Examining later-in-life health risks associated with sport-related concussion and repetitive head impacts: a systematic review of case-control and cohort studies

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjsports-2023-106890).

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Accepted 26 April 2023

To cite: Iverson GL, Castellani RJ, Cassidy JD, *et al. Br J Sports Med* 2023;**57**:810–824.

ABSTRACT

Objective Concern exists about possible problems with later-in-life brain health, such as cognitive impairment, mental health problems and neurological diseases, in former athletes. We examined the future risk for adverse health effects associated with sport-related concussion, or exposure to repetitive head impacts, in former athletes.

Design Systematic review.

Data sources Search of MEDLINE, Embase, Cochrane, CINAHL Plus and SPORTDiscus in October 2019 and updated in March 2022.

Eligibility criteria Studies measuring future risk (cohort studies) or approximating that risk (case-control studies).

Results Ten studies of former amateur athletes and 18 studies of former professional athletes were included. No postmortem neuropathology studies or neuroimaging studies met criteria for inclusion. Depression was examined in five studies in former amateur athletes, none identifying an increased risk. Nine studies examined suicidality or suicide as a manner of death, and none found an association with increased risk. Some studies comparing professional athletes with the general population reported associations between sports participation and dementia or amyotrophic lateral sclerosis (ALS) as a cause of death. Most did not control for potential confounding factors (eg, genetic, demographic, health-related or environmental), were ecological in design and had high risk of bias.

Conclusion Evidence does not support an increased risk of mental health or neurological diseases in former amateur athletes with exposure to repetitive head impacts. Some studies in former professional athletes suggest an increased risk of neurological disorders such as ALS and dementia; these findings need to be confirmed in higher quality studies with better control of confounding factors.

PROSPERO registration number CRD42022159486.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Survey studies reveal that some former contact and collision sport athletes report difficulties with cognitive functioning and mental health.
⇒ Some cross-sectional studies of former contact and collision sport athletes, compared with control subjects, have identified changes in brain structure, physiology or biochemistry.
⇒ Some death certificate studies of former professional soccer and American-style football players have reported associations between amyotrophic lateral sclerosis (ALS) and dementia as a cause of death and participation in sports.

INTRODUCTION

There is considerable interest, and concern, about possible problems with later-in-life brain health, such as cognitive impairment, mental health problems and neurological diseases, in former athletes who have sustained concussions and repetitive head impacts during participation in youth and adult sports. Later-in-life health, in this context, refers to many years or decades after athletes' participation in sports. Several systematic reviews on this topic have been published over the past 5 years.[1–13] The two primary exposure variables of interest in this steadily growing literature have been sport-related concussions (SRC) and exposure to repetitive head impacts.[14] Of note, most studies estimate exposure to repetitive head impacts by the number of years of participation in contact or collision sports, although some studies take additional factors such as position played into account when estimating exposure to repetitive head impacts.

Problems with later-in-life brain health usually refer to the development of psychiatric conditions, such as a depressive disorder or suicidality, and neurological or neurodegenerative disorders or diseases such as Alzheimer's disease or other causes of dementia, Parkinson's disease and amyotrophic lateral sclerosis (ALS).[13] It can also refer to mental health problems or cognitive decline[15] but not to the point of meeting clinical criteria for a disorder or disease per se. Other topics of interest include changes in brain structure, physiology or biochemistry that are quantifiable using neuroimaging,[12 16 17] the accumulation of pathological

WHAT THIS STUDY ADDS

- ⇒ The case-control and cohort studies included in this review suggest that (i) former amateur athletes are not at increased risk for depression or suicidality, (ii) former professional soccer players are not at increased risk for psychiatric hospitalisation and (iii) former professional American-style football and soccer players are not at increased risk for mortality from psychiatric disorders or suicide.
- ⇒ The studies included suggest that men who participated in amateur sports are not at increased risk for cognitive impairment, neurological disorders or neurodegenerative diseases compared with men from the general population.
- ⇒ In contrast, studies of men who participated in professional sports reported an association with neurological diseases (eg, ALS) and dementia in former professional American-style football players and professional soccer players.
- ⇒ Well-designed case-control and cohort studies with better control of confounding factors, including genetic, demographic and environmental factors, are needed to determine if these associations are causal.
- ⇒ We did not identify any published case-control or cohort studies that (i) examined age of first exposure to sports-related head impacts and later-in-life health risks, (ii) used neuroimaging as an outcome, (iii) examined later-in-life risks for women or (iv) were considered postmortem cohort studies of chronic traumatic encephalopathy neuropathological change.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ There are many methodological factors to consider when studying whether there is an association between concussions or participation in sports during adolescence and early adulthood and the development of neurological conditions or neurodegenerative diseases much later in life.
- ⇒ These include genetic, demographic, health and environmental factors, socioeconomic status and social determinants of health, alcohol use and substance abuse disorders, obstructive sleep apnoea, cardiovascular disease, peripheral vascular disease and cognitive reserve.
- ⇒ Future well-designed case-control and cohort studies that include more careful control of confounding factors are urgently needed.

protein surrogates during life using positron emission tomography[18–22] and pathological protein aggregates after death using immunohistochemistry.[23–26]

Chronic traumatic encephalopathy

There are a number of case series and cross-sectional studies related to postmortem neuropathological changes in former contact, collision and combat sport athletes in the past 17 years,[23–30] and many recent reviews of the literature relating to chronic traumatic encephalopathy (CTE).[4 17 29 31–57] Historically, chronic traumatic brain injury in boxers was described as a clinical condition using terms like punch drunk,[58] dementia pugilistica,[59] traumatic encephalopathy of pugilists[60] and CTE.[61 62] In recent years, CTE has been described as a neuropathological entity,[26 63] with the defining feature (ie, the 'pathognomonic' lesion), based on the updated 2021 consensus criteria, described as 'p-tau aggregates in neurons, with or without thorn-shaped astrocytes, at the depth of a sulcus around a small blood vessel, deep in the parenchyma and not restricted to the subpial or superficial region of the sulcus' (p. 217).[64] We refer to the postmortem neuropathology as CTE neuropathological change (CTE-NC).

CTE-NC is a postmortem diagnosis by means of neuropathological examination. The clinical phenotype (ie, clinical presentation) associated with CTE-NC during life has not been determined. In 2021, the first consensus criteria for traumatic encephalopathy syndrome (TES) were published.[65] This consensus effort was sponsored by the National Institute of Neurological Disorders and Stroke (NINDS). A personal history of substantial exposure to repetitive head impacts is required before considering a clinical diagnosis. The consensus group emphasised that the diagnosis of TES required cognitive impairment, neurobehavioural dysregulation or both—and the condition must have a progressive course. These new criteria need to be validated through diagnostic studies.

Neuroimaging, surveys and neuropsychological studies

Cross-sectional neuroimaging studies have examined differences between former professional athletes and control subjects in neurochemistry, as measured by magnetic resonance spectroscopy[66 67]; neurophysiology, as measured by functional MRI[68 69]; microstructure, as measured by diffusion weighted imaging[70–72] and macrostructure.[73–80] Differences between former athletes and control subjects have been reported in some studies using each of these imaging modalities. The imaging findings are heterogeneous, and systematic reviews of these studies have encouraged more refined work to better understand the associations between the imaging findings and clinical outcomes.[2 12]

Survey studies, with and without control groups, have examined self-reported symptoms of depression,[81–87] cognitive impairment[15 84 88 89] and symptoms of TES.[90] These studies reveal that some former athletes report significant difficulties with cognitive functioning[15 89 91 92] and mental health.[15 93–95] In a recent survey, more than one-third of former National Football League (NFL) players reported being 'extremely concerned' about memory problems, their thinking skills and/or developing CTE.[96] Another survey of former NFL players found that modifiable factors, such as depression, anxiety, pain, physical impairment, sleep apnoea and lack of exercise were associated with impairment in cognition-related quality of life.[97]

There are also cross-sectional studies involving objective neuropsychological testing, with and without control groups.[6 7 98 99] Systematic reviews relating to the literature on neuropsychological outcomes have concluded that former contact, collision and combat sport athletes perform, on average, more poorly on cognitive testing than control participants.[5–7] These reviews have also concluded that the general quality of the evidence was low, and high-quality case-control and cohort studies are needed.

Research designs needed to examine risk for future health problems

There is a large and steadily growing body of cross-sectional studies on problems with brain health, broadly defined, in former amateur and professional athletes, and these studies have been the focus of multiple past narrative and systematic reviews.[1–13 29 31 34 37–41 47 49 50 53 55 100 101] Case series are often the first type of study to appear when investigating new entities that may not have an established clinical diagnostic phenotype in living patients and may only have a pathological definition, such as is currently the case with CTE-NC.[63 64] Survey studies are important because they illustrate how common it is for a group to have certain health problems, such as depression, and they can describe factors associated with those health problems. These types of studies are important because they raise hypotheses to be investigated in future cohort and case-control studies. However, because they are a snapshot in time and include only prevalent cases, they should not be used to infer causation.[102] Case series and cross-sectional studies are not designed to examine causal relationships, but they help us direct efforts to examine these issues in more rigorous study designs.[103 104] The Concussion in Sport Group consensus paper, published in 2017, emphasised the importance of future well-designed case-control and cohort studies for testing causal hypotheses.[105] Moreover, the authors of recently published narrative and systematic reviews have emphasised the need for better designed epidemiological studies that can assess risk of disease and problems with later-in-life brain health, such as cohort and case-control studies, to further understand possible risks associated with SRC and exposure to repetitive head impacts.

Purpose of this review

We designed this systematic review to examine future risk for possible adverse health effects associated with single and multiple SRC, or exposure to repetitive head impacts, during participation in sports. Our a priori focus was on studies that can measure future risk (cohort studies) or approximate that risk (case-control studies). Relying on those types of studies, our two primary questions for this review were: (i) what are the possible long-term effects of single and multiple SRC and (ii) what are the possible long-term effects of exposure to contact sports and/or repetitive head impacts? Subquestions relating to these primary questions were as follows: (i) is the age at commencement of contact sport associated with long-term outcomes; (ii) what is the risk of developing either neurological or neurodegenerative diseases in athletes after SRC and (iii) what is the risk of developing either neurological or neurodegenerative diseases in athletes after exposure to contact sports and/or repetitive head impacts?

METHODS

The following databases were searched: MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (via Ovid), Embase (via Ovid), Cochrane Central Register of Controlled Trials (via Ovid), Cochrane Database of Systematic Reviews (via Ovid), CINAHL Plus with Full Text (via EBSCO) and SPORTDiscus with Full Text (via EBSCO). The initial search was conducted in October 2019 and a top-up search was run in March 2022 (PROSPERO registration: CRD42022159486). The search strategies for all databases are available in the online supplemental file. The Medline search is annotated to provide a search narrative, outlining the different components of the systematic search.[106] See the online supplemental material for more information relating to the search strategy and search terms.

Study eligibility

Studies were eligible for inclusion if they were: (i) original research in humans (cohort and case-control studies); (ii) included former athletes and examined repetitive head impacts or SRC; (iii) evaluated incidence/prevalence, risk factors or causation related to brain health, such as neurodegenerative disease and (iv) evaluated potential long-term sequelae (defined as ≥5 years after sports-related injury or participation in sports). Studies were excluded if they were: (i) review articles, commentaries, editorials, case studies, case series or cross-sectional studies; (ii) not related to former athletes and/or SRC or (iii) conducted <5 years following concussion or participation in sports.

The authors designed this review to search the literature for research designs that could measure future risk to former athletes (ie, cohort studies) or approximate that risk (ie, case-control studies). In cohort studies, an exposed and an unexposed group from a representative sample or population of 'persons at risk' are followed through time to the outcome. In a prospective cohort study, data are collected into the future. In a retrospective cohort study, the data already exist for other reasons (eg, health registries and health administrative data). The incidence of the disease is then compared between the exposed and unexposed groups, producing a relative risk. In a case-control study, cases of the disease of interest are collected first, and their past exposure status is compared with a control group of similar subjects. Case-control studies are retrospective by design and the relative risk is approximated by the odds of exposure in the cases divided by the odds of exposure in the controls. The resulting OR approximates the relative risk in a well-designed case-control study.

Study selection

A rapid screen was completed by one author (GMS) to remove citations that were clearly irrelevant to the review (ie, non-human research, opinion papers, conference proceedings, etc). For all screening, data extractions and risk of bias assessments, reviewers independently completed each phase and to capture both methodological quality and content expertise, one designated methods author and one content expert coauthor were paired. For the title and abstract screen, inter-rater agreement was assessed by authors completing 50 randomly selected citations with an acceptable level of 80% agreement. The title and abstract screenings were then completed by pairs of two authors independently (RJC, JDC, KJS, GMS). Conflicts were settled by a third author. Combinations of two authors independently reviewed the articles for the full-text screen (RJC, JDC, GMS). Any disagreements resulted in engagement of a third author who also completed the full-text screen and a meeting between the three authors was held to come to a final decision.

Risk of bias

Risk of bias was investigated using a modified version of the SIGN criteria for cohort and case-control studies.[107] These criteria prompt the reviewer to examine the methodology of the study in detail, including the purpose, selection of subjects, attrition, measurement bias, observer bias, control of confounding factors and statistical methods. Teams of two reviewers (GMS, GLI, JDC, RJC, RJE, KJS), one methods author and one content expert coauthor completed these forms on each paper and came to consensus on risk of bias before presenting to the larger group of authors for consideration and final rating of each study.

Equity, diversity and inclusion statement

All eligible studies were included in this systematic review, and no exclusions were applied relating to sex, gender, race, ethnicity, socioeconomic status, social determinants of health or representation from marginalised groups. The author team included 12 men and 3 women; all mid-career or senior in their careers; from North America, Europe and Africa; with education, training and expertise in diverse medical and scientific disciplines.

RESULTS

The search identified 14 813 records (figure 1). After duplicate removal, 7512 underwent rapid title screening and 1318

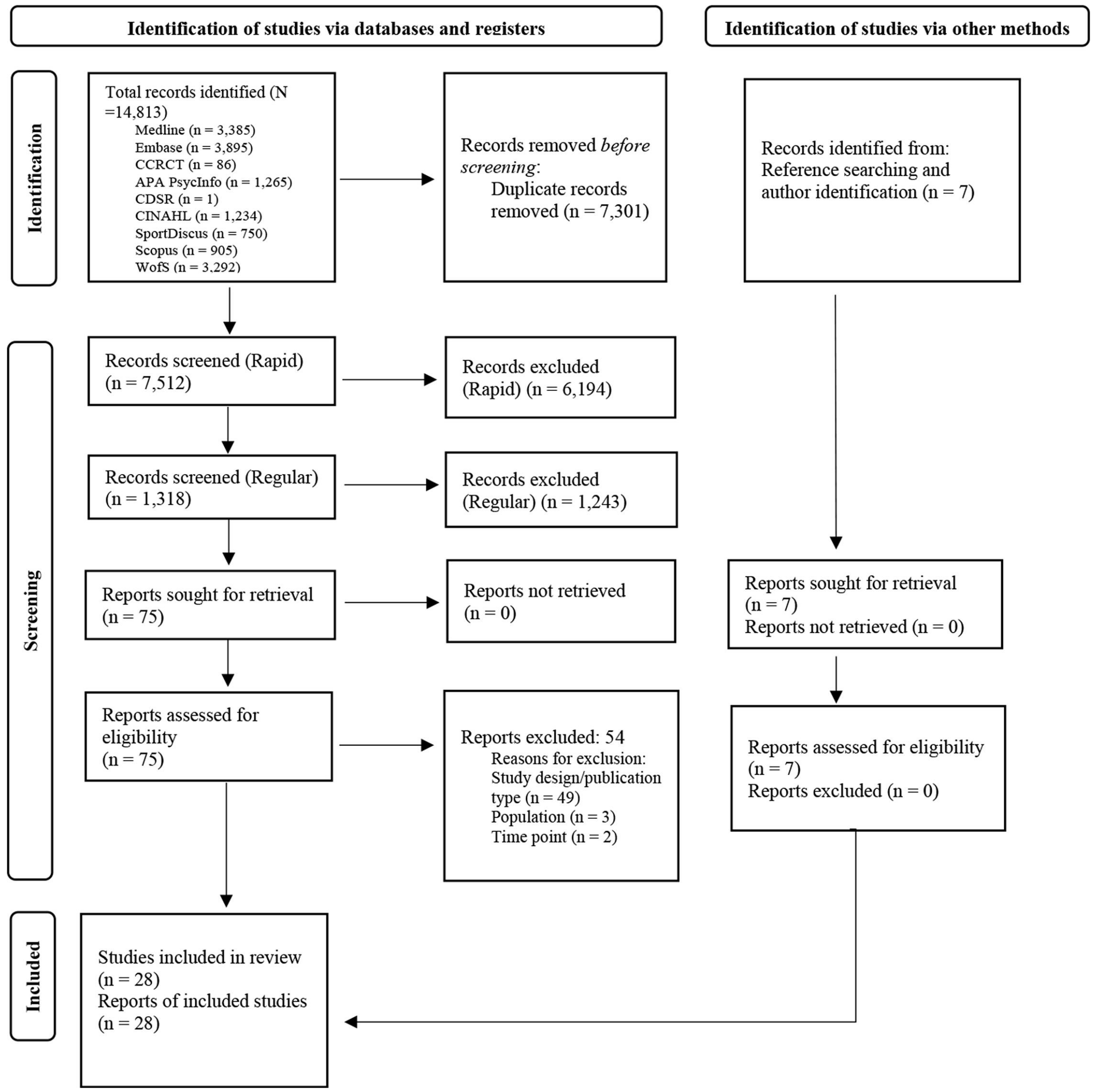

Figure 1 PRISMA. APA, American Psychological Association; CCRCT, Cochrane Central Register of Controlled Trials; CDSR, Cochrane Database of Systematic Reviews; WofS, Web of Science.

underwent regular title and abstract screening. Of those, 75 were retrieved for full-text review. Of those 21 met criteria for inclusion. An additional seven articles that were published within the timeline of this systematic review were identified by authors, or by reviewing reference lists from recently published systematic reviews on this topic. No postmortem studies relating to CTE-NC or neuroimaging studies met criteria for inclusion as case-control or cohort studies. No studies relating to age of first exposure to contact or collision sports met criteria for inclusion.

There were 28 studies that met inclusion criteria, and they were published between 2003 and March 2022.[94 108–134] Four studies included women,[111 121 123 131] but no specific outcomes were reported for women. Some of the studies had some modest control for confounding variables,[110 111 114 120 122 124] with one study controlling for many confounding variables[134] (table 1). There was only one study that was rated as having low-medium (ie, 'acceptable') risk of bias.[134] All other studies were rated as having high risk of bias, primarily because of lack of control for confounding.

Seventeen studies were conducted in the USA,[94 108–119 125–127 134] three in Scotland,[120 122 124] seven in Italy[128–133] and one each in Sweden[121] and Australia.[123] Ten studies involved former amateur athletes[108–113 121 125 131 134] (table 2). Four of the studies with amateur athletes used the same longitudinal cohort.[108–111]

Eighteen studies involved former professional athletes.[94 114–120 122–124 126–130 132 133] One study with current athletes was a study of concussion with professional jockeys.[123] Two studies with former professional football players[119 126] and three studies with former professional Scottish soccer players[120 122 124] used the same subjects.

Sixteen of the 28 studies included athletes who played American football.[94 108–119 126 127 134] Seven studies involved men who played football during high school[108–113 134] and nine studies involved men who played professional football[94 114–119 126 127] (table 3). Seven studies examined the association between playing football and later-in-life neurological disorders (eg, dementia) and neurodegenerative diseases (eg, Alzheimer's disease, Parkinson's disease and ALS). Two were with former high school football players, using a medical record linkage methodology,[112 113] and five were with former professional football players and relied on data recorded on death certificates.[115 117 119 126 127] Two studies with former high school football players[112 113] and two studies with former professional players[126 127] did not find an association, but three studies with former professional players

Table 1 Risk of bias assessment

Study	Study group	Exposure	Examined concussion history	Admissible	Well controlled for confounding	Low or medium risk of bias
Amateur sports						
Bohr *et al*[111]	High school sports	Sports participation	No	Yes	Some	No
Deshpande *et al*[110]	High school sports	Sports participation	No	Yes	Some	No
Iverson *et al*[109]	High school football	Football participation	No	Yes	No	No
Iverson and Terry[108]	High school football	Football participation	No	Yes	No	No
Deshpande *et al*[134]	High school football	Football participation	No	Yes	Yes	Yes
Savica *et al*[113]	High school football	Football participation	No	Yes	No	No
Janssen *et al*[112]	High school football	Football versus sports participation	No	Yes	No	No
Valenti *et al*[131]	People with ALS and controls	Soccer and other sports	No	Yes	No	No
Porter[125]	Amateur boxers	Boxing participation	Yes	Yes	No	No
Weiss *et al*[121]	Amateur collision/contact sports	Sports participation	No	Yes	No	No
Professional sports						
Kerr *et al*[94]	Football (American)	Concussions	Yes	Yes	No	No
Brett *et al*[114]	Football (American)	Concussions and years of participation	Yes	Yes	Some	No
Daneshvar *et al*[115]	Football (American)	Sports participation	No	Yes	No	No
Kmush *et al*[116]	Football (American)	Repetitive head impacts*	No	Yes	No	No
Nguyen *et al*[117]	Football (American)	Sports participation	No	Yes	No	No
Baron *et al*[126]	Football (American)	Sports participation	No	Yes	No	No
Lincoln *et al*[127]	Football (American)	Sports participation	No	Yes	No	No
Lehman *et al*[118]	Football (American)	Sports participation	No	Yes	No	No
Lehman *et al*[119]	Football (American)	Sports participation	No	Yes	No	No
Piantella *et al*[123]	Jockeys	Concussions	Yes	Yes	No	No
Taioli[128]	Soccer	Sports participation	No	Yes	No	No
Belli and Vanacore[129]	Soccer (Italian)	Sports participation	No	Yes	No	No
Chio *et al*[132]	Soccer (Italian)	Sports participation	No	Yes	No	No
Chio *et al*[133]	Soccer (Italian)	Sports participation	No	Yes	No	No
Pupillo *et al*[130]	Soccer (Italian)	Sports participation	No	Yes	No	No
Russell *et al*[120]	Soccer (Scottish)	Sports participation	No	Yes	Some	No
Russell *et al*[122]	Soccer (Scottish)	Sports participation	No	Yes	Some	No
Mackay *et al*[124]	Soccer (Scottish)	Sports participation	No	Yes	Some	No

If the analyses considered minimal potential confounders (eg, only age and sex), the study was rated as 'no' for being well controlled for confounding.
*Repetitive head impacts were derived from playing position and career duration.
ALS, amyotrophic lateral sclerosis.

did find an association.[115 117 119] The positive findings, and the null findings, all reflect the presence or absence of a minimally adjusted association between playing football and later-in-life neurological diseases. A minimally adjusted association means that only age and sex were considered in the analyses, and thus the analyses were unadjusted for many factors that could confound associations with later-in-life neurological diseases.

Ten of the 28 studies did not have American football as the primary focus.[120–125 128–131] Eight of those studies examined data relating to former professional Scottish and Italian soccer players[120 122 124 128–130 132 133] (table 4).

DISCUSSION

This systematic review focused on studies that could inform our understanding of risk for future problems with brain health and functioning associated with single or multiple SRC or exposure to repetitive head impacts during participation in sports. No postmortem neuropathology studies or neuroimaging studies met criteria for inclusion. No studies included in this review examined possible long-term effects in women, and thus we can draw no conclusions relating to women. There were also no studies of former university or college-level athletes that met criteria for inclusion in this review. One of our review questions pertained to age of first exposure to contact or collision sports and whether earlier age was associated with worse later-in-life brain health.[81 100 135–137] There were no studies on this topic included in this review, and we cannot draw any conclusions.

All the studies that involved former amateur athletes reported no association between participation in amateur sports and later-in-life brain health problems.[108–113 121 125 131 134] In contrast, most studies examining neurological disorders or neurodegenerative diseases with former professional athletes reported mostly weak associations between playing professional soccer and football and problems with future brain health.[115 117 119 120 122 124 128–130 132 133] Some of these studies reported associations without consideration of potential confounding factors, and in others, control for confounding was considered rudimentary and insufficient. The same applies to some of the studies with former amateur athletes, such as the studies examining risk for future neurological diseases[112 113]; only minimally adjusted associations were reported without considering other potential confounding factors.

Minimally adjusted associations mean that the studies did not consider factors known to be associated with the exposure and later-in-life mental health, neurological diseases or cognitive functioning. The studies did not examine genetic factors,[138] such as

Table 2 Summary of findings from studies of former amateur athletes

Study	Country	N	Study group	Age (years)	Exposure	Topic/Outcome	Significant findings/risk
Bohr *et al*[111]	USA	10 951 (54.3% women)	High school sports	29.0 (1.7)	Sports participation	Football associated with reduced odds of lifetime history of depression, and it was not associated with worse cognitive functioning, current depression or suicidality in the past year.	Yes/Lesser for lifetime history of depression
Deshpande *et al*[110]	USA	2197; 521 (23.7%) football	High school sports	Football M=28.8 Controls M=29.1	Sports participation	Self-reported current depression; prior diagnosis of depression, anxiety or PTSD; suicidality.	No
Iverson *et al*[109]	USA	Wave IV=2318 Wave III=1856	High school football	Wave IV M=29.1, SD=1.8 Wave III M=21.9, SD=1.8	Football participation	Wave IV: lifetime diagnosis of depression, suicide ideation, current depression. Wave III: suicide ideation.	No
Iverson and Terry[108]	USA	1762 Football=369 No football=952	High school football	M=38.03, SD=1.95	Football participation	Lifetime diagnosis of depression, anxiety disorder or panic disorder; mental health treatment past year; suicidal ideation past year; current depression.	No
Deshpande *et al*[134]	USA	2 692; 834 (31.0%) played football	High school football	M=64.4, SD=0.8	Football participation	Former football players did not report greater symptoms of depression or perform worse on cognitive testing.	No
Savica *et al*[113]	USA	512 Football=438 Controls=140	High school football	Football: 68.4 (IQR=31.5–75.6); Controls: 59.1 (IQR=26.7–73.4)	Football participation	Neurological and neurodegenerative diseases.	No
Janssen *et al*[112]	USA	486 Football=296 Other sports=190	High school football	62–78	Football versus sports participation	Neurological and neurodegenerative diseases.	No
Valenti *et al*[131]	Italy	300 people with ALS (36% women) and 300 controls	ALS	ALS sample: males 59 (SD=8); females 60 (SD=9)	Sports participation, particularly soccer	No association between playing sports, and soccer in particular, and having ALS.	No
Porter *et al*[125]	USA	20 boxers 20 controls	Amateur boxers	16–25 at start	Boxing participation	Cognitive functioning over 9 years; neuropsychological test scores did not appear to change.	No
Weiss *et al*[121]	Sweden	660, 58.2% women	Amateur collision or contact sports	M=62.8, SD=7.9	Sports participation; n=77 men and n=1 woman	Cognitive impairment in older adulthood.	No

None of these studies examined concussions as the exposure variable of interest. All examined exposure to amateur (eg, high school) sports, but none of the studies quantified that exposure (eg, years of participation, position played or playing time).
ALS, amyotrophic lateral sclerosis; M, mean; n, sample size.

the apolipoprotein E genotype,[139–143] and usually did not consider or control for known and potential confounding factors related to brain injury and brain health in the general population, such as socioeconomic status, educational attainment, cognitive reserve, smoking, hypertension and cardiovascular disease, diabetes, sleep apnoea, substance abuse, white matter hyperintensities, social isolation, diet, physical activity or exercise.[144–154] The one study that did examine genetic factors in a subanalysis reported that it did not affect the lack of association between exposure to football and worse mental health or cognitive functioning in older age.[134] To establish a clear causal association between sports participation, cognitive impairment and dementia, or to quantify that association, it is important to consider and control for factors that could confound these associations.

Mental health

Depression, anxiety or both were included in five studies of former amateur athletes (mostly former American football

Table 3 Summary of findings from studies of former professional American football players

Study	Country	N	Group	Age	Exposure	Topic/Outcome	Significant findings/risk
Kerr *et al*[94]	USA	2001 cohort=3729 of which 2536 completed the survey; 1044 with complete data in 2010	Football (NFL)	NR	Concussions	Between 2001 and 2010, 10.2% reported a diagnosis of depression. Greater concussion history associated with greater risk for depression (eg, 3.0% in those with no prior concussions and 26.8% in those with 10+ prior concussions).	Yes/Greater
Brett *et al*[114]	USA	2001 cohort=3729 of which 2536 completed the survey; 333 had results in 2019	Football (NFL)	Age in 2001: M=48.95, SD=9.37; Approx. average age in 2019=67	Self-reported concussions and years of participation	Depression not greater than general population. Physical functioning rated worse than general population and decline in physical function associated with depression. Symptoms of depression associated with greater concussion history, but not years of participation.	Yes/Greater
Daneshvar *et al*[115]	USA	19 423; 38 ALS cases	Football (NFL)	Cohort range=23–78 ALS age of diagnosis M=51.0, SD=13.8	Sports participation	ALS more common in former NFL players than general population and associated with a longer career.	Yes/Greater
Kmush *et al*[116]	USA	14 366; 763 deaths	Football (NFL)	Age at death: M=53.3, SD=14.6	Repetitive head impacts derived from playing position and career duration	Repetitive head impacts (ie, player position) associated with greater all-cause mortality.	Yes/Greater
Nguyen *et al*[117]	USA	NFL=3419, 517 deaths; MLB=2708, 431 deaths	Football (NFL)	Age at death: NFL M=59.6, SD=13.2; MLB M=66.7, SD=12.3	Sports participation	Former NFL players had greater neurodegenerative disease mortality (7.5% of former NFL players (39/517) and 3.7% of former MLB players (16/431). Suicide was not significantly greater in former NFL players (11/517; 2.1%) compared with former MLB players (5/431; 1.2%).	Yes/Greater
Baron *et al*[126]	USA	3439, 334 deaths	Football (NFL)	At death: Md=54, Range=27–81	Sports participation	Lower risk of mortality from mental disorders and suicide in former NFL players compared with men in the general population. No difference in diseases of the nervous system and sense organs.	No Yes/Lesser
Lincoln *et al*[127]	USA	9778; 227 deaths	Football (NFL)	At death: Md=38, Range=23–61	Sports participation	Lower risk of mortality from mental disorders and suicide in retired NFL players; No difference in diseases of the nervous system and sense organs.	No Yes/Lesser
Lehman *et al*[118]	USA	3439; 537 deaths	Football (NFL)	NR	Sports participation	Former NFL players less likely to have suicide as manner of death than men from the general population.	Yes/Lesser
Lehman *et al*[119]	USA	3439; 334 deaths	Football (NFL)	Md=54 at death	Sports participation	Neurodegenerative disease mortality (17/334 deaths, 5.1%), primarily dementia and ALS, greater in former NFL players than the general population.	Yes/Greater

ALS, amyotrophic lateral sclerosis; M, mean; MCI, mild cognitive impairment; Md, median; MLB, Major League Baseball; NA, not available; NFL, National Football League; NR, not reported.

players), and none of them identified an increased risk for these mental health problems in the former contact or collision sport athletes.[108–111 134] Two studies of former professional football players found an association between a greater number of past concussions and an increased risk for depression.[94 114] One of those studies reported that former players endorsed symptoms of depression similar to people from the general population and there was an association between symptoms of depression and worse physical functioning in the former players.[114] Death certificate studies revealed that former professional football players are at significantly *lower* risk for death relating to psychiatric disorders,[126 127] and a medical records study illustrated that hospitalisation for psychiatric problems was *less* common in former professional soccer players than men from the general population.[122] In aggregate, the studies suggest that former amateur and professional athletes are not at increased risk for mental health problems compared with men from the general population.

Suicidality

Nine studies examined suicidal ideation, suicidal behaviours or suicide as a manner of death,[108–111 118 122 126–128] four of which were with former amateur athletes[108–111] and five with former professional athletes.[118 122 126–128] None of the nine studies found an association between playing contact or collision sports and later-in-life risk for suicidality or suicide. Playing high school football was not associated with future risk for suicidal ideation

Table 4 Summary of findings from studies of former elite and professional athletes from Europe and Australia

Study	Country	N	Group	Age	Exposure	Topic/Outcome	Significant Findings/ risk
Piantella *et al*[123]	Australia	58 (8 women) (no concussion=41; concussion=17)	Jockeys	Concussion: 31.2 (1.8) No concussion: 36.1 (1.5)	Concussions	Professional jockeys tested twice over a 5-year interval did not show evidence of clear decline or impairment (as defined by two or more reliably worsened test scores).	No
Taioli[128]	Italy	5389; 63 had died	Soccer	At death: 36.3 (10.3)	Sports participation	No significant difference in risk for suicide as manner of death than general population. Greater risk for ALS.	No for suicide Yes, greater for ALS
Russell *et al*[122]	Scotland	Soccer=7676 Controls=23 028	Scottish Soccer	At first hospitalisation: soccer: M=52.3, SD=13.6; controls: M=46.8, SD=14.7	Sports participation	Hospitalisation for psychiatric and substance abuse problems *less* common in former soccer players. No difference in suicide.	Yes, lesser for psychiatric and substance abuse No for suicide
Belli *et al*[129]	Italy	24 000; 350 had died	Italian Soccer	At death: M=50.8, SD=15.2	Sports participation	ALS more common in former soccer players; other disease of the nervous system not more common.	Yes, greater for ALS No for other diseases
Pupillo *et al*[130]	Italy	23 586; 34 cases of ALS	Italian Soccer	M=45.0, SD=12.6 at diagnosis	Sports participation	ALS more common in former Italian soccer players.	Yes/Greater
Chio *et al*[132]	Italy	7325; 5 cases of ALS	Italian Soccer	Age of onset M=43.4 (SD=9.1; range 33–56)	Sports participation	ALS more common in former Italian soccer players.	Yes/Greater
Chio *et al*[133]	Italy	7325; 5 cases of ALS	Italian Soccer	Age of onset M=41.6 years (SD=7.5, range 33–56 years).	Sports participation	ALS more common in former Italian soccer players.	Yes/Greater
Russell *et al*[120]	Scotland	Soccer=7676; controls=23 028	Scottish Soccer	NR	Sports participation	Neurodegenerative disease mortality greater in former soccer players, varied by position played and increased with career length.	Yes/Greater
Mackay *et al*[124]	Scotland	Soccer=7676, 1180 deaths; controls=23 028, 3807 deaths	Scottish Soccer	At death: soccer M=67.9, SD=13.0; controls M=64.7, SD=14.0	Sports participation	Neurodegenerative disease mortality greater in former soccer players (eg, AD, ALS and PD).	Yes/Greater

The two studies by Chio *et al* used the same cohort of players,[132 133] and the three studies with former Scottish players used the same cohort.[120 122 124] Many of these studies are ecological analyses with positive associations being important hypothesis-generating findings; more meticulously designed cohort studies with better control for confounding factors are needed.
AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; M, mean; NR, not reported; PD, Parkinson's disease.

in four studies.[108–111] Specifically, there was not an association at an average age of 22 years,[109] 29 years[109–111] or 38 years[108] in men participating in the National Longitudinal Study of Adolescent to Adult Health.[155] All studies that examined suicide as a manner of death in former professional football players or former professional soccer players reported either significantly lower risk[118 126 127] or no difference compared with men in the general population.[122 128] In aggregate, the studies suggest that former amateur athletes are not at increased risk for suicidality and former professional football players and soccer players are not at increased risk for suicide, compared with men from the general population.

Neurological disorders and neurodegenerative diseases

Two studies reported that playing high school football was not associated with increased risk for dementia, Parkinson's disease or ALS.[112 113] A case-control study of people with ALS found no association with sports participation in general, or with playing amateur soccer, and having ALS.[131] Men who played high school football, compared with those who did not play football, did not have worse cognitive functioning at the age of 65 years in one longitudinal study.[134] In a Swedish twin study, there was not an association between sports involving repetitive head hits and the experience of cognitive impairment during older adulthood.[121] In aggregate, the studies included in this review suggest that most former amateur athletes are not at increased risk for cognitive impairment, neurological disorders or neurodegenerative diseases compared with men from the general population.

Neurological conditions (eg, dementia) and neurodegenerative diseases (eg, Alzheimer's disease and ALS) were outcomes in 12 studies involving former professional athletes,[115 117 119 120 124 126–130 132 133] and many of these studies reported worse outcomes for the former professional athletes. Most of the studies examined minimally adjusted associations without controlling for confounding factors and some were ecological analyses with no individual-level analyses. Greater risk for neurological conditions and neurodegenerative diseases was reported for both former professional football players[119] and former professional soccer players.[124] The study with former soccer players was unique in that they included a variable relating to socioeconomic status at the time of death, and they also conducted sensitivity analyses that considered competing risks for death associated with ischaemic heart disease and cancer.[124] Regarding absolute numbers, the study examining causes of death of 1180 former professional soccer players reported that 222 (18.8%) had a neurological or neurodegenerative disease listed on their death certificate, compared with 6.0% (228/3807) of a matched control sample of men who had died.[124] Another study reported that 7.5% of former professional football players (39/517) compared with 3.7% of former professional baseball players (16/431) had a neurological or neurodegenerative disease listed on their death certificate.[117]

Eight studies found an association between ALS and participation in professional sports.[115 119 124 128–130 132 133] ALS, a rare disease with a possible genetic cause in a substantial number of men who develop the disease before age 50 years,[156] involves a highly selective population of neurons, about half of which are in the spinal cord, which makes identifying a specific trauma-related mechanism challenging. Researchers have been examining possible environmental and lifestyle risk factors for ALS for many years.[157 158] The total number of ALS cases reported in the studies included in this systematic review tended to be small, with five studies identifying fewer than 10 cases,[119 128 129 132 133] which limits the statistical power. One study of former professional football players identified ALS on 7 of 334 death certificates (2.1%),[119] and another study of former professional football players identified ALS in 38 of a cohort of 19 423 former players (0.2%).[115] No study reported pathological confirmation. More research relating to possible mechanisms underlying the association is needed.

In aggregate, the studies show an association between playing professional football and professional soccer and some neurological disorders and diseases. Higher quality studies that control for potential confounding factors are needed to confirm or refute these findings.

Methodological considerations and limitations with the studies included in this review

By design, this systematic review focused on concussions and exposure to repetitive head impacts in former athletes. We did not attempt to review the literature relating to associations between mild traumatic brain injury and depression, suicidality, neurological disorders or neurodegenerative diseases in people from the general population or military service members or veterans.

The literature on possible long-term effects of concussions and repetitive head impacts experienced during participation in youth, amateur and professional sports, employing a case-control or cohort study design, is limited, but evolving. The studies involving amateur athletes yielded entirely negative results. Negative results in cohort studies are important in this regard because cohort studies provide the most rigorous study design available in this literature, but these studies must be interpreted within the context of a variety of methodological limitations that are common in this literature. For example, these studies, as a rule, did not quantify or examine the amount of exposure to concussions or repetitive head impacts. Although the studies with former amateur athletes all yielded negative findings, that does not mean that there are no possible later-in-life adverse health effects associated with participation in amateur sports. Future research, using well-designed case-control and cohort studies, is needed to better measure potential health risks.

Some of the studies in this review had some modest control for confounding variables,[110 111 114 120 122 124] with one study controlling for many confounding variables and being considered to have low-to-medium risk of bias[134] (table 1). All other studies were considered to have high risk of bias, primarily because of a lack of control for confounding. As a rule, the studies did not consider many genetic, lifestyle or medical factors that could potentially confound associations between later-in-life adverse health outcomes and earlier-in-life participation in sports. A 2020 Lancet Commission report, for example, presented a *life-course model for potentially modifiable risk factors* for dementia in the general population that included factors in early life (ie, age <45 years) such as less education, midlife (ie, age 45–65 years) such as hearing loss, traumatic brain injury, hypertension, excessive alcohol consumption and obesity, and later life (age >65 years) such as smoking, depression, social isolation, physical inactivity, diabetes and air pollution.[159]

Another methodological consideration is whether the 'general population' is the preferred comparison group for studies involving the brain health of former contact and collision sport athletes. It is unlikely that control subjects selected from the general population are similar in all risk factors as professional athletes. Comparing with the general population might underestimate or overestimate certain risks. For example, former athletes are more likely to experience the health benefits from a life of physical exercise. However, they may also experience more chronic pain and be prescribed more medications than controls from the general population.

Several studies included in this review relied on data from death certificates. Some of these studies have relatively small sample sizes (eg, fewer than 500 deaths).[119 126 127] In these studies, there is no explicit exposure other than belonging to a group—the exposure is playing a professional sport, such as football. Thus, these are ecological studies with no control of confounding at the individual level. Cardiovascular disease, for example, is associated with risk for cognitive impairment and dementia, and one study included in this review reported that 96.3% of former professional football players and 52.2% of former professional baseball players had cardiovascular disease listed on their death certificates.[117] These ecological studies are hypothesis generating and cannot be used to draw specific causal conclusions. Moreover, errors on death certificates are common, and include the coding of causes of death, comorbidities and manner of death.[160 161] Additionally, there is evidence that dementia as a cause of death is under-reported on death certificates.[162] Methodological limitations associated with the 28 studies included in this review are discussed in greater detail in the online supplemental material.

Chronic traumatic encephalopathy neuropathological change and traumatic encephalopathy syndrome

Case series and cross-sectional studies relating to CTE-NC in former athletes have been published over the past 17 years,[23–30] as well as many published reviews.[4 17 29 31–57] A recent narrative review paper[57] examined the issue of association versus causation relating to repetitive head impacts and CTE-NC, through the lens of nine viewpoints proposed by Sir Austin Bradford Hill in 1965.[163] The authors of that review concluded that the evidence supporting repetitive head impacts causing CTE-NC was compelling. (As part of that review, the authors identified six studies that they referred to as case-control studies and calculated ORs for an association between sports exposure and CTE-NC. In the present systematic review, we did not consider those six studies to be case-control or cohort studies that were designed to examine risk for CTE-NC or risk for later-in-life clinical conditions or disorders. In addition, the original authors of most of the studies did not conceptualise them as case-control studies designed to measure risk.)[57] The postmortem studies of CTE-NC were not included in this systematic review because they did not meet the a priori inclusion criteria for research design. However, given considerable interest in this topic, a review of the neuropathology studies, a summary of gaps in knowledge and directions for future research is provided below and in the online supplemental material (which should be read in conjunction with this paper).

The brain donation programme at Boston University has specialised, for years, in procuring donations from families of former athletes, especially football players. Their research has identified CTE-NC in virtually all former professional American football players in their sample (ie, 99%), 91% of former college players and 21% of former high school players.[24] Those researchers have reported that the prevalence of CTE-NC in all former football players and athletes from other sports is unknown, and ascertainment bias, associated with the decision to donate a person's brain, would inflate the proportions of the samples identified as having the pathology. Other researchers have identified CTE-NC in former elite and professional athletes in smaller case studies and case series of former high exposure boxers (7/14 from the seminal 1973 Corsellis study),[164 165] former soccer players (5/7),[23] rugby union players (3/4),[23] rugby league players (2/2),[166] Canadian professional football players (11/24)[25] and Canadian ice hockey players (6/11).[25] The Canadian studies are from a brain bank established in 2010 at the Canadian Concussion Centre to study the neuropathology of brain degeneration in professional athletes.[30]

In 2020, Bieniek *et al* published a postmortem study of former amateur athletes, compared with those who did not participate in sports, and identified CTE-NC in 2.8% of the total sample (21/750), 5.0% (15/300) of those who played sports, 1.3% who did not play sports (6/450), 0% of women (of 273), 4.4% (21/477) of men, 7.9% of men who played football (11/140) and 2.4% (6/245) of men who did not play sports.[167] Those men who had CTE-NC were, on average, 10 years older at the time of death than those who were negative for CTE-NC, and they were much more likely to have Alzheimer's disease neuropathological change (ie, 47.6% vs 20.2%). The authors concluded that participation in football, specifically beyond the high school level, was associated with a greater OR for having CTE-NC. None of the aforementioned studies can provide an accurate estimate of the incidence or prevalence of CTE-NC in these sports, which are essential to calculating risk—but they raise important hypotheses concerning potential risks.

Recently published postmortem studies from a brain bank in Australia (n=636)[168] and a community sample in the USA (n=532)[169] have revealed very few cases of CTE-NC (<1%), and a large European study (n=310) reported no cases of CTE-NC,[170] using 'strict' criteria for case ascertainment. In a study of 180 consecutive autopsies in Australia, four cases of mild CTE-NC were identified (2.2%).[171] In a recent study of 225 former military personnel, CTE-NC was identified in 4.4%, and it usually involved minimal microscopic changes on p-tau immunohistochemistry—with half of the identified cases having only a single pathognomonic lesion—and the authors concluded that it is unclear whether the minimal histopathological findings were of clinical significance.[172]

There are important gaps in knowledge that provide directions for future research. At present, the incidence and prevalence of CTE-NC (a neuropathological entity), or TES (a proposed clinical diagnosis), in former athletes, military veterans and people from the general population is not known. Moreover, it is not known whether CTE-NC causes specific neurological or psychiatric problems, the extent to which larger amounts of CTE-NC can be clearly identified within the presence of Alzheimer's disease neuropathological change, or whether the neuropathology is inexorably progressive. The NINDS consensus group made numerous important recommendations to address gaps in knowledge relating to CTE-NC and TEC.[65] They encouraged researchers to address topics such as determining whether patchy areas of perivascular p-tau deposition at the depths of cerebral sulci and more limited amounts of CTE-NC have direct clinical correlates, and whether more abundant CTE-NC is associated with specific cognitive and neuropsychiatric symptoms. They also encouraged studies relating to the inter-rater reliability and predictive validity of the new proposed criteria for TEC. They emphasised that the new diagnostic criteria are designed primarily for research use, and it is possible that a number of factors unrelated to sporting history might be associated with the clinical features underlying this condition, including 'medical and psychosocial variables, such as sleep disorders, vascular risk factors, chronic pain and racial and associated inequities in social determinants of health' (p. 859).[65]

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

In recent years, there have been many published narrative and systematic reviews relating to possible long-term effects of SRC and participation in contact, collision and combat sports.[1–13 29 31 34 37–41 47 49 50 53 55 100 101] The topics of those reviews included neurological diseases, CTE, psychiatric disorders, suicide, neuroimaging and neuropsychological outcomes. The authors of past reviews have often concluded that the general quality of the evidence was low, and that high-quality cohort studies were needed. The present systematic review differed from prior reviews in that it focused only on case-control and cohort studies with the goal of drawing conclusions about future *risk* to former amateur and professional athletes. An important finding from this review, and gap in the literature, was documenting the lack of case-control or cohort studies involving age of first exposure to sports, neuroimaging as an outcome, women and postmortem studies (ie, CTE-NC). The postmortem studies are a particularly important direction for future research, especially for antemortem biomarker development.

The case-control and cohort studies included in this review suggest that (i) former amateur athletes are not at increased risk for depression or suicidality,[108–111] (ii) former professional soccer players are not at increased risk for psychiatric hospitalisation[122] and (iii) former professional football and soccer players are not at increased risk for mortality from psychiatric disorders[126 127] or suicide.[118 122 126–128] However, some former athletes, like men in the general population, might experience serious mental health problems and suicidality as they age; therefore, it is important to study these athletes to understand why, and to provide treatment.

Four cohort studies and one case-control study suggest that former amateur athletes are not at increased risk for cognitive impairment, neurological disorders or neurodegenerative diseases compared with men from the general population.[112 113 121 131 134] In contrast, some studies of former professional athletes examining causes of death reported an association with neurological diseases and dementia in former professional football players[115 117 119] and professional soccer players.[124] Moreover, there were six publications that reported an association between participation in professional soccer and ALS.[124 128–130 132 133] Most of the studies with professional athletes are ecological in nature and the associations are not at the individual level. Well-designed case-control and cohort studies are needed to determine if these associations are causal.

There are many potential factors to consider when studying whether there is an association between concussions or participation in sports during adolescence and early adulthood and the development of neurological conditions or neurodegenerative diseases later in life, such as genetic, demographic, health and environmental factors, socioeconomic status and social determinants of health, alcohol use and substance abuse disorders, obstructive sleep apnoea, cardiovascular disease, peripheral vascular disease and cognitive reserve. Future well-designed case-control and cohort studies that include more careful control of confounding factors are urgently needed.

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Correction notice This article has been corrected since it published. Typographical errors have been made to the online version only and not in print.

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Acknowledgements A preliminary version of this systematic review was presented at the 6th International Conference on Concussion in Sport in Amsterdam, the Netherlands, on 28 October 2022. The authors acknowledge the work of librarians Drs Zahra Premji (search strategy), Diane Lorenzetti (PRESS review) and Shauna Rutherford (reference retrieval and organisation in Covidence) for their contributions.

Contributors Original conceptualisation of the systematic review: IKK, JD, JDC, JB, AH, KJS, GLI, GMS, GM, RCC, RJC and RJE. The title and abstract screenings were completed by RJC, JDC, KJS and GMS. Reviewed the articles for the full-text screen: RJC, JDC and GMS. Completed all risk of bias assessments: GMS, GLI, JDC, RJC, RJE and KJS. Data extractions from the articles were completed primarily by GLI, RJC and RJE. Separate from the data extractions and risk of bias reviews, JDC and GLI reviewed all articles for clinical and methodological content. GLI was primarily responsible for designing the structure of the manuscript and drafting the manuscript. JDC provided leadership in methodology. A separate review of chronic traumatic encephalopathy-neuropathological change and traumatic encephalopathy syndrome was conducted primarily by GLI, RCC and RJC, with one author primarily responsible for writing the content for the article and the online supplement (GLI) and two authors carefully reviewing this content (RCC, RJC). All authors reviewed and edited drafts of the online supplement and the manuscript, and approved the documents for submission for publication. GLI as the guarantor accepts full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish.

Funding Funding for some of the administrative aspects of the numerous systematic reviews prepared for the 6th International Consensus Conference on Concussion in Sport was provided through an educational grant from the Concussion in Sport International Consensus Conference Organising Committee through Public Creations for partial administrative and operational costs associated with the writing of the systematic reviews. Partial support for travel to the Consensus Conference, for some of the authors, also was provided by the International Olympic Committee.

Competing interests GLI serves as a scientific advisor for NanoDX, Sway Operations and Highmark. He has a clinical and consulting practice in forensic neuropsychology, including expert testimony, involving individuals who have sustained mild TBIs (including former athletes), and on the topic of suicide. He has received past research support or funding from several test publishing companies, including ImPACT Applications, CNS Vital Signs and Psychological Assessment Resources. He receives royalties from the sales of one neuropsychological test (WCST-64). He has received travel support and honorariums for presentations at conferences and meetings. He has received research funding as a principal investigator from the National Football League (NFL), and subcontract grant funding as a collaborator from the Harvard Integrated Programme to Protect and Improve the Health of NFL Players Association Members. He has received research funding from the Wounded Warrior Project. He acknowledges unrestricted philanthropic support from ImPACT Applications, the Mooney-Reed Charitable Foundation, the National Rugby League, Boston Bolts and the Schoen Adams Research Institute at Spaulding Rehabilitation. RJC is a collaborator on a grant funded by the NFL to study the spectrum of concussion, including possible long-term effects. He has a consulting practice in forensic neuropathology, including expert testimony, which has involved former athletes at amateur and professional levels. JDC has provided expert epidemiological testimony in court cases on the long-term effects of concussions in sports. GMS is an owner of a multidisciplinary practice (managing patients with MSK pain disorders). He is a board member of Hockey Calgary (Calgary, Alberta, Canada) and Chair of the Alberta Association of Physiotherapy. He received funding for the administrative aspects of the writing of two of the systematic reviews that informed the consensus process. KJS has received grant funding from the CIHR, NFL Scientific Advisory Board, International Olympic Committee Medical and Scientific Research Fund, World Rugby, Mitacs Accelerate, University of Calgary, with funds paid to her institution and not to her personally. She is an Associate Editor of BJSM (unpaid), Independent consultant to World Rugby and has received travel and accommodation support for meetings where she has presented. She coordinated the writing of the systematic reviews that informed Amsterdam International Consensus on Concussion in Sport, for which she has received an educational grant to assist with the administrative costs associated with the writing of the reviews (with funds paid to her institution). She is a member of the AFL Concussion Scientific Committee (unpaid position), Brain Canada (unpaid positions) and Board member of the Concussion in Sport Group (CISG)(unpaid). She works as a physiotherapy consultant and treats athletes of all levels of sport from grass roots to professional. RJE is a paid consultant for the NHL and cochair of the NHL/NHLPA Concussion Subcommittee. He is also a paid consultant and chair of the Major League Soccer concussion committee, and a consultant to the US Soccer Federation. He previously served as a neuropsychology consultant to Princeton University Athletic Medicine and EyeGuide. He is currently a co-Principal Investigator for a grant funded by the NFL (NFL-Long) through Boston Children's Hospital. He occasionally provides expert testimony in matters related to MTBI and sports concussion, and occasionally receives honoraria and travel support/reimbursement for professional meetings. JB serves as the Chairman of the Medical Advisory Committee of Pop Warrner Football and is a member of the NFL Head, Neck, and Spine Committee, NFLPA Mackey-White Health and Safety Committee and the NCAA Concussion Task Force, all without remuneration. He is a consultant for BrainLab and has provided expert testimony on TBI medicolegal cases. IKK is a professor at Ludwig-Maximilians-Universität Munich (paid position). She serves as European Editor at Journal of Neurotrauma (unpaid position) and as Vice President of the European Neurotrauma Organisation (unpaid position). She receives research grant funding from the National Institutes of Health, the European Research Council, the German Ministry for Research and Education. She receives funding for a research study on sport-related concussion from Abbott. The university hospital received donations for her research from the Schatt Foundation and Mary Ann Liebert. She receives royalties for book chapters published by Thieme Publishers. Her spouse is employee at Siemens and she thus holds stock options at Siemens and Siemens

Healthineers. In-kind contribution: PhD students working under her supervision receive scholarships from the Villigst Foundation, the China Scholarship Council collaboration with Ludwig-Maximilians-University Munich and Fulbright. GM discloses grants from the United States Department of Defense—TBI End points Development Initiative (grant #W81XWH-14-2-0176), TRACK-TBI Precision Medicine (grant # W81XWH-18-2-0042) and TRACK-TBI NETWORK (grant # W81XWH-15-9-0001); NIH-NINDS–TRACK-TBI (grant #U01NS086090) and the NFL Scientific Advisory Board—TRACK-TBI LONGITUDINAL. The United States Department of Energy supports GM for a precision medicine collaboration. One Mind has provided funding for TRACK-TBI patients stipends and support to clinical sites. He has received an unrestricted gift from the NFL to the UCSF Foundation to support research efforts of the TRACK-TBI NETWORK. GM has also received funding from NeuroTruama Sciences to support TRACK-TBI data curation efforts. Additionally, Abbott Laboratories has provided funding for add-in TRACK-TBI clinical studies. MMcN has the following disclosures: (i) Chair, Ethics Expert Group, WADA (2021–23) (paid); (ii) Member, International Boxing Association, Ethics and Integrity Committee, (2021–22; resigned October 2022) (paid); (iii) Chair, Therapeutic Use Exemption Fairness Committee (2020–Present) (paid); (iv) Member, Steering Group, Sex Segregation in Sport, IAAF/World Athletics (2019–20) (unpaid); (v) Member, International Ice Hockey Federation, Ethics and Integrity Committee (2019–21) (paid); (vi) Member, IOC Consensus Statement Expert Group on Injuries in Children and Adolescents (2017) (unpaid); (vii) Member, Ethics Expert Group, WADA (2016–21) (unpaid) and (viii) Member, IOC Consensus Statement Expert Group on Pain Management (2016) (unpaid). JP is a sports and exercise medicine physician at Waterfall Sports Orthopaedic Surgery, Johannesburg, South Africa. He is Director of Sports Concussion South Africa and a Visiting Professor, Wits Sport and Health (WiSH), School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand. As an Editor of BJSM, he receives an honorarium and serves as a consultant (unremunerated) to World Rugby Concussion Advisory Group, South African Rugby, EyeGuide Scientific Advisory Board and the Union of European Football Associations. He is co-chair of the Scientific Committee, 6th International Conference on Concussion in Sport (unpaid) and a Board member of the Concussion in Sport Group (unpaid). RCC serves as a scientific advisor for the NFL's Head Neck and Spine Committee, VP and Chair of the Scientific Advisory Committee for the National Operating Committee on Standards for Athletic Equipment (NOCSAE), and as co-founder and Medical Director of the Concussion Legacy Foundation. He currently receives research support from the NINDS UNITE and Diagnose CTE grants. He has received travel support and honorariums for presentations at conferences and meetings. He receives royalties from Houghton Mifflin Harcourt publishing. He has a clinical and consulting practice in forensic neurology and neurosurgery, including expert testimony, especially individuals with traumatic brain and spinal cord injuries. He is a member of the National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation Medical Science Committee.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES

1 Morales JS, Valenzuela PL, Saco-Ledo G, *et al*. Mortality risk from neurodegenerative disease in sports associated with repetitive head impacts: preliminary findings from a systematic review and meta-analysis. *Sports Med* 2022;52:835–46.
2 Echlin HV, Rahimi A, Wojtowicz M. Systematic review of the long-term neuroimaging correlates of mild traumatic brain injury and repetitive head injuries. *Front Neurol* 2021;12:726425.
3 Morales JS, Castillo-García A, Valenzuela PL, *et al*. Mortality from mental disorders and suicide in male professional American football and soccer players: a meta-analysis. *Scand J Med Sci Sports* 2021;31:2241–8.
4 Sparks P, Lawrence T, Hinze S. Neuroimaging in the diagnosis of chronic traumatic encephalopathy: a systematic review. *Clin J Sport Med* 2020;30 Suppl 1:S1–10.
5 Gallo V, Motley K, Kemp SPT, *et al*. Concussion and long-term cognitive impairment among professional or elite sport-persons: a systematic review. *J Neurol Neurosurg Psychiatry* 2020;91:455–68.
6 Cunningham J, Broglio SP, O'Grady M, *et al*. History of sport-related concussion and long-term clinical cognitive health outcomes in retired athletes: a systematic review. *J Athl Train* 2020;55:132–58.
7 Zhang Y, Ma Y, Chen S, *et al*. Long-Term cognitive performance of retired athletes with sport-related concussion: a systematic review and meta-analysis. *Brain Sci* 2019;9:199.
8 Cunningham J, Broglio S, Wilson F. Influence of playing rugby on long-term brain health following retirement: a systematic review and narrative synthesis. *BMJ Open Sport Exerc Med* 2018;4:e000356.
9 Lee BG, Leavitt MJ, Bernick CB, *et al*. A systematic review of positron emission tomography of tau, amyloid beta, and neuroinflammation in chronic traumatic encephalopathy: the evidence to date. *J Neurotrauma* 2018;35:2015–24.
10 Vos BC, Nieuwenhuijsen K, Sluiter JK. Consequences of traumatic brain injury in professional American football players: a systematic review of the literature. *Clin J Sport Med* 2018;28:91–9.
11 Manley G, Gardner AJ, Schneider KJ, *et al*. A systematic review of potential long-term effects of sport-related concussion. *Br J Sports Med* 2017;51:969–77.
12 Legarreta AD, Monk SH, Kirby PW, *et al*. Long-Term neuroimaging findings in American football players: systematic review. *World Neurosurg* 2018;120:e365–79.
13 Bellomo G, Piscopo P, Corbo M, *et al*. A systematic review on the risk of neurodegenerative diseases and neurocognitive disorders in professional and varsity athletes. *Neurol Sci* 2022;43:6667–91.
14 Bailes JE, Petraglia AL, Omalu BI, *et al*. Role of subconcussion in repetitive mild traumatic brain injury. *J Neurosurg* 2013;119:1235–45.
15 Plessow F, Pascual-Leone A, McCracken CM, *et al*. Self-Reported cognitive function and mental health diagnoses among former professional american-style football players. *J Neurotrauma* 2020;37:1021–8.
16 Zivadinov R, Polak P, Schweser F, *et al*. Multimodal imaging of retired professional contact sport athletes does not provide evidence of structural and functional brain damage. *J Head Trauma Rehabil* 2018;33:E24–32.
17 Asken BM, Rabinovici GD. Identifying degenerative effects of repetitive head trauma with neuroimaging: a clinically-oriented review. *Acta Neuropathol Commun* 2021;9:96.
18 Stern RA, Adler CH, Chen K, *et al*. Tau positron-emission tomography in former national football League players. *N Engl J Med* 2019;380:1716–25.
19 Mantyh WG, Spina S, Lee A, *et al*. Tau positron emission tomographic findings in a former us football player with pathologically confirmed chronic traumatic encephalopathy. *JAMA Neurol* 2020;77:517–21.
20 Small GW, Kepe V, Siddarth P, *et al*. Pet scanning of brain tau in retired National football League players: preliminary findings. *The American Journal of Geriatric Psychiatry* 2013;21:138–44.
21 Barrio JR, Small GW, Wong K-P, *et al*. In vivo characterization of chronic traumatic encephalopathy using [F-18] FDDNP PET brain imaging. *Proc Natl Acad Sci USA* 2015;112:E2039–2047.
22 Omalu B, Small GW, Bailes J, *et al*. Postmortem autopsy-confirmation of antemortem [F-18] fddnp-pet scans in a football player with chronic traumatic encephalopathy. *Neurosurgery* 2018;82:237–46.
23 Lee EB, Kinch K, Johnson VE, *et al*. Chronic traumatic encephalopathy is a common co-morbidity, but less frequent primary dementia in former soccer and rugby players. *Acta Neuropathol* 2019;138:389–99.
24 Mez J, Daneshvar DH, Kiernan PT, *et al*. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA* 2017;318:360.
25 Schwab N, Wennberg R, Grenier K, *et al*. Association of position played and career duration and chronic traumatic encephalopathy at autopsy in elite football and hockey players. *Neurology* 2021;96:e1835–43.
26 McKee AC, Stern RA, Nowinski CJ, *et al*. The spectrum of disease in chronic traumatic encephalopathy. *Brain* 2013;136(Pt 1):43–64.
27 Omalu B, Bailes J, Hamilton RL, *et al*. Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. *Neurosurgery* 2011;69:173–83;
28 McKee AC, Cantu RC, Nowinski CJ, *et al*. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol* 2009;68:709–35.
29 McKee AC. The neuropathology of chronic traumatic encephalopathy: the status of the literature. *Semin Neurol* 2020;40:359–69.
30 Hazrati L-N, Tartaglia MC, Diamandis P, *et al*. Absence of chronic traumatic encephalopathy in retired football players with multiple concussions and neurological symptomatology. *Front Hum Neurosci* 2013;7:222.

31 Murray HC, Osterman C, Bell P, *et al*. Neuropathology in chronic traumatic encephalopathy: a systematic review of comparative post-mortem histology literature. *Acta Neuropathol Commun* 2022;10:108.
32 Mavroudis I, Kazis D, Chowdhury R, *et al*. Post-concussion syndrome and chronic traumatic encephalopathy: narrative review on the neuropathology, neuroimaging and fluid biomarkers. *Diagnostics (Basel)* 2022;12:740.
33 Bergauer A, van Osch R, van Elferen S, *et al*. The diagnostic potential of fluid and imaging biomarkers in chronic traumatic encephalopathy (CTE). *Biomed Pharmacother* 2022;146:112602.
34 Shively SB, Priemer DS, Stein MB, *et al*. Pathophysiology of traumatic brain injury, chronic traumatic encephalopathy, and neuropsychiatric clinical expression. *Psychiatr Clin North Am* 2021;44:443–58.
35 Hugon J, Hourregue C, Cognat E, *et al*. Chronic traumatic encephalopathy. *Neurochirurgie* 2021;67:290–4.
36 Pierre K, Dyson K, Dagra A, *et al*. Chronic traumatic encephalopathy: update on current clinical diagnosis and management. *Biomedicines* 2021;9:415.
37 Alosco ML, Culhane J, Mez J. Neuroimaging biomarkers of chronic traumatic encephalopathy: targets for the academic memory disorders clinic. *Neurotherapeutics* 2021;18:772–91.
38 Willer BS, Haider MN, Wilber C, *et al*. Long-Term neurocognitive, mental health consequences of contact sports. *Clin Sports Med* 2021;40:173–86.
39 Albayram O, Albayram S, Mannix R. Chronic traumatic encephalopathy-a blueprint for the bridge between neurological and psychiatric disorders. *Transl Psychiatry* 2020;10:424.
40 Lesman-Segev OH, Edwards L, Rabinovici GD. Chronic traumatic encephalopathy: a comparison with Alzheimer's disease and frontotemporal dementia. *Semin Neurol* 2020;40:394–410.
41 Cantu RC, Bernick C. History of chronic traumatic encephalopathy. *Semin Neurol* 2020;40:353–8.
42 Shahim P, Gill JM, Blennow K, *et al*. Fluid biomarkers for chronic traumatic encephalopathy. *Semin Neurol* 2020;40:411–9.
43 Mariani M, Alosco ML, Mez J, *et al*. Clinical presentation of chronic traumatic encephalopathy. *Semin Neurol* 2020;40:370–83.
44 Abdolmohammadi B, Dupre A, Evers L, *et al*. Genetics of chronic traumatic encephalopathy. *Semin Neurol* 2020;40:420–9.
45 Phelps A, Mez J, Stern RA, *et al*. Risk factors for chronic traumatic encephalopathy: a proposed framework. *Semin Neurol* 2020;40:439–49.
46 Cherry JD, Babcock KJ, Goldstein LE. Repetitive head trauma induces chronic traumatic encephalopathy by multiple mechanisms. *Semin Neurol* 2020;40:430–8.
47 Stein TD, Crary JF. Chronic traumatic encephalopathy and neuropathological comorbidities. *Semin Neurol* 2020;40:384–93.
48 Wolfson DI, Kuhn AW, Kerr ZY, *et al*. Chronic traumatic encephalopathy research viewed in the public domain: what makes headlines? *Brain Inj* 2020;34:528–34.
49 LoBue C, Schaffert J, Cullum CM. Chronic traumatic encephalopathy: understanding the facts and debate. *Curr Opin Psychiatry* 2020;33:130–5.
50 Iverson GL, Gardner AJ, Shultz SR, *et al*. Chronic traumatic encephalopathy neuropathology might not be inexorably progressive or unique to repetitive neurotrauma. *Brain* 2019;142:3672–93.
51 Cantu R, Budson A. Management of chronic traumatic encephalopathy. *Expert Rev Neurother* 2019;19:1015–23.
52 Katsumoto A, Takeuchi H, Tanaka F. Tau pathology in chronic traumatic encephalopathy and Alzheimer's disease: similarities and differences. *Front Neurol* 2019;10:980.
53 Smith DH, Johnson VE, Trojanowski JQ, *et al*. Chronic traumatic encephalopathy-confusion and controversies. *Nat Rev Neurol* 2019;15:179–83.
54 Turk KW, Budson AE. Chronic traumatic encephalopathy. *CONTINUUM: Lifelong Learning in Neurology* 2019;25:187–207.
55 Brett BL, Wilmoth K, Cummings P, *et al*. The neuropathological and clinical diagnostic criteria of chronic traumatic encephalopathy: a critical examination in relation to other neurodegenerative diseases. *J Alzheimers Dis* 2019;68:591–608.
56 Ruprecht R, Scheurer E, Lenz C. Systematic review on the characterization of chronic traumatic encephalopathy by MRI and MRS. *J Magn Reson Imaging* 2019;49:212–28.
57 Nowinski CJ, Bureau SC, Buckland ME, *et al*. Applying the Bradford Hill criteria for causation to repetitive head impacts and chronic traumatic encephalopathy. *Front Neurol* 2022;13:938163.
58 Martland HS. Punch drunk. *JAMA* 1928;91:1103.
59 Millspaugh JA. Dementia pugilistica. *US Naval Medicine Bulletin* 1937;35:297–303.
60 Bowman KM, Blau AD. Psychotic states following head and brain injury in adults and children. In: Brock S, ed. *Injuries of the skull, brain an spinal cord: Neuro-psychiatric, surgical, and medico-legal aspects*. Williams & Wilkins Co, 1940: 309–60.
61 CRITCHLEY M. Medical aspects of boxing, particularly from a neurological standpoint. *Br Med J* 1957;1:357–62.
62 Critchley M. Punch-drunk syndromes: the chronic traumatic encephalopathy of boxers. In: *Hommage a Clovis Vincent*. Strasbourg: Imprimerie Alascienne, 1949: 131–45.
63 McKee AC, Cairns NJ, Dickson DW, *et al*. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol* 2016;131:75–86.
64 Bieniek KF, Cairns NJ, Crary JF, *et al*. The second NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *J Neuropathol Exp Neurol* 2021;80:210–9.
65 Katz DI, Bernick C, Dodick DW, *et al*. National Institute of neurological disorders and stroke consensus diagnostic criteria for traumatic encephalopathy syndrome. *Neurology* 2021;96:848–63.
66 Alosco ML, Tripodis Y, Rowland B, *et al*. A magnetic resonance spectroscopy investigation in symptomatic former NFL players. *Brain Imaging Behav* 2020;14:1419–29.
67 Gardner AJ, Iverson GL, Wojtowicz M, *et al*. Mr spectroscopy findings in retired professional rugby League players. *Int J Sports Med* 2017;38:241–52.
68 Walton SR, Powell JR, Brett BL, *et al*. Associations of lifetime concussion history and repetitive head impact exposure with resting-state functional connectivity in former collegiate American football players: an NCAA 15-year follow-up study. *PLoS ONE* 2022;17:e0273918.
69 Guell X, Arnold Anteraper S, Gardner AJ, *et al*. Functional connectivity changes in retired rugby League players: a data-driven functional magnetic resonance imaging study. *J Neurotrauma* 2020;37:1788–96.
70 Stamm JM, Koerte IK, Muehlmann M, *et al*. Age at first exposure to football is associated with altered corpus callosum white matter microstructure in former professional football players. *J Neurotrauma* 2015;32:1768–76.
71 Strain JF, Didehbani N, Spence J, *et al*. White matter changes and confrontation naming in retired aging national football League athletes. *J Neurotrauma* 2017;34:372–9.
72 Strain J, Didehbani N, Cullum CM, *et al*. Depressive symptoms and white matter dysfunction in retired NFL players with concussion history. *Neurology* 2013;81:25–32.
73 Koerte IK, Hufschmidt J, Muehlmann M, *et al*. Cavum septi pellucidi in symptomatic former professional football players. *J Neurotrauma* 2016;33:346–53.
74 Lepage C, Muehlmann M, Tripodis Y, *et al*. Limbic system structure volumes and associated neurocognitive functioning in former NFL players. *Brain Imaging Behav* 2019;13:725–34.
75 Alosco ML, Tripodis Y, Baucom ZH, *et al*. White matter hyperintensities in former American football players. *Alzheimers Dement* 2023;19:1260–73.
76 Kaufmann D, Sollmann N, Kaufmann E, *et al*. Age at first exposure to tackle football is associated with cortical thickness in former professional American football players. *Cereb Cortex* 2021;31:3426–34.
77 Alosco ML, Tripodis Y, Koerte IK, *et al*. Interactive effects of racial identity and repetitive head impacts on cognitive function, structural mri-derived volumetric measures, and cerebrospinal fluid tau and Aβ. *Front Hum Neurosci* 2019;13:440.
78 Gardner RC, Hess CP, Brus-Ramer M, *et al*. Cavum septum pellucidum in retired American pro-football players. *J Neurotrauma* 2016;33:157–61.
79 Stanwell P, Iverson GL, Van Patten R, *et al*. Examining for cavum septum pellucidum and ventricular enlargement in retired elite-level rugby League players. *Front Neurol* 2022;13:817709.
80 Brett BL, Walton SR, Meier TB, *et al*. Head impact exposure, gray matter volume, and moderating effects of estimated intelligence quotient and educational attainment in former athletes at midlife. *Journal of Neurotrauma* 2022;39:497–507.
81 Roberts AL, Pascual-Leone A, Speizer FE, *et al*. Exposure to American football and neuropsychiatric health in former national football League players: findings from the football players health study. *Am J Sports Med* 2019;47:2871–80.
82 Gouttebarge V, Frings-Dresen MHW, Sluiter JK. Mental and psychosocial health among current and former professional footballers. *Occup Med (Lond)* 2015;65:190–6.
83 Iverson GL, Terry DP, Caccese JB, *et al*. Age of first exposure to football is not associated with midlife brain health problems. *Journal of Neurotrauma* 2021;38:538–45.
84 Montenigro PH, Alosco ML, Martin BM, *et al*. Cumulative head impact exposure predicts later-life depression, apathy, executive dysfunction, and cognitive impairment in former high school and College football players. *J Neurotrauma* 2017;34:328–40.
85 DeFreese JD, Walton SR, Kerr ZY, *et al*. Transition-Related psychosocial factors and mental health outcomes in former national football League players: an NFL-LONG study. *J Sport Exerc Psychol* 2022;44:169–76.
86 Gouttebarge V, Kerkhoffs G, Lambert M. Prevalence and determinants of symptoms of common mental disorders in retired professional rugby union players. *Eur J Sport Sci* 2016;16:595–602.
87 Fernandes GS, Parekh SM, Moses J, *et al*. Depressive symptoms and the general health of retired professional footballers compared with the general population in the UK: a case-control study. *BMJ Open* 2019;9:e030056.
88 Van Patten R, Iverson GL, Terry DP, *et al*. Predictors and correlates of perceived cognitive decline in retired professional rugby League players. *Front Neurol* 2021;12:676762.

89 Guskiewicz KM, Marshall SW, Bailes J, *et al*. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery* 2005;57:719–26.
90 Iverson GL, Merz ZC, Terry DP. Examining the research criteria for traumatic encephalopathy syndrome in middle-aged men from the general population who played contact sports in high school. *Front Neurol* 2021;12:632618.
91 Randolph C, Karantzoulis S, Guskiewicz K. Prevalence and characterization of mild cognitive impairment in retired National football League players. *J Int Neuropsychol Soc* 2013;19:873–80.
92 Walton SR, Brett BL, Chandran A, *et al*. Mild cognitive impairment and dementia reported by former professional football players over 50 yr of age: an NFL-LONG study. *Med Sci Sports Exerc* 2022;54:424–31.
93 Guskiewicz KM, Marshall SW, Bailes J, *et al*. Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc* 2007;39:903–9.
94 Kerr ZY, Marshall SW, Harding HP, *et al*. Nine-year risk of depression diagnosis increases with increasing self-reported concussions in retired professional football players. *Am J Sports Med* 2012;40:2206–12.
95 Brett BL, Kerr ZY, Chandran A, *et al*. A dominance analysis of subjective cognitive complaint comorbidities in former professional football players with and without mild cognitive impairment. *J Int Neuropsychol Soc* 2022:1–12.
96 Walton SR, Kerr ZY, Mannix R, *et al*. Subjective concerns regarding the effects of sport-related concussion on long-term brain health among former NFL players: an NFL-LONG study. *Sports Med* 2022;52:1189–203.
97 Roberts AL, Zafonte RD, Speizer FE, *et al*. Modifiable risk factors for poor cognitive function in former american-style football players: findings from the Harvard football players health study. *J Neurotrauma* 2021;38:189–95.
98 Schaffert J, LoBue C, Fields L, *et al*. Neuropsychological functioning in ageing retired NFL players: a critical review. *Int Rev Psychiatry* 2020;32:71–88.
99 Terpstra AR, Vasquez BP, Colella B, *et al*. Comprehensive neuropsychiatric and cognitive characterization of former professional football players: implications for neurorehabilitation. *Front Neurol* 2019;10:712.
100 Iverson GL, Büttner F, Caccese JB. Age of first exposure to contact and collision sports and later in life brain health: a narrative review. *Front Neurol* 2021;12:727089.
101 Brand KP, Finkel AM. A decision-analytic approach to addressing the evidence about football and chronic traumatic encephalopathy. *Semin Neurol* 2020;40:450–60.
102 Kristman VL, Borg J, Godbolt AK, *et al*. Methodological issues and research recommendations for prognosis after mild traumatic brain injury: results of the International collaboration on mild traumatic brain injury prognosis. *Archives of Physical Medicine and Rehabilitation* 2014;95:S265–77.
103 Kent P, Cancelliere C, Boyle E, *et al*. A conceptual framework for prognostic research. *BMC Med Res Methodol* 2020;20:172.
104 Doherty M. What value case reports? *Ann Rheum Dis* 1994;53:1–2.
105 McCrory P, Meeuwisse W, Dvorak J, *et al*. Consensus statement on concussion in sport—the 5 th International Conference on concussion in sport held in Berlin, October 2016 . *Br J Sports Med* 2017;51:bjsports–2017
106 Cooper C, Dawson S, Peters J, *et al*. Revisiting the need for a literature search narrative: a brief methodological note. *Res Synth Methods* 2018;9:361–5.
107 Cancelliere C, Cassidy JD, Li A, *et al*. Systematic search and review procedures: results of the International collaboration on mild traumatic brain injury prognosis. *Arch Phys Med Rehabil* 2014;95:S101–31.
108 Iverson GL, Terry DP. High school football and risk for depression and suicidality in adulthood: findings from a national longitudinal study. *Front Neurol* 2022;12:812604.
109 Iverson GL, Merz ZC, Terry DP. Playing high school football is not associated with an increased risk for suicidality in early adulthood. *Clin J Sport Med* 2021;31:469–74.
110 Deshpande SK, Hasegawa RB, Weiss J, *et al*. The association between adolescent football participation and early adulthood depression. *PLoS One* 2020;15:e0229978.
111 Bohr AD, Boardman JD, McQueen MB. Association of adolescent sport participation with cognition and depressive symptoms in early adulthood. *Orthop J Sports Med* 2019;7:2325967119868658.
112 Janssen PHH, Mandrekar J, Mielke MM, *et al*. High school football and late-life risk of neurodegenerative syndromes, 1956-1970. *Mayo Clin Proc* 2017;92:66–71.
113 Savica R, Parisi JE, Wold LE, *et al*. High school football and risk of neurodegeneration: a community-based study. *Mayo Clin Proc* 2012;87:335–40.
114 Brett BL, Kerr ZY, Walton SR, *et al*. Longitudinal trajectory of depression symptom severity and the influence of concussion history and physical function over a 19-year period among former national football League (NFL) players: an NFL-LONG study. *J Neurol Neurosurg Psychiatry* 2022;93:272–9.
115 Daneshvar DH, Mez J, Alosco ML, *et al*. Incidence of and mortality from amyotrophic lateral sclerosis in national football League athletes. *JAMA Netw Open* 2021;4:e2138801.
116 Kmush BL, Mackowski M, Ehrlich J, *et al*. Association of professional football cumulative head impact index scores with all-cause mortality among national football League players. *JAMA Netw Open* 2020;3:e204442.
117 Nguyen VT, Zafonte RD, Chen JT, *et al*. Mortality among professional american-style football players and professional American baseball players. *JAMA Netw Open* 2019;2:e194223.
118 Lehman EJ, Hein MJ, Gersic CM. Suicide mortality among retired National football League players who played 5 or more seasons. *Am J Sports Med* 2016;44:2486–91.
119 Lehman EJ, Hein MJ, Baron SL, *et al*. Neurodegenerative causes of death among retired National football League players. *Neurology* 2012;79:1970–4.
120 Russell ER, Mackay DF, Stewart K, *et al*. Association of field position and career length with risk of neurodegenerative disease in male former professional soccer players. *JAMA Neurol* 2021;78:1057–63.
121 Weiss J, Rabinowitz AR, Deshpande SK, *et al*. Participation in collision sports and cognitive aging among Swedish twins. *Am J Epidemiol* 2021;190:2604–11.
122 Russell ER, McCabe T, Mackay DF, *et al*. Mental health and suicide in former professional soccer players. *J Neurol Neurosurg Psychiatry* 2020;91:1256–60.
123 Piantella S, McDonald SJ, Maruff P, *et al*. Assessing the long-term impact of concussion upon cognition: a 5-year prospective investigation. *Arch Clin Neuropsychol* 2020;35:482–90.
124 Mackay DF, Russell ER, Stewart K, *et al*. Neurodegenerative disease mortality among former professional soccer players. *N Engl J Med* 2019;381:1801–8.
125 Porter MD. A 9-year controlled prospective neuropsychologic assessment of amateur boxing. *Clin J Sport Med* 2003;13:339–52.
126 Baron SL, Hein MJ, Lehman E, *et al*. Body mass index, playing position, race, and the cardiovascular mortality of retired professional football players. *Am J Cardiol* 2012;109:889–96.
127 Lincoln AE, Vogel RA, Allen TW, *et al*. Risk and causes of death among former national football League players (1986–2012). *Med Sci Sports Exerc* 2018;50:486–93.
128 Taioli E. All causes of mortality in male professional soccer players. *Eur J Public Health* 2007;17:600–4.
129 Belli S, Vanacore N. Proportionate mortality of Italian soccer players: is amyotrophic lateral sclerosis an occupational disease? *Eur J Epidemiol* 2005;20:237–42.
130 Pupillo E, Bianchi E, Vanacore N, *et al*. Increased risk and early onset of ALS in professional players from Italian soccer teams. *Amyotroph Lateral Scler Frontotemporal Degener* 2020;21:403–9.
131 Valenti M, Pontieri FE, Conti F, *et al*. Amyotrophic lateral sclerosis and sports: a case-control study. *Eur J Neurol* 2005;12:223–5.
132 Chiò A, Benzi G, Dossena M, *et al*. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain* 2005;128:472–6.
133 Chiò A, Calvo A, Dossena M, *et al*. Als in Italian professional soccer players: the risk is still present and could be soccer-specific. *Amyotrophic Lateral Sclerosis* 2009;10:205–9.
134 Deshpande SK, Hasegawa RB, Rabinowitz AR, *et al*. Association of playing high school football with cognition and mental health later in life. *JAMA Neurol* 2017;74:909–18.
135 Stamm JM, Bourlas AP, Baugh CM, *et al*. Age of first exposure to football and later-life cognitive impairment in former NFL players. *Neurology* 2015;84:1114–20.
136 Iverson GL, Caccese JB, Merz ZC, *et al*. Age of first exposure to football is not associated with later-in-life cognitive or mental health problems. *Front Neurol* 2021;12:647314.
137 Schultz V, Stern RA, Tripodis Y, *et al*. Age at first exposure to repetitive head impacts is associated with smaller thalamic volumes in former professional American football players. *J Neurotrauma* 2018;35:278–85.
138 Kunkle BW, Schmidt M, Klein H-U, *et al*. Novel Alzheimer disease risk loci and pathways in African American individuals using the African genome resources panel: a meta-analysis. *JAMA Neurol* 2021;78:102–13.
139 Guo Y, Liu F-T, Hou X-H, *et al*. Predictors of cognitive impairment in Parkinson's disease: a systematic review and meta-analysis of prospective cohort studies. *J Neurol* 2021;268:2713–22.
140 Qin W, Li W, Wang Q, *et al*. Race-related association between APOE genotype and Alzheimer's disease: a systematic review and meta-analysis. *JAD* 2021;83:897–906.
141 Wang Y-Y, Ge Y-J, Tan C-C, *et al*. The proportion of ApoE4 carriers among non-demented individuals: a pooled analysis of 389,000 community-dwellers. *JAD* 2021;81:1331–9.
142 Emrani S, Arain HA, DeMarshall C, *et al*. Apoe4 is associated with cognitive and pathological heterogeneity in patients with Alzheimer's disease: a systematic review. *Alzheimers Res Ther* 2020;12:141.
143 Lumsden AL, Mulugeta A, Zhou A, *et al*. Apolipoprotein E (ApoE) genotype-associated disease risks: a phenome-wide, registry-based, case-control study utilising the UK Biobank. *EBioMedicine* 2020;59:102954.
144 Yu J-T, Xu W, Tan C-C, *et al*. Evidence-Based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry* 2020;91:1201–9.
145 Li X-Y, Zhang M, Xu W, *et al*. Midlife modifiable risk factors for dementia: a systematic review and meta-analysis of 34 prospective cohort studies. *Curr Alzheimer Res* 2019;16:1254–68.
146 Desai R, John A, Stott J, *et al*. Living alone and risk of dementia: a systematic review and meta-analysis. *Ageing Res Rev* 2020;62:101122.

147 Tokgöz S, Claassen JAHR. Exercise as potential therapeutic target to modulate Alzheimer's disease pathology in APOE ε4 carriers: a systematic review. *Cardiol Ther* 2021;10:67–88.
148 Roseborough AD, Saad L, Goodman M, *et al*. White matter hyperintensities and longitudinal cognitive decline in cognitively normal populations and across diagnostic categories: a meta-analysis, systematic review, and recommendations for future study harmonization. *Alzheimers Dement* 2023;19:194–207.
149 van den Berg E, Geerlings MI, Biessels GJ, *et al*. White matter hyperintensities and cognition in mild cognitive impairment and Alzheimer's disease: a domain-specific meta-analysis. *JAD* 2018;63:515–27.
150 Iso-Markku P, Kujala UM, Knittle K, *et al*. Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case-control studies. *Br J Sports Med* 2022;56:701–9.
151 García-Casares N, Gallego Fuentes P, Barbancho MÁ, *et al*. Alzheimer's disease, mild cognitive impairment and Mediterranean diet. A systematic review and dose-response meta-analysis. *J Clin Med* 2021;10:4642.
152 Guay-Gagnon M, Vat S, Forget M-F, *et al*. Sleep apnea and the risk of dementia: a systematic review and meta-analysis. *J Sleep Res* 2022;31:e13589.
153 Yap NLX, Kor Q, Teo YN, *et al*. Prevalence and incidence of cognitive impairment and dementia in heart failure-a systematic review, meta-analysis and meta-regression. *Hellenic J Cardiol* 2022;67:48–58.
154 Qin J, He Z, Wu L, *et al*. Prevalence of mild cognitive impairment in patients with hypertension: a systematic review and meta-analysis. *Hypertens Res* 2021;44:1251–60.
155 Harris KM. *The National Longitudinal Study of Adolescent to Adult Health (Add Health), Waves I & II, 1994–1996; Wave III, 2001–2002; Wave IV, 2007-2009 [machine-readable data file and documentation]*. Chapel Hill, NC: Carolina Population Center, University of North Carolina at Chapel Hill, 2009.
156 Grassano M, Calvo A, Moglia C, *et al*. Systematic evaluation of genetic mutations in ALS: a population-based study. *J Neurol Neurosurg Psychiatry* 2022;93:1190–3.
157 Longinetti E, Mariosa D, Larsson H, *et al*. Physical and cognitive fitness in young adulthood and risk of amyotrophic lateral sclerosis at an early age. *Eur J Neurol* 2017;24:137–42.
158 Ingre C, Roos PM, Piehl F, *et al*. Risk factors for amyotrophic lateral sclerosis. *Clin Epidemiol* 2015;7:181–93.
159 Livingston G, Huntley J, Sommerlad A, *et al*. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020;396:413–46.
160 Alipour J, Payandeh A. Common errors in reporting cause-of-death statement on death certificates: a systematic review and meta-analysis. *J Forensic Leg Med* 2021;82:102220.
161 Pritt BS, Hardin NJ, Richmond JA, *et al*. Death certification errors at an academic institution. *Arch Pathol Lab Med* 2005;129:1476–9.
162 Romero JP, Benito-León J, Louis ED, *et al*. Under reporting of dementia deaths on death certificates: a systematic review of population-based cohort studies. *JAD* 2014;41:213–21.
163 HILL AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295–300.
164 Goldfinger MH, Ling H, Tilley BS, *et al*. The aftermath of boxing revisited: identifying chronic traumatic encephalopathy pathology in the original corsellis boxer series. *Acta Neuropathol* 2018;136:973–4.
165 Corsellis JA, Bruton CJ, Freeman-Browne D. The aftermath of boxing. *Psychol Med* 1973;3:270–303.
166 Buckland ME, Sy J, Szentmariay I, *et al*. Chronic traumatic encephalopathy in two former Australian National rugby League players. *Acta Neuropathol Commun* 2019;7:97.
167 Bieniek KF, Blessing MM, Heckman MG, *et al*. Association between contact sports participation and chronic traumatic encephalopathy: a retrospective cohort study. *Brain Pathol* 2020;30:63–74.
168 McCann H, Bahar AY, Burkhardt K, *et al*. Prevalence of chronic traumatic encephalopathy in the Sydney brain bank. *Brain Commun* 2022;4:fcac189.
169 Postupna N, Rose SE, Gibbons LE, *et al*. The delayed neuropathological consequences of traumatic brain injury in a community-based sample. *Front Neurol* 2021;12:624696.
170 Forrest SL, Kril JJ, Wagner S, *et al*. Chronic traumatic encephalopathy (CTE) is absent from a European community-based aging cohort while cortical aging-related tau astrogliopathy (ARTAG) is highly prevalent. *J Neuropathol Exp Neurol* 2019;78:398–405.
171 Suter CM, Affleck AJ, Lee M, *et al*. Chronic traumatic encephalopathy in a routine neuropathology service in Australia. *J Neuropathol Exp Neurol* 2022;81:790–5.
172 Priemer DS, Iacono D, Rhodes CH, *et al*. Chronic traumatic encephalopathy in the brains of military personnel. *N Engl J Med* 2022;386:2169–77.