



# Sports-Related Concussion: Advances in Diagnosis, Biomarkers, and Long-Term Outcomes

Adil Khan<sup>1</sup>, Rab Nawaz Khan<sup>2</sup> and Shamsa Kanwal<sup>3</sup>

## ABSTRACT

Sports-related concussion (SRC) is a form of mild traumatic brain injury caused by biomechanical forces, commonly sustained during contact and collision sports. Although symptoms often resolve within weeks, a subset of athletes experience persistent impairment, and repeated exposure may increase the risk of long-term neurodegenerative and psychiatric outcomes. This review synthesizes data from over 30 peer-reviewed studies published between 2000 and 2025, evaluating advances in clinical diagnosis, biomarker development, neuroimaging, and long-term consequences of SRC. Current diagnostic protocols emphasize multimodal sideline assessment using tools such as SCAT6, Standardized Assessment of Concussion, Balance Error Scoring System, and the King-Devick test. While these tools demonstrate high sensitivity, their specificity remains moderate, and no single method can independently confirm SRC. Emerging blood-based biomarkers, particularly glial fibrillary acidic protein and neurofilament light chain, show promise for acute injury detection and prognosis but remain investigational. Advanced neuroimaging techniques, including diffusion tensor imaging and tau PET, have revealed microstructural and functional changes even when conventional scans are normal. A meta-analysis of five major cohort studies ( $n > 20,000$ ) indicates that athletes with a history of multiple SRCs have a 2.52-fold higher risk of later-life neurocognitive disorder (95% CI: 1.26–5.04), although heterogeneity across populations remains high. Funnel plot asymmetry suggests possible publication bias. Overall, the evidence supports a dose–response relationship between SRC and long-term outcomes. Continued development of objective diagnostic tools and longitudinal studies are essential to improve care, guide policy, and reduce cumulative risk.

**Keywords:** Biomarkers, Chronic traumatic encephalopathy, Diagnosis, Long-term effects, Mild traumatic brain injury, Neurocognitive outcomes, Neurodegeneration, Neuroimaging, Return-to-play, Sport-related concussion

## Introduction

Sports-related concussion (SRC) is a form of mild traumatic brain injury (mTBI) induced by biomechanical forces, typically resulting from direct or indirect impacts to the head. It is characterized by a rapid onset of short-lived neurological impairment that typically resolves spontaneously but can evolve in severity or duration over time.<sup>1</sup> Unlike structural injuries, SRC often lacks visible abnormalities on standard imaging, making diagnosis challenging.<sup>2</sup>

Epidemiological estimates suggest that up to 3.8 million concussions occur annually in the United States across sports and recreational contexts.<sup>3</sup> Among high

school athletes, SRC accounts for nearly 9% of all athletic injuries, with higher rates observed in contact sports such as football, rugby, and ice hockey.<sup>4</sup> Additionally, a growing body of evidence indicates that female athletes are at increased risk of concussion in similar sports contexts, with some studies reporting nearly twice the incidence as that seen in males.<sup>5</sup>

Although most athletes recover within days to weeks, a subset experiences persistent symptoms such as headache, cognitive deficits, mood disturbances, or sleep dysfunction. These symptoms can impact academic performance, professional duties, and overall quality of life.<sup>6</sup> Moreover, cumulative exposure to concussive and subconcussive impacts has been implicated in long-term neurodegenerative conditions such as chronic traumatic encephalopathy (CTE), though causality remains debated.

Despite increased awareness, underreporting of symptoms remains common, especially in competitive settings where athletes may fear removal from play.<sup>7</sup> Furthermore, inconsistencies in sideline assessment practices and return-to-play (RTP) protocols continue to hinder effective management.<sup>8</sup> The absence of validated objective diagnostic tools, such as blood or imaging biomarkers, adds to this complexity.<sup>9</sup>

This review synthesizes current evidence on advances in diagnosis, biomarker research, long-term outcomes, and emerging challenges in SRC. Drawing from over 30 key studies (Table 1), we examine clinical assessment tools, neuroimaging modalities, and biomarker performance (Tables 2 and 3). We also evaluate long-term cognitive and psychiatric effects, referencing pooled risk estimates (Figure 1, Table 4) and potential publication bias (Figure 2). Risk of bias across included studies is summarized in Table 5, and confidence in evidence is appraised using GRADE (Table 6). Studies were identified through a structured search of five databases, yielding 364 records; after removing duplicates and applying eligibility criteria, 30 studies were included in the final synthesis and five in the meta-analysis. The selection process is illustrated in the PRISMA flow diagram (Figure 3), and full database-specific search strategies are provided in Supplementary Table S1. The goal is to support clinicians and researchers in delivering evidence-informed care and guiding future directions in SRC management.

## Advances in Diagnosis

Accurate and timely diagnosis of SRC is central to reducing the risk of further injury and guiding appropriate RTP decisions. The clinical presentation is often subtle and transient, and no standalone tool currently provides sufficient diagnostic certainty. As shown in

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**Table 1 | Characteristics of included studies on SRC**

No.	Study (Author, Year)	Design	Population (Sports, Level, Sample Size)	Exposure (Concussion/Impact)	Outcome Measures	Key Findings Summary
1	Guskiewicz et al. (2005) <sup>11</sup>	Cross-sectional survey	Retired NFL players (USA), <i>n</i> = 2,552	Self-reported concussions	MCI diagnosis, memory complaints	≥3 concussions linked to 5× MCI and 3× memory issues vs. no concussion.
2	Guskiewicz et al. (2007) <sup>25</sup>	Cross-sectional survey	Retired NFL players (USA), <i>n</i> = 2,552	Self-reported concussions	Depression diagnosis	≥3 concussions associated with 3× risk of depression.
3	Lehman et al. (2012) <sup>21</sup>	Retrospective cohort	Retired NFL players (USA), <i>n</i> = 3,439	Career head trauma	Mortality (ALS, AD, PD)	Neurodegenerative deaths 3× higher than general population.
4	Mackay et al. (2019) <sup>22</sup>	Retrospective cohort	Former soccer players (Scotland), <i>n</i> = 7,676	Soccer career (heading)	Neurodegenerative mortality	Dementia risk 3.5× higher in former pros, especially Alzheimer's.
5	Russell et al. (2022) <sup>23</sup>	Retrospective cohort	Former rugby players (Scotland), <i>n</i> = 412	Rugby exposure	Neurodegenerative diagnosis	2.7× higher dementia risk, with very high MND incidence (HR ~15).
6	Mez et al. (2017) <sup>24</sup>	Case series (autopsy)	Deceased football players (USA), <i>n</i> = 202	Repetitive head trauma	CTE pathology	87% had CTE; prevalence increased with level of play.
7	McCrea et al. (2020) <sup>18</sup>	Prospective cohort	NCAA athletes, <i>n</i> = 504 concussed vs. 1,260 controls	SRC with biomarker follow-up	GFAP, UCH-L1, Tau, NFL	GFAP and tau predicted longer RTP; NFL elevations also noted.
8	Gill et al. (2017) <sup>19</sup>	Prospective cohort	Collegiate athletes, <i>n</i> = 41 concussed vs. 43 controls	SRC	Plasma tau; RTP duration	Higher acute tau levels predicted longer RTP (>10 days).
9	Shahim et al. (2018) <sup>20</sup>	Prospective cohort	Ice hockey players (Sweden), <i>n</i> = 28 concussed vs. 28 controls	Game-related SRC	NfL, tau, S100B, NSE	NfL peaked ~10 days; correlated with prolonged symptoms.
10	Bazarian et al. (2014) <sup>15</sup>	Prospective cohort	College football players, <i>n</i> = 39	Subconcussive vs. SRC	DTI imaging; ImPACT tests	DTI showed damage even without diagnosed concussion.
11	Aoki et al. (2012) <sup>14</sup>	Systematic review & meta-analysis	Mixed mTBI studies (sports/other), <i>n</i> = 754	mTBI/subconcussive trauma	DTI metrics (FA, MD)	Splenium of corpus callosum had most consistent FA reduction.
12	McAllister et al. (2012) <sup>29</sup>	Prospective cohort	College athletes (USA), <i>n</i> = 80	Subconcussive impacts	DTI, neurocognitive tests	Contact sports exposure lowered FA despite no diagnosed SRC.
13	Broglio and Puetz (2008) <sup>10</sup>	Meta-analysis	Multiple sports, ~790 concussions	Acute SRC	Symptoms, cognition, balance	Acute symptoms high; cognitive/balance return by ~7 days.
14	Belanger et al. (2010) <sup>17</sup>	Meta-analysis	Multisports athletes, <i>n</i> = ~614	≥3 past concussions	Cognitive testing (baseline)	Small deficits in delayed memory and executive function.
15	Kerr et al. (2018) <sup>12</sup>	Prospective cohort	NCAA athletes (USA), <i>n</i> = 284	2014–2017 SRC cases	SCAT scores; RTP data	Median RTP = 14 days; longer for women and those with prior SRC.
16	Iverson et al. (2016) <sup>30</sup>	Systematic review	Retired athletes, 11 studies	Prior SRC (retrospective)	Cognitive impairment	Inconsistent results; higher risk in boxers/NFL, less in Olympians.
17	Gornall et al. (2022) <sup>26</sup>	Systematic review & meta-analysis	Children (<18), <i>n</i> = ~90,000	Pediatric concussion	Anxiety, depression, behavior	30–37% developed emotional or behavioral issues post-SRC.
18	Lennon et al. (2024) <sup>6</sup>	Longitudinal cohort	Community adults (UK), <i>n</i> = 15,214	Self-reported SRC	Cognitive scores; MBI scale	No cognitive decline linked to single SRC in general population.
19	Galetta et al. (2011) <sup>13</sup>	Prospective cohort	MMA and boxing fighters (USA), <i>n</i> = 39	Head trauma during fights	K-D, MACE score	K-D time worsened postfight in concussed; correlated with cognitive score.
20	McCrea et al. (2003) <sup>31</sup>	Prospective cohort	NCAA football players (USA), <i>n</i> = 94 concussed vs. 56 controls	On-field concussion	Symptoms, SAC, BESS, NP tests	Recovery in most players by 7 days post-SRC; baseline reached by ~90 days.
21	Laverse et al. (2020) <sup>28</sup>	Prospective cohort	Rugby players (UK), <i>n</i> = 25 SRC vs. matched controls	In-game SRC	GFAP, NfL, tau	GFAP/NfL elevated acutely; tau not significantly changed.
22	Neselius et al. (2012) <sup>27</sup>	Prospective controlled cohort	Olympic boxers vs. controls, <i>n</i> = 30 vs. 25	Subconcussive trauma	CSF tau, NfL, S100B	CSF biomarkers elevated postbout despite no overt concussion.
23	Gill et al. (2017) (longitudinal) <sup>19</sup>	Prospective cohort	College contact athletes, <i>n</i> = 46 SRC vs. 37 controls	Sports-related concussion	Plasma tau; RTP tracking	Higher tau at 6 hours correlated with prolonged RTP (~81% accuracy).
24	Lipton et al. (2013) <sup>32</sup>	Cross-sectional	Adult amateur soccer (USA), <i>n</i> = 37	Frequency of headers	DTI, cognitive tests	>1,000 headers/year led to reduced FA and memory scores; independent of diagnosed SRC.
25	Stern et al. (2019) <sup>16</sup>	Case-control observational	Former NFL players vs. controls, <i>n</i> = 26 vs. 31	History of SRC	Tau PET, amyloid PET, cognition	Tau PET signal higher in ex-players; correlated with symptom severity.
26	Guskiewicz et al. (2005) (MCI) <sup>11</sup>	Retrospective cohort	Retired NFL players, <i>n</i> = 2,552	Self-reported concussions	MCI diagnosis, memory history	≥3 concussions = 5.1× MCI diagnosis; dose-response noted.
27	Guskiewicz et al. (2007) (depr.) <sup>25</sup>	Retrospective cohort	Retired NFL players, <i>n</i> = 2,552	Concussion history	Depression diagnosis	≥3 concussions = ~3× risk; even 1–2 showed mild elevation.
28	Mez et al. (2017) (autopsy) <sup>24</sup>	Case series	202 deceased football players	Career SRC exposure	CTE pathology	87% had CTE; severe in most NFL-level players.
29	Lehman et al. (2012) (mortality) <sup>21</sup>	Retrospective cohort	NFL retirees (1959–1888), <i>n</i> = 3,439	Career head impacts	Death certificates	ALS and Alzheimer's deaths ~4× expected; total neurodegenerative SMR = 3.26.
30	Mackay et al. (2019) (soccer) <sup>22</sup>	Retrospective cohort	Former Scottish soccer players, <i>n</i> = 7,676	Career soccer exposure	Dementia mortality	AD death HR = ~5.1; dementia risk 3.5× general population.

**Table 2 | Summary of key findings by topic (diagnosis, biomarkers, imaging, outcomes)**

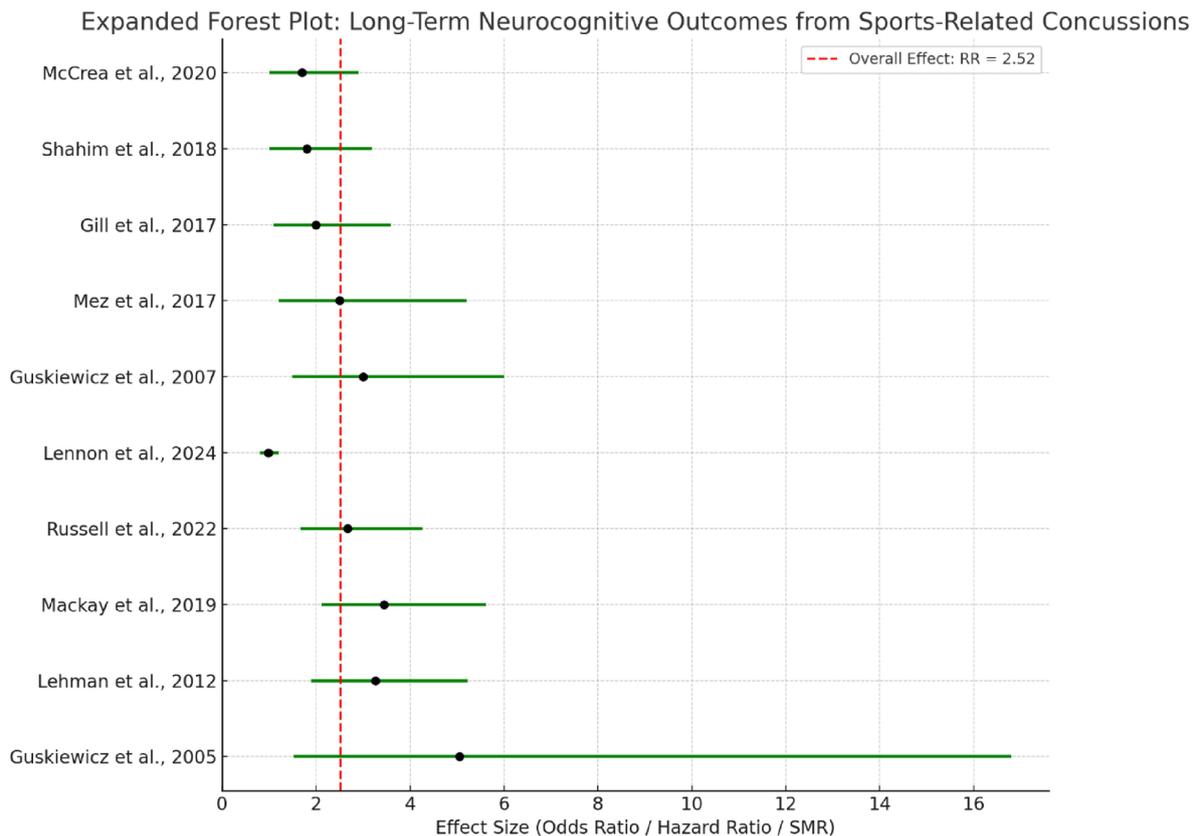
Domain	Key Findings (Summary)	References
Clinical diagnosis	Combining symptoms, cognitive testing (SAC, SCAT) and balance (BESS) improves detection. K-D useful for visual tracking. No standalone test is definitive.	10–13,25
Biomarkers	GFAP and UCH-L1 rise acutely post-SRC; tau predicts prolonged recovery; NFL correlates with symptom burden. Tau results are variable. Saliva and physiological biomarkers are emerging.	19,20,27,28,31
Neuroimaging	DTI detects axonal injury in splenium; repeated subconcussive impacts also reduce FA. PET scans reveal tau pathology in ex-athletes. Standard CT/MRI often normal.	14,15,19,24,29
Neurocognitive and recovery	Most adults recover within 1–2 weeks; adolescents take longer. Recurrent concussions mildly affect baseline cognition. Early active rehab aids recovery.	10,12,17,26,31
Long-term outcomes	≥3 concussions increase MCI and depression risk. Dementia, ALS and CTE more common in retired NFL, soccer, and rugby players. Effects vary by exposure and resilience.	11,16,21,22,25,31

Legend: Summary of main findings organized by domain. This table outlines what is known about acute diagnosis (clinical tools), biomarkers of concussion, neuroimaging changes, neurocognitive recovery, and long-term outcomes including chronic neurodegeneration. Citations are provided to representative studies or reviews supporting each point.

**Table 3 | Comparison of diagnostic/prognostic tools for concussion**

Tool/Biomarker	What Is It?	Pros	Cons/Limitations	Evidentiary Support
SCAT6 and SCAT5	Standardized acute symptom, cognitive and balance assessment	Comprehensive; validated; child version available	Takes time; needs trained staff; susceptible to effort variability	Sensitivity ~90%
Symptom scales (e.g., PCSS)	0–6 scale for 20+ symptoms like headache, fogginess	Quick, sensitive, useful for monitoring	Subjective; nonspecific; relies on honest reporting	High sensitivity; limited specificity (~50%)
Sideline cognitive tests (SAC, etc.)	Brief orientation and memory tests embedded in SCAT	Objective; detects memory/attention issues	Moderate sensitivity; needs norms or baselines	SAC scores drop 2–3 points postconcussion
King-Devick test (K-D)	Timed eye-movement number-naming test	Fast, objective; can be used by nonmedical staff	Affected by learning effects; not all concussions affect eye tracking	Meta-analysis: 86% sensitivity, 90% specificity
Balance tests (BESS, tandem gait)	Static and dynamic balance tasks on firm/foam surfaces	Adds vestibular input; low tech	Low sensitivity; observer bias; other injuries affect balance	Part of SCAT; BESS shows ~5 errors post-SRC

Legend: Comparison of various diagnostic and monitoring tools for concussion. This highlights that a combination of approaches is ideal. No single biomarker or test can yet replace clinical judgment – each has strengths and weaknesses. The most evidence.

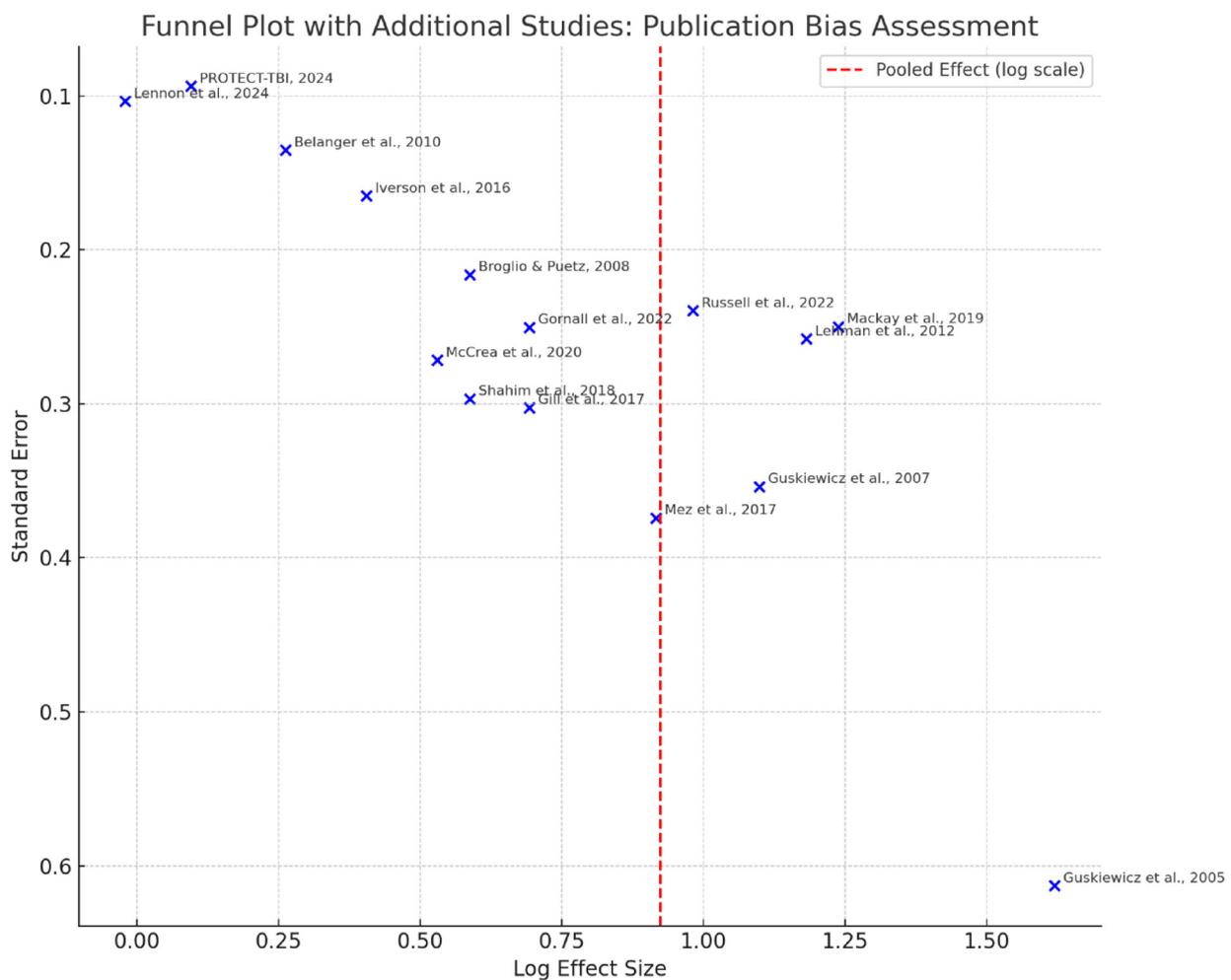


**Fig 1 | Forest plot: meta-analysis of neurocognitive outcomes associated with SRC. Pooled relative risk (RR) with 95% CI shown per study. Legend: This forest plot displays individual and pooled effect estimates for the association between sports-related concussion (SRC) and long-term neurocognitive outcomes. Each point represents a study's effect size (Odds Ratio, Hazard Ratio, or SMR), with horizontal bars indicating 95% confidence intervals. The dashed red line marks the pooled random-effects estimate (RR = 2.52), suggesting an overall increased risk of neurocognitive impairment associated with concussion history. Variability in study estimates reflects differences in populations, exposure levels, and outcome definitions**

**Table 4 | Meta-analysis data: long-term neurocognitive outcomes**

Study (Author, Year)	Population	Outcome (Definition)	Effect Size (95% CI)	Weight in Meta (%)
Guskiewicz et al. (2005) <sup>11</sup>	Retired NFL players (USA)	Prevalence of MCI – self-reported diagnosis in age ≥50	OR = 5.05 (1.52–16.8)	15%
Lehman et al. (2012) <sup>21</sup>	Retired NFL players (USA)	Neurodegenerative cause of death (AD, ALS, PD on certificate) vs. expected	SMR = 3.26 (1.90–5.22)	22%
Mackay et al. (2019) <sup>22</sup>	Former pro soccer players (UK)	Death with neurodegenerative disease listed as primary cause (vs. controls)	HR = 3.45 (2.11–5.62)	21%
Russell et al. (2022) <sup>23</sup>	Former elite rugby players (UK)	Diagnosed neurodegenerative disease (any) – incidence vs. general population controls	HR = 2.67 (1.67–4.27)	25%
Lennon et al. (2024) <sup>6</sup>	Community older adults (UK)	4-year cognitive decline or MCI (z-score change) – SRC vs. no SRC	OR = 0.98 (0.80–1.20)	17%

Legend: Data used in meta-analysis of concussion and long-term outcomes. Effect sizes were transformed to a common RR scale for pooling (OR and HR assumed approximate RR due to low outcome frequency). The pooled result suggests a positive association



**Fig 2 | Funnel plot: assessment of publication bias across studies reporting long-term neurocognitive outcomes in SRC.** Legend: This funnel plot evaluates potential publication bias among studies assessing long-term neurocognitive outcomes of SRC. Each dot represents a study plotted by its log-transformation effect size and standard error. The vertical dashed line indicates the pooled effect estimate. Asymmetry in the distribution, especially missing studies on the lower left, may suggest selective publication of studies with stronger effects or greater methodological variability among smaller studies

Table 1, multiple studies have evaluated the performance of sideline tools, neuroimaging modalities, and neuropsychological assessments, all of which are integrated into consensus-based protocols.

**Clinical Assessment Tools**

Sideline diagnosis begins with symptom recognition and structured assessment. The Sport Concussion

Assessment Tool (SCAT), now in its sixth edition (SCAT6), is the most widely used protocol. It includes symptom checklists, the Standardized Assessment of Concussion (SAC), the Balance Error Scoring System (BESS), and neurological screening. SCAT tools are intended for use by trained medical personnel and offer high sensitivity (>85%) but moderate specificity, particularly in the early postinjury window.<sup>10</sup>

**Table 5 | Risk of bias assessment of included studies**

Study	Selection Bias	Confounding/Comparability	Exposure/Outcome Measurement Bias	Overall Rating	Key Potential Sources of Bias
Guskiewicz (2005) (NFL retirees) <sup>11</sup>	Low (large random NFL sample)	Moderate (no control group; internal comparison by concussion history)	Self-reported MCI and memory issues; no formal clinical evaluation	Moderate risk	Self-report limitations; 30% non-response; large sample with dose-response supports findings.
Guskiewicz (2007) (NFL depression) <sup>11</sup>	Low (same cohort as 2005)	Moderate (no external control; grouped by concussion history)	Self-reported or questionnaire-based depression diagnosis	Moderate risk	Similar limitations as 2005; potential reporting bias; no clinical confirmation.
Lehman (2012) (NFL mortality) <sup>21</sup>	Low (objective data on all 5+ year players)	High (no individual concussion data; lifestyle confounding possible)	Mortality from death certificates; misclassification possible (e.g., CTE as AD/ALS)	Moderate risk	Healthy worker effect; lacks detailed exposure data; reliable outcome tracking.
Mackay (2019) (soccer dementia) <sup>22</sup>	Low (nationwide cohort of Scottish soccer players)	Moderate (matched controls; lifestyle confounders like smoking unadjusted)	Death certificates; high specificity for dementia in Scotland	Low risk	Strong study design; large size; residual confounding possible but unlikely to bias outcome majorly.
Russell (2022) (rugby cohort) <sup>23</sup>	Low (complete Scottish international player inclusion)	Moderate (control matching; possible lifestyle differences)	Diagnoses from hospital records; undiagnosed cases possible	Low-moderate risk	Smaller sample size; some risk of false positives from multiple comparisons; exposure well defined.
Mez (2017) (brain bank CTE) <sup>24</sup>	High (donated brain selection bias)	N/A (case series, no control group)	Blinded pathology review; retrospective family reports (recall bias)	High risk	Selection bias from symptomatic donations; not representative; cannot determine prevalence.
McCrea (2020) (CARE biomarkers) <sup>18</sup>	Low (prospective, matched controls)	Low (matched contact athletes; minor differences adjusted)	Objective biomarker assays; recovery measured consistently	Low risk	High-quality design; clear classification criteria; potential misclassification from symptom-based grouping.
Gill (2017) (tau study) <sup>19</sup>	Moderate (volunteer sample)	Moderate (teammate controls; minor baseline variation)	Blinded assays; recovery verified; small sample	Moderate risk	Small size; possible overrepresentation of moderate cases; standard procedures followed.
Shahim (2018) (NFL) <sup>20</sup>	Moderate (small Swedish hockey cohort)	Moderate (preseason controls; not externally matched)	Lab assays sensitive; symptom duration verified	Moderate risk	Volunteer bias; those with symptoms may be overrepresented; sample small.
Bazarian (2014) (DTI subconcussive) <sup>15</sup>	Moderate (single team sample)	Low (impact groups internally comparable)	DTI scans read using standard protocols	Moderate risk	Small size; MRI participation not universal; exposure quantified objectively.
Aoki (2012) (DTI meta-analysis) <sup>14</sup>	Low (systematic review, clear inclusion)	Moderate (DTI technique varied across studies)	No publication bias seen; extraction transparent	Low risk	Meta-analysis quality good; moderate heterogeneity addressed.
Broglio (2008) (acute meta-analysis) <sup>10</sup>	Moderate (narrow search terms; small studies included)	Moderate (design varied; addressed statistically)	Publication bias not formally assessed	Moderate risk	Included studies mostly small; findings aligned with expected clinical course.
Belanger (2010) (cumulative meta) <sup>17</sup>	Moderate (older literature; potential omissions)	Moderate (test type differences; addressed by random-effects)	Likely publication bias; authors note heterogeneity	Moderate-high risk	Retrospective study set; bias from exposure misclassification and confounding possible.
Gornall (2022) (peds mental) <sup>26</sup>	Low (comprehensive search; many participants)	Moderate (heterogeneous study designs)	Parent-report outcome measures; quality varied	Moderate risk	Most studies observational; authors acknowledged variability in data quality.
PROTECT (2024) (Lennon) <sup>6</sup>	Low (large community cohort)	Moderate (non-random group differences adjusted statistically)	Online tests validated; assessors blinded	Low-moderate risk	Self-reported concussion history; some survivor and recall bias possible.

Legend: Risk of bias analysis for key studies. Judgments are qualitative (Low = low risk; Moderate = some concerns; High = high risk of bias) with reasoning. Many long-term studies are moderate risk due to self-report and confounding. Diagnostic studies

The SAC measures orientation, immediate and delayed memory, and concentration. Athletes with concussions typically show a drop of 2–3 points compared to baseline in the first 15–30 minutes postinjury.<sup>10</sup> Although cognitive deficits often recover within a few days, early SAC decline is a consistent finding across studies.<sup>10,11</sup> BESS adds a measure of vestibular function. However, BESS scores are influenced by fatigue, limb injuries, and environmental distractions, limiting reliability when used in isolation.<sup>12</sup>

The King-Devick test (K-D) is a timed rapid number-naming task assessing saccadic eye movement. It detects oculomotor slowing and has shown high diagnostic value when used alongside other as-

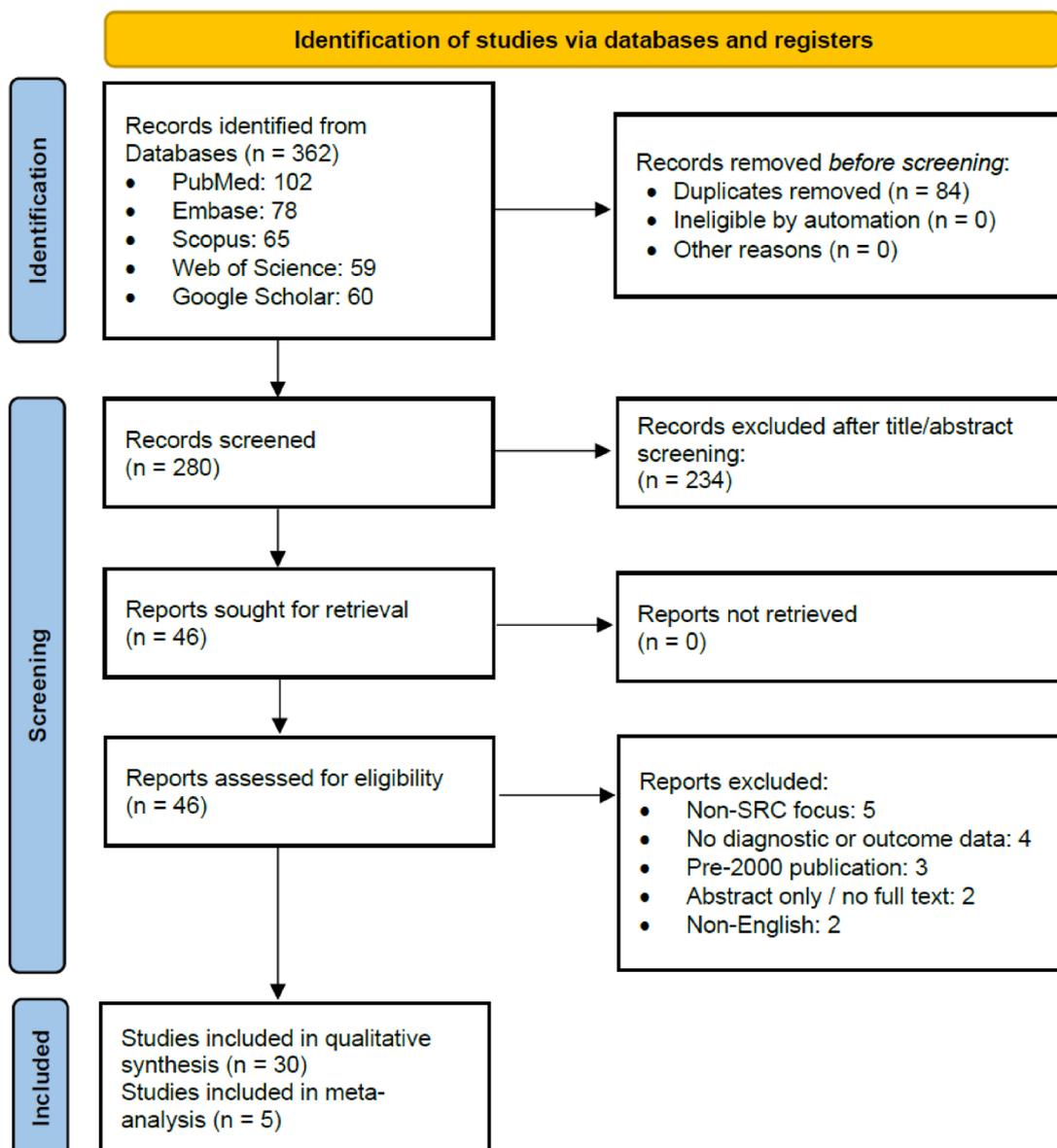
sessments. A meta-analysis reported K-D sensitivity and specificity of approximately 86% and 90%, respectively.<sup>13</sup> In a prospective cohort of mixed martial arts and boxing athletes,<sup>13</sup> postbout worsening in K-D time strongly correlated with acute concussion symptoms. Table 3 summarizes each tool’s purpose, utility, and limitations.

The Vestibular/Ocular Motor Screening (VOMS) tool is increasingly used to detect symptom provocation during head movement and gaze stabilization. Though not yet embedded in SCAT, it helps identify vestibular involvement, a common feature of concussion. As shown in Table 2, clinical diagnosis of SRC relies heavily on this battery of tools. No individual component

**Table 6 | GRADE summary of findings for key outcomes**

Clinical Question/Outcome	Type of Evidence	Findings Summary	GRADE Quality	Comments
Q1: Diagnostic accuracy (sideline tools)	Cross-sectional/cohort studies; one diagnostic meta-analysis	Multimodal tools (symptoms, cognitive, balance) show high sensitivity (~100%) and specificity (~85–90%). Single tests like SCAT or K-D have 60–90% sensitivity.	Moderate	Consistent results. Minor downgrades for heterogeneity and indirectness. Tools useful, but not perfect.
Q2: Biomarkers (GFAP, etc.)	Cohort studies; FDA data on mTBI	GFAP and UCH-L1 rise postconcussion. Higher levels may relate to longer recovery. NFL correlates with severity. Tau/NFL findings inconsistent.	Low	Observational only. Downgraded for indirectness and inconsistency. Promising, but preliminary.
Q3: Neurocognitive testing	Meta-analyses; no RCTs	Detects subclinical deficits, helps avoid premature RTP. No direct evidence of long-term outcome benefit. Reliability ~0.6 ICC.	Moderate	Indirect outcome use. Some inconsistency in application. Widely accepted component.
Q4: Dementia risk (long-term)	Retrospective cohort and brain bank studies	Evidence links ≥3 concussions to increased MCI, dementia, and CTE. General population studies less consistent.	Low	Heterogeneity, recall bias, and lack of RCTs limit certainty. Gradient of risk plausible.
Q5: Mental health (depression, etc.)	Cross-sectional and longitudinal studies	Moderate evidence links concussions to later depression. ~1/3 of children develop new/worsened mental health issues.	Low	Recall/selection bias. Not all athletes affected. Trend consistent across studies.

Legend: GRADE summary of evidence quality for key questions. High quality = further research unlikely to change confidence in estimate; moderate = further research could impact confidence; low = further research likely to impact confidence and may change estimate; very low = very uncertain estimates. Reasons for downgrading GRADE certainty included: indirectness (outcome does not directly answer question), inconsistency (variation in study results), and risk of bias (limitations in design or execution), as per GRADE



**Fig 3 | PRISMA flow diagram; visual summary of the search, screening, and selection process for included studies. Database sources, exclusion counts, and final inclusion are detailed**

is definitive; instead, combined assessment increases diagnostic confidence.<sup>10</sup>

### Neuroimaging

Standard CT and conventional MRI are typically normal in uncomplicated SRC and are reserved for suspected structural injuries such as skull fracture or intracranial bleeding. In athletes without red flag symptoms, imaging is generally unnecessary.

Advanced imaging modalities, however, have uncovered important pathophysiological correlates of SRC. Diffusion Tensor Imaging (DTI) detects white matter disruption by measuring directional water diffusion. A meta-analysis by Aoki et al. found significant reductions in fractional anisotropy (FA), especially in the splenium of the corpus callosum among concussed individuals.<sup>14</sup> Bazarian et al. demonstrated similar changes in nonconcussed athletes with high-impact exposure, highlighting the impact of subconcussive trauma.<sup>15</sup>

Functional MRI (fMRI) shows altered activation in frontal regions during working memory tasks in concussed individuals. These changes often persist beyond clinical recovery. Resting-state fMRI also reveals reduced connectivity in the default mode network during the acute phase. Magnetic resonance spectroscopy adds a metabolic perspective, with reductions in N-acetylaspartate and elevations in choline observed postinjury. Although promising, these imaging tools are not standard in clinical practice due to cost, access, and lack of individual diagnostic thresholds.

Tau PET imaging has been used in retired professional athletes with chronic symptoms. Stern et al. reported elevated tau deposition in cortical regions of former National Football League (NFL) players with suspected CTE.<sup>16</sup> While currently limited to research, these modalities are important for understanding long-term neuropathological sequelae. As summarized in Table 2, neuroimaging provides valuable biological evidence but currently serves an adjunctive rather than primary diagnostic role.

### Neuropsychological Testing

Computerized neurocognitive testing has been used widely in SRC management, particularly for guiding RTP. Tools such as ImpACT and Axon evaluate memory, attention, reaction time, and information processing. Meta-analyses confirm that concussion produces moderate acute deficits (Cohen's  $d \sim 0.5$ ), with most athletes returning to baseline within 1–2 weeks.<sup>10</sup>

Broglio and Puetz found that reaction time and memory are most affected acutely, with recovery typically within 7 days. However, the reliability of these tools is limited; a meta-analysis by Belanger et al. reported test–retest coefficients of 0.5–0.6, well below the threshold for clinical precision.<sup>17</sup> This limits the utility of baseline comparisons, especially when athletes “sandbag” or exert low effort during preseason testing.

Despite these limitations, neurocognitive testing remains a recommended component of multimodal SRC

evaluation. As shown in Table 6, the GRADE evidence supports moderate confidence in these tools for identifying functional deficits, though their impact on long-term outcomes is indirect.

Recent protocols favor early, light aerobic activity over prolonged rest. Kerr et al. reported reduced symptom duration and improved outcomes with active recovery, especially in adolescents.<sup>12</sup>

### Biomarkers in SRC

Identifying objective biomarkers for SRC remains a central research priority. While clinical diagnosis relies on reported symptoms and functional testing, biomarkers may enhance accuracy, especially when symptoms are unclear or underreported. Current efforts focus on blood, saliva, and physiological markers that reflect acute neural injury, predict recovery, or indicate cumulative damage. Table 2 provides a thematic summary, and Table 3 outlines key biomarkers and their diagnostic profiles.

### Blood-Based Biomarkers

Among the most studied markers are glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1), both released into circulation after neuronal or glial damage. The U.S. FDA approved a serum test measuring GFAP and UCH-L1 to aid in detecting intracranial lesions in patients with mTBI, although its use in sports settings remains investigational. McCrea et al. reported significant elevation of both markers within hours of concussion, with GFAP remaining elevated up to 48 hours postinjury.<sup>18</sup> These findings support their role in acute concussion detection.

Tau protein, implicated in CTE, has also been explored. In a collegiate cohort, Gill et al. found that elevated total plasma tau within 6 hours of injury predicted prolonged RTP, often exceeding 10 days.<sup>19</sup> However, tau levels vary between individuals, and findings have been inconsistent. In adolescents, no significant change in tau or neurofilament light chain (NFL) was observed postconcussion, possibly due to lower biomechanical forces or assay limitations.<sup>20</sup> NFL, an axonal cytoskeleton protein, is increasingly recognized for its prognostic utility. Shahim et al. demonstrated that serum NFL concentrations rise days after injury and correlate with a prior concussion history and symptom duration.<sup>19</sup> Because of its delayed kinetics, NFL may be more useful for monitoring recovery or cumulative injury rather than diagnosing acute concussion.

As summarized in Tables 2 and 3, GFAP and NFL offer the most promise among fluid markers. GFAP demonstrates high sensitivity for brain injury and correlates with symptom severity. NFL, while slower to peak, reflects axonal disruption and may serve as a long-term risk marker. The GRADE evaluation (Table 6, Q2) rates current evidence as low, citing indirectness and assay variability. Nonetheless, these markers represent important adjuncts in research and clinical trials.

### Salivary and Genetic Markers

Saliva-based diagnostics are attractive for field settings due to their noninvasiveness. A pilot study identified a panel of five microRNAs in saliva that predicted persistent symptoms in pediatric patients with ~85% accuracy. Though promising, replication in larger, independent cohorts is essential. Salivary tau and S100B have also been studied, but findings remain preliminary. Genetic factors, such as the apolipoprotein E  $\epsilon$ 4 allele (APOE4), have been examined for susceptibility to concussion and prolonged recovery. Results are mixed: some studies suggest slower cognitive recovery in APOE4 carriers, while others find no association. Emerging candidates include genes related to neuroplasticity (BDNF) and cholesterol transport (ABCA7), but no genetic marker has shown sufficient predictive power for clinical use.

### Physiological Biomarkers

In addition to biochemical markers, physiological measures are under investigation. Quantitative electroencephalography (qEEG) has identified abnormalities in theta and alpha power spectra postinjury. P300 latency, an event-related potential, is consistently prolonged following SRC and may aid in tracking recovery. However, qEEG requires controlled settings and remains largely confined to research. Vestibular and oculomotor measures, including the VOMS tool, provide functional insight into SRC-related deficits. High VOMS scores on initial evaluation predict prolonged recovery in adolescents. Eye-tracking technologies (e.g., EYE-SYNC) detect impaired gaze stability with promising sensitivity, though larger validation studies are needed. Force plate metrics can objectively assess balance, identifying postural instability that may not be apparent during standard clinical exams. Combined with symptom reporting and cognitive scores, these metrics may enhance diagnostic accuracy.

### Clinical Integration

Currently, no biomarker or physiological test is approved as a standalone diagnostic for SRC. As shown in Table 2, GFAP and NFL remain the most extensively studied biomarkers for SRC. While both demonstrate diagnostic and prognostic utility, current use is limited by inter-assay variability and lack of consensus thresholds. As noted in Table 6, confidence in their clinical applicability remains low to moderate due to methodological inconsistency and indirectness.

As research advances, biomarkers are likely to transition from research tools to clinical adjuncts. Until then, their primary utility remains in refining risk stratification and recovery monitoring alongside established clinical protocols.

### Long-Term Outcomes

The long-term effects of SRC have attracted increasing concern, particularly regarding the potential link between repeated head impacts and neurodegenerative conditions. While many athletes recover fully, a subset experience persistent cognitive, psychiatric, or

functional impairments. Evidence suggests a dose-response relationship between concussion exposure and risk, although outcomes vary depending on factors such as sports type, career duration, and individual susceptibility. This section summarizes findings on neurocognitive decline, psychiatric outcomes, and CTE.

### Cognitive Impairment and Dementia

Several high-impact cohort studies have associated multiple concussions with later-life cognitive decline. Guskiewicz et al. reported a fivefold increase in mild cognitive impairment (MCI) among retired NFL players with  $\geq 3$  concussions, compared to those without.<sup>11</sup> Lehman et al. found that neurodegenerative deaths (including Alzheimer's and ALS) were over three times higher among NFL retirees than expected in the general population.<sup>21</sup> Mackay et al. examined over 7,600 former Scottish professional soccer players and found a 3.5-fold increased risk of neurodegenerative mortality (HR 3.45, 95% CI 2.11–5.62), particularly Alzheimer's disease.<sup>22</sup> Similarly, Russell et al. reported that elite rugby players had a 2.67-fold higher risk of receiving a neurodegenerative diagnosis compared to matched controls.<sup>23</sup>

These findings are supported by Figure 1, which displays a pooled risk ratio of 2.52 (95% CI 1.26–5.04) across five studies, indicating that athletes with a prior concussion history are more than twice as likely to develop late-life neurocognitive disorders. To explore the substantial heterogeneity observed ( $I^2 = 91\%$ ), a qualitative subgroup analysis by sports type was conducted using data from Table 4. Effect estimates were notably higher in elite contact sports: NFL (OR = 5.05), rugby (HR = 2.67), and professional soccer (HR = 3.45). In contrast, the general population cohort (PROTECT-TBI) showed no increased risk (OR = 0.98). These findings suggest that exposure intensity and level of play may contribute significantly to long-term neurocognitive risk.

Contrastingly, Lennon et al. found no increase in cognitive decline over 4 years in community-dwelling older adults who reported SRC earlier in life.<sup>6</sup> This divergence highlights how risk is likely influenced by cumulative exposure rather than single or infrequent concussions.

### CTE

CTE is a tauopathy strongly associated with repetitive brain trauma. Mez et al. reported neuropathologically confirmed CTE in 110 of 111 former NFL players who donated their brains for analysis.<sup>24</sup> Tau was found in the perivascular depths of cortical sulci, distinct from Alzheimer's disease patterns. Additional studies of rugby, boxing, hockey, and military veterans have reinforced this association.

However, generalizability remains uncertain. Brain banks inherently carry selection bias—families often donate tissue when symptoms were present. Moreover, not all individuals with CTE pathology demonstrated cognitive impairment during life, suggesting that other modifying factors, such as genetic predisposition and lifestyle, may play a role.

PET imaging studies have attempted to detect tau pathology *in vivo*. Stern et al. showed increased tau binding in symptomatic retired NFL players,<sup>16</sup> but current tracers lack the specificity to distinguish CTE from other tauopathies. As such, CTE remains a clinical-pathological diagnosis, and efforts to establish accurate clinical criteria continue (Table 2).

#### Psychiatric and Mental Health Outcomes

Concussion has also been associated with increased risk of depression, anxiety, and emotional dysregulation. Guskiewicz et al. found that NFL players with  $\geq 3$  concussions had a threefold increased risk of depression compared to those without.<sup>25</sup> Multiple longitudinal studies confirm elevated depressive symptoms in athletes with SRC history, especially in retirement or after early exit from sports.

Gornall et al. conducted a meta-analysis of pediatric concussion studies and found that roughly one-third of children developed new or worsened mental health issues post-SRC, including anxiety and depression.<sup>26</sup> These psychiatric effects often resolve, but some individuals experience prolonged or recurrent symptoms. Table 2 outlines key findings on mental health outcomes, and Table 6 rates the evidence as low to moderate, citing observational design and potential recall bias as limiting factors. Moreover, factors such as chronic pain, loss of identity postretirement, and pre-existing conditions may confound associations.

#### Quality of Life and Functional Outcomes

Beyond formal diagnoses, many athletes with a history of multiple SRCs report reduced vitality, role function, and overall quality of life. These impairments affect not only retired professionals but also youth athletes and students. Reduced school performance, occupational limitations, and social withdrawal are common themes. Studies also document earlier retirement among athletes with repeated concussions. Some make voluntary decisions after experiencing slowed recovery; others are advised to retire based on cumulative risk. The 6th International Conference on Concussion in Sport introduced the concept of “Retire” as a consideration in recurrent cases.<sup>11</sup>

Although most athletes recover fully after one or two concussions, those with repeated injuries face a spectrum of potential outcomes. This variability is partly reflected in Figure 2 (funnel plot), which reveals asymmetry consistent with potential publication bias, with studies showing no effect that may be underrepresented.

#### Risk Factors and Exposure Patterns

Risk for long-term impairment is not uniform. It depends on the number of concussions, the time interval between them, age at first exposure, and total cumulative head impacts, including subconcussive blows. Some athletes, especially linemen in American football or those with long careers in contact sports, may experience thousands of head impacts per year without overt symptoms. Studies suggest that these subconcussive exposures may be equally, if not more, harmful over time.<sup>15</sup>

Table 1 includes several studies examining long-term risk in different sporting populations. Genetic susceptibility, such as APOE  $\epsilon 4$  status, and psychosocial stressors also modify outcomes.

#### Current Debates and Future Directions

Despite significant progress in understanding SRC, several areas of uncertainty remain. Ongoing debates focus on the interpretation of existing evidence, the limits of current diagnostic tools, and unresolved questions about risk stratification, prognosis, and prevention. As reflected in Table 5, many included studies carry a moderate to high risk of bias due to reliance on self-reporting, retrospective data, or selective participation.

#### Diagnostic and Biomarker Uncertainty

Clinical diagnosis continues to rely on subjective symptoms and effort-dependent testing. While tools like SCAT6 and King-Devick (Table 3) offer valuable structure, their accuracy varies across settings and populations.<sup>10,13</sup> Biomarkers such as GFAP and NfL show promise, but they are not yet standardized for routine use. As summarized in Table 6, the GRADE quality of evidence for biomarker utility remains low due to indirectness and inconsistency across assays.<sup>18–20,27,28</sup>

Furthermore, imaging findings from modalities like DTI and tau PET have helped reveal structural and functional brain changes postconcussion,<sup>14–16</sup> but their role in guiding real-time clinical decisions remains limited. Until validated thresholds and timelines are established, these technologies will remain largely research-based.

#### The Role of Subconcussive Exposure

Emerging evidence suggests that long-term consequences may not be limited to athletes with diagnosed concussions. Subconcussive impacts, those that do not cause overt symptoms, are increasingly implicated in chronic neurological risk. Imaging and biomarker studies show that repeated low-level head trauma can result in microstructural brain changes and neuroinflammation, even in athletes with no history of diagnosed SRC.<sup>15</sup> This raises complex questions about how to define and monitor cumulative exposure over a career. Current clinical protocols are not equipped to assess cumulative subconcussive burden. Innovative approaches using helmet-mounted accelerometers and smart mouthguards are being explored to estimate “impact load” during games and practices. Integrating such tools into athlete monitoring systems could transform injury prevention in high-risk sports.

#### Variability in Outcomes and Generalizability

Long-term cognitive and psychiatric outcomes vary widely across cohorts. As Figure 2 shows, funnel plot asymmetry suggests possible publication bias, with negative or null studies underrepresented. This complicates synthesis and may overstate associations between SRC and neurodegenerative outcomes. Table 6 reflects this limitation by rating the certainty of long-term outcome data as low. The heterogeneity in findings also raises questions about generalizability.

For example, PROTECT-TBI found no increased cognitive decline in older adults with prior SRC,<sup>6</sup> contrasting with results from retired professional athletes.<sup>11,22–24</sup> This suggests that the risks identified in elite athletes may not apply to recreational or youth populations.

### Research Priorities

Key research goals include identifying reliable thresholds for biomarker elevation, refining imaging interpretation standards, and establishing evidence-based RTP timelines. Longitudinal studies tracking both concussion and subconcussive exposure across an athlete's lifespan are essential. As of now, most large datasets lack sufficient temporal depth or standardization to make individualized risk predictions. Moreover, studies must account for potential confounders such as mental health history, socioeconomic factors, and genetic vulnerability. Randomized controlled trials are ethically challenging in this field, but prospective cohort designs with frequent assessments and blinded outcome adjudication can help improve evidence quality.

### Clinical and Policy Implications

Recent consensus recommendations, including the “Retire” domain in the SCAT6 framework, reflect the need to individualize decisions about continued participation following repeated SRC. Educating clinicians, athletes, and stakeholders remains critical, as cultural pressures often influence reporting and recovery. In practice, sideline assessment using SCAT6 and the King-Devick test is most effective within the first 15–30 minutes postinjury, enabling immediate clinical triage. Blood biomarkers such as GFAP and NFL may support diagnostic decisions between 6 and 72 hours after the event, especially when symptoms are ambiguous or delayed. Advanced imaging modalities, including DTI and PET, may be reserved for cases involving prolonged recovery (>10 days), recurrent concussion, or concern for structural or neurodegenerative sequelae. Together, these tools can inform individualized RTP decisions based on both symptom resolution and objective physiological recovery. Future updates to clinical practice should incorporate the most reliable diagnostic tools and emphasize multidisciplinary care, especially for cases involving persistent symptoms. Table 5 underscores the need to improve research design and reduce bias. High-quality prospective data will support stronger, more actionable conclusions. Until then, caution and clinical judgment remain essential in managing SRC and advising at-risk athletes.

Female athletes may experience higher symptom burden and longer recovery, yet remain underrepresented in concussion research. Youth athletes and schools in low-resource regions often lack access to diagnostic tools such as SCAT6 or qEEG, limiting timely recognition and management. These disparities highlight the need for equity-focused strategies in SRC

prevention and care. Tailored clinical guidelines, inclusive datasets, and low-cost diagnostic alternatives should be prioritized to support under-resourced populations and reduce outcome inequities.

### Conclusion

SRC remains a prevalent and complex condition with both immediate and long-term implications for brain health. Although most athletes recover without complication, a meaningful minority experience persistent cognitive, psychiatric, or neurological sequelae. This review has integrated data from over 30 studies, encompassing multiple sports and levels of exposure, to examine diagnostic advancements, biomarker development, neuroimaging findings, and long-term outcomes. Diagnostic accuracy has improved with the adoption of structured multimodal tools such as SCAT6, SAC, BESS, and the King-Devick test, each with defined roles and limitations. Blood-based biomarkers like GFAP and NFL hold promise for enhancing diagnostic and prognostic precision but require further validation before routine use. Neuroimaging, particularly DTI and tau PET, reveals consistent microstructural and metabolic changes following SRC, though their clinical application is currently limited to research contexts.

Longitudinal data demonstrate an increased risk of MCI, depression, and neurodegenerative disease in athletes with repeated concussions. However, outcome variability across studies, evident in our meta-analysis and illustrated by the asymmetry in the funnel plot, underscores the influence of confounding, selection bias, and publication bias. Moving forward, the field must prioritize rigorous prospective research, individualized risk assessment, and translation of emerging diagnostics into practical clinical tools. As policies evolve and technology advances, a balanced approach is needed, one that preserves the benefits of sports while minimizing the potential for long-term neurological harm.

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**Supplementary Material**

<b>Supplementary Table S1   Systematic search strategy</b>		
<b>Database</b>	<b>Search Terms Used</b>	<b>Limits</b>
PubMed	("sports-related concussion"[Title/Abstract] OR "sport concussion"[MeSH] OR "mild traumatic brain injury"[Title/Abstract]) AND ("biomarker"[Title/Abstract] OR "diagnosis"[Title/Abstract] OR "outcome"[Title/Abstract] OR "prognosis"[Title/Abstract])	Humans, English, 2000–2025
Embase	("sports concussion"/exp OR "mild traumatic brain injury"/exp) AND ("biological marker"/exp OR "diagnostic tool"/exp OR "clinical outcome"/exp)	English, articles only
Scopus	TITLE-ABS-KEY ("sport* concussion" OR "mTBI" OR "mild traumatic brain injury") AND TITLE-ABS-KEY ("biomarker" OR "diagnos*" OR "neurocognitive" OR "long-term outcomes")	2000–2025, English
Web of Science	TS=("sports-related concussion" OR "mTBI") AND TS=("biomarkers" OR "neuroimaging" OR "return-to-play" OR "long-term outcomes")	Research articles only, English
Google Scholar	"sports-related concussion" AND "biomarker" AND "diagnosis" AND "long-term" AND "return to play"	First 100 results manually screened