill et al., 2018; Lynall et al., 2015; Cross et al., 2016; Hollis et al., 2009; Schulz et al., 2004; Makdissi et al., 2009)	Athletes Concussion = 1047 No concussion = 26,224	0.00	1.72 (1.49, 1.98)

sustaining a secondary concussion is 1.88 (95%CI 1.43, 2.48) compared to those with no previous concussion.

3.3.3. Risk of extremity injury

Across all studies, three studies reported a hazard ratio for risk of extremity injury (upper or lower) in service members and athletes with a total of 537,157 participants (Kardouni et al., 2018; Whitehead et al., 2014; Fino et al., 2017). Results are presented in Table 5. The mean HR is 1.61 (95% CI 1.25, 2.06) for an extremity injury in those with a concussion compared to those with no previous concussion. In service members only, two studies reported on risk of upper and lower extremity injuries with a total of 536,937 participants (Kardouni et al., 2018; Whitehead et al., 2014). The mean HR is 1.60 (95% CI 1.16, 2.21) for an extremity injury for those with a concussion compared to those with no previous concussion.

Looking specifically at lower extremity injuries in military members and athletes, seven studies reported an OR including a total of 44,999 participants (Brooks et al., 2016; Kardouni et al., 2018; Gilbert et al., 2016; Herman et al., 2017; Houston et al., 2018; Lynall et al., 2017; Pietrosimone et al., 2015). The summary estimate of those with a previous concussion sustaining a lower extremity injury is 1.60 (95%CI 1.32, 1.94) compared to those with no previous concussion. Two studies reported a HR for service members and athletes with 23,264 participants (Kardouni et al., 2018; Fino et al., 2017). The pooled HR for lower extremity injury is 1.39 (95% CI 1.31, 1.47) compared to those with no previous concussion.

Considering lower extremity injury in athletes only, six studies reported an OR including a total of 21,955 participants (Brooks et al., 2016; Gilbert et al., 2016; Herman et al., 2017; Houston et al., 2018; Lynall et al., 2017; Pietrosimone et al., 2015). The mean OR of those

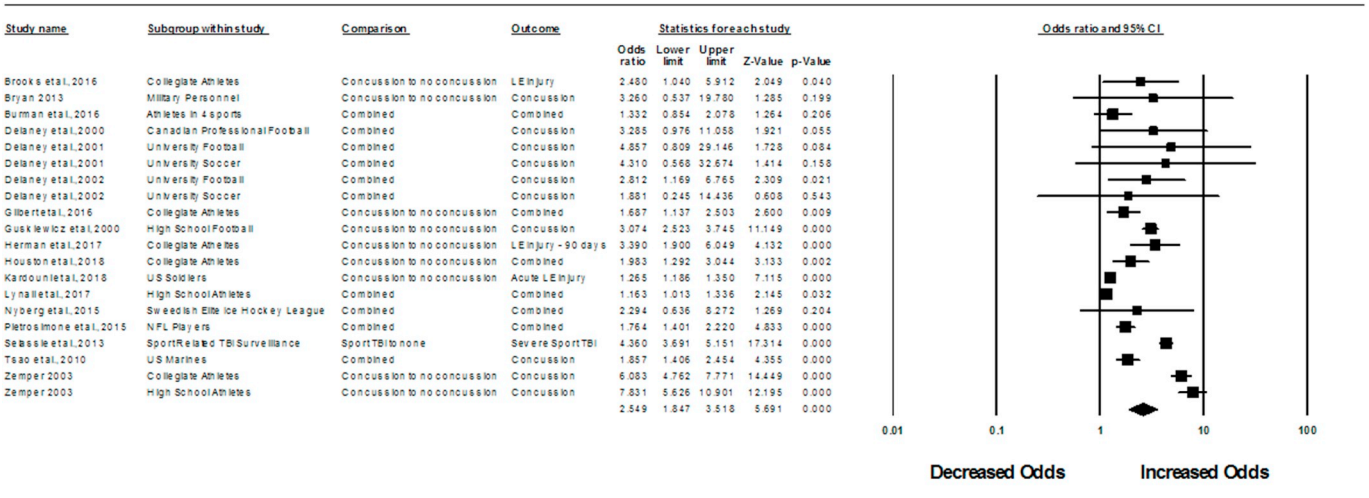

Fig. 2. Meta Analysis for odds ratios of any injury in service members and athletes, referent group: no concussion.

with a history of concussion sustaining a lower extremity injury is 1.82 (95% CI 1.34, 2.47) compared to athletes with no history of a concussion. Two studies reported a rate ratio including a total of 164 participants (Krill et al., 2018; Lynall et al., 2015). The pooled RR for athletes with a previous concussion sustaining a lower extremity injury was 1.74 (95%CI 1.16, 2.62) compared to those with no previous concussion.

3.3.4. Risk of bias across studies

Visual inspection of the funnel plots for risk of all injury by exposure status revealed low potential for risk of publication bias (for odds ratio, rate ratio, and hazard ratio). Upon additional inspection of the meta-analysis quantifying overall odds ratio, publication bias was not identified using Begg and Mazumdar's rank correlation (tau = 0.00; p-value = 1.0). The fail-safe N revealed that an additional 2443 studies with a null effect would have to be identified to bring the results obtained here to the null. Upon additional inspection of the meta-analysis quantifying rate ratio, publication bias was not identified using Begg and Mazumdar's rank correlation (tau = 0.21; p-value = 0.46). The fail-safe N revealed that an additional 92 studies with a null effect would have to be identified to bring the results obtained here to the null. Finally, with inspection of the meta-analysis quantifying hazard ratio, publication bias was not identified using Begg and Mazumdar's rank correlation (tau = 0.00; p-value = 1.00). The fail-safe N revealed that an additional 91 studies with a null effect would have to be identified to bring the results obtained here to the null. Based on these assessments, it is very unlikely that publication bias accounts for the results reported here.

4. Discussion

4.1. Summary of evidence

This systematic review and meta-analysis included 27 studies of good (n = 15) or acceptable (n = 11) methodological quality and only one with low methodological quality according to the Q-Coh II. In addition, it does not appear that risk of bias across studies accounts for the results obtained. The meta-analyses varied greatly in the amount of heterogeneity between the included studies, requiring nine to be completed as random effects and eight to be completed as fixed effects models. Accounting for these factors, it is believed that this review presents summary estimates of what has been published on this topic with low overall of bias.

Across the 17 meta-analyses completed, the results revealed significantly increased risk of all injuries; concussion; any extremity injury, and lower extremity injuries in service members and athletes with a history of concussion when compared to those with no history of concussion. This significant increase in risk is apparent when looking at odds of injury; time to event data (hazard), and rate of injury based on number of exposures.

Looking at pooled point estimate for the odds of injury in both populations, the odds of any injury is 2.55 times higher; the odds of a secondary concussion is nearly 3.73 times higher; and for lower extremity injury only, the odds of those with a history of concussion sustaining a lower extremity injury is 1.60 to those without a history of a concussion. In athletes only, the odds of any injury is 2.75 times higher; the odds of concussion is 4.44 times higher; and the odds of lower extremity injury is 1.82 for athletes with a history of concussion compared to those with no history of a concussion. This finding of increased odds of lower extremity injury is in line with the results of a recent systematic review and meta-analysis which reported the odds of any musculoskeletal injury is 2.11 (95%CI 1.46, 3.06) in athletes with a history of sports-related concussion is compared to athletes without a history of sports-related concussion (McPherson et al., 2018). In service members only, the odds of any injury is 54% higher and the odds of a secondary concussion (or mild TBI) is 88% higher in those with a history of a concussion compared to those without.

Summarizing the combined time-to-event data (reported as the pooled point estimate of hazard ratios) for all injuries in both populations, those with a history of concussion were injured nearly 40% sooner in military or sport contexts respectively within the timeframe of study. For upper or lower extremity injury, those with a history of concussion were injured nearly 61% sooner during the time of study than those without a history of a concussion. For lower extremity injury only, those with a history of concussion were injured nearly 39% sooner during the time of study than those without a history of a concussion.

Finally, looking at rate of injury (reported as the pooled point estimate rate ratios), among athletes only, there is a 72% higher rate of injury per 1000 athlete exposures for all injuries in those with a history of a concussion than those without a history of a concussion. The rate of concussion is 97% greater and the rate of lower extremity injury is 74% higher per 1000 athlete exposures in individuals with a history of concussion compared to those without a history of a concussion.

4.2. Potential risk contributors

Across the studies included in this review, the reasons suggested for the increased incidence of subsequent injury after concussion vary and include: differences in injury recall and reporting behaviors (Delaney et al., 2000, 2001, 2002),and individual propensities for injury (i.e. risk taking behavior and being injury prone) (Burman et al., 2016; Houston et al., 2018; Schulz et al., 2004; Nordstrom et al., 2014). While the behavioral mechanisms certainly may account for some of the association, it is difficult to believe that across 27 studies in different ages,

Table 4
Meta-analyses for risk of concussion.

Outcome	Included Studies	Participants	I-Square	Summary Estimate (95% CI)
Summary Estimate: Odds Ratio				
Concussion	7 (Tsao et al., 2017; Bryan, 2013; Delaney et al., 2000, 2001, 2002; Zemper, 2003; Guskiewicz et al., 2000)	Athletes and Military Concussion = 3087 No concussion = 33,313	85.80	3.73 (2.41, 5.78)
Concussion	5 (Delaney et al., 2000, 2001, 2002; Zemper, 2003; Guskiewicz et al., 2000)	Athletes Concussion = 1926 No concussion = 31,701	78.76	4.44 (2.90, 6.79)
Concussion	2 (Tsao et al., 2017; Bryan, 2013)	Military Concussion = 1161 No concussion = 1612	0.00	1.88 (1.43, 2.48)
Summary Estimate: Risk Ratio				
Concussion	3 (Guskiewicz et al., 2003; Hollis et al., 2009; Schulz et al., 2004)	Athletes Concussion = 703 No concussion = 25,312	0.00	1.97 (1.47, 2.63)

Table 5
Meta-analyses for risk of Extremity Injury.

Outcome	Included Studies	Participants	I-Square	Summary Estimate (95% CI)
Summary Estimate: Odds Ratio				
Lower extremity injury	7 (Brooks et al., 2016; Kardouni et al., 2018; Gilbert et al.,2016; Herman et al., 2017; Houston et al., 2018; Lynall et al., 2017; Pietrosimone et al., 2015)	Athletes and Military Concussion = 15,450 No concussion = 29,549	78.54	1.60 (1.32, 1.94)
Lower extremity injury	6 (Brooks et al., 2016; Gilbert et al., 2016; Herman et al., 2017; Houston et al., 2018; Lynall et al., 2017; Pietrosimone et al., 2015)	Athletes Concussion = 3928 No concussion = 18,027	79.78	1.82 (1.34, 2.47)
Summary Estimate: Hazard Ratio				
Lower extremity injury	2 (Kardouni et al., 2018; Fino et al., 2017)	Athletes and Military Concussion = 11,632 No concussion = 11,632	0.00	1.39 (1.31,1.47)
Summary Estimate: Hazard Ratio				
Upper or lower extremity injury	3 (Kardouni et al., 2018; Whitehead et al., 2014; Fino et al., 2017)	Athletes and Military Concussion = 16,697 No concussion = 520,460	75.55	1.61 (1.25, 2.06)
Upper or lower extremity injury	2 (Kardouni et al., 2018; Whitehead et al., 2014)	Military Concussion = 16,587 No concussion = 520,350	86.72	1.60 (1.16, 2.21)
Summary Estimate: Rate Ratio				
Lower extremity injury	2 (Krill et al., 2018; Lynall et al., 2015)	Athletes Concussion = 56 No concussion = 108	0.00	1.74 (1.16, 2.62)

populations, contexts, and study designs, behavior is the only factor contributing to the apparent increased risk.

A secondary postulate for the association between concussion and secondary injury that has been suggested is residual physiological effects from a primary concussion, mainly deficits in neurocognition and neuromotor control (Brooks et al., 2016; Kardouni et al., 2018; Herman et al., 2017; Cross et al., 2016; Pietrosimone et al., 2015), as well as sensorimotor control (McPherson et al., 2018). It is known that the immediate effects of concussion frequently include functional disturbances of these systems (Hides et al., 2017; Alsalaheen et al., 2010; Reneker et al., 2018). Research findings have identified objectively measured deficits in vestibular, visual, and proprioception senses as well as postural and oculomotor control systems after a concussion (Leddy et al., 2015; Yorke et al., 2017; Doherty et al., 2017). In studies of athletes, despite symptomatic recovery, medical clearance, and return-to-sport, research findings have reported that sub-clinical deficits in function remain long after an athlete is returned to the playing field (Cavanaugh et al., 2005; Fino, 2016; Meier et al., 2017).

These studies provide evidence of persistent disturbances in those judged fit for return to normal activity which could negatively impact agility and reaction, leading to increased risk of injury.

4.3. Implications for practice and research

Physical therapy may offer some solutions to mitigate the risk demonstrated here. A recent clinical trial has demonstrated the effectiveness of physical therapy interventions after concussion during the acute phase of recovery for those with a complaint of dizziness (Reneker et al., 2017). Together with observational data, it is now believed that individualized oculomotor, vestibular, and manual therapies are effective for attaining recovery from the functional deficits associated with concussion (McCrory et al., 2017). The diffusion of innovation has not yet resulted in the adoption of this as standard of care in clinical management post-concussion.

It is possible that all people who sustain a concussion would benefit from examination and individually tailored active intervention directed towards sensorimotor and neuromotor deficits (as indicated), but it is a bit premature to reach this conclusion. Consideration should be given to the establishment of rigorous physical performance criteria (including speed, agility, and reaction time) for all athletes and service members to meet after attainment of medical clearance and prior to return to play/duty to "test" fitness for performance, potentially identifying deficits which could then be addressed. Until the reasons for the increased risk of injury after a primary concussion are well understood and effective strategies to attenuate this risk are developed, healthcare providers need to educate and inform coaches, parents and athletes; and military officers and service members regarding the increased risk of injury after a concussion.

Original research describing differences in injury risk between athletes and service members who did and did not receive adjunctive physical therapy after a concussion, exactly what types of rehabilitation treatments were utilized, and the timeframe for delivery of such treatment, could reveal the effectiveness of specific interventions for tertiary prevention.

4.4. Limitations

The electronic search terms were limited in their effectiveness of identifying all relevant articles as evidenced by the seven additional articles identified through other methods. Thorough hand searching of the included studies was utilized to identify additional relevant articles and while it is possible that other literature exists, the authors attempted to be exhaustive in their search. It is believed that this review includes the breadth of available published full-text literature on this topic (published in English).

Secondarily, although several studies did control for known confounders through matching or through statistical procedures, several of the included studies did not control for any confounders. Therefore, it is possible that risk estimates are overly attributed to concussion. Alternatively, it is unknown if any of the participants in the studies included in this review received adjunctive rehabilitation therapies after their primary concussion. Therefore, it is also not known if the increased risk of secondary injury demonstrated here represents natural history alone or if this risk is moderated in any way by therapeutic rehabilitative treatment.

An additional limitation is the diagnosis of concussion itself. There continues to be no gold standard for definitive affirmative diagnosis of

concussion. Establishing a diagnosis necessitates assessment of a range of brain functions by an adequately trained medical professional (McCrory et al., 2017; McCrea et al., 2017). Additionally, it is well established that under reporting of concussion is common (specifically in sports environments) (Baugh et al., 2019). Self-reported history of concussion, even using a standardized definition, also carries the possibility of mis-classification (Wojtowicz et al., 2017). Given these universal difficulties with establishing a definitive concussion or non-concussion exposure status and the differences between the included studies in how exposure status was determined, it is possible that the true effect of a previous concussion on risk of injury is different (either larger or smaller) than the results presented here. Considering these limitations however, in light of the large number of studies included, the agreement across studies of an increased risk (although variable in size) of injury for those with a history of concussion, and the low risk of publication bias identified, we believe that the overall finding of increased injury risk is supported.

Finally, because all observational designs were permitted in this review, there were nine cross-sectional studies included. It is well accepted that cross-sectional studies do not permit temporality between exposure and outcome, therefore only association from the ORs can be inferred (Setia, 2016). This is, however, balanced with the time-to-event summary measures which came from studies that were prospective or retrospective in nature. To check for the presence of overestimation of the summary effect by including cross-sectional studies, three exploratory meta-analyses were run (results not presented) with the removal of all cross-sectional studies on each outcome: odds of any injury, odds of concussion and odds of extremity injury. All three analyses revealed similar effect magnitude and significant associations between a history of concussion and odds of injury. Additionally, the use of random effects models, where indicated (which are inherently more conservative), assists in ensuring less chance for a bias and a more correct metric of the true relationship.

5. Conclusion

The results of this review describe injury risk estimates in service members and athletes with and without a history of concussion. Across odds, hazard, and rate estimates, all revealed significantly increased risk for injury (including secondary concussion and extremity injury) in those with a history of concussion when compared to those with no history of concussion. While the reasons for the increased risk of injury are not yet understood, there are potentially behavioral attributes as well as motor control deficits that contribute to these relationships. Outcomes research describing injury risk after specific types of rehabilitation post-concussion could reveal whether specific interventions are effective and decrease risk of subsequent injury.

Conflicts of interest

None declared.

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