INPLASY

INPLASY202690091

doi: 10.37766/inplasy2026.9.0091

Received: 21 September 2026

Published: 22 September 2026

Corresponding author:
Daniel H. Daneshvar

ddaneshvar@mgh.harvard.edu

Author Affiliation:
Spaulding Rehabilitation Hospital, Massachusetts General Hospital, Harvard Medical School.

Interventions to Reduce Chronic Traumatic Encephalopathy Risk in American Football Players: Protocol for Systematic Review and Meta-Analysis

Luster, CB; El-Sururi, M; Nowinski, CJ; Arabandi, RL; Mastrodicasa, MJ; Feigel, ED; Williams, B; Abdolmohammadi, B; Torp, WH; Rovito, CA; Connors, EJ; Baugh, CB; Alosco, ML; McKee, AC ; Mez, J; Daneshvar, DH

ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - DHD reported receiving personal fees for providing expert testimony related to traumatic brain injury and spinal cord injury, serving as a medical advisor and options holder for StataDx, receiving research funding from the Football Players Health Study at Harvard University (FPHS) funded by the NFL Players Association (NFLPA), serving as a volunteer member of the Mackey-White Committee of the NFLPA, and receiving clinical funding from the Brain and Body Program funded by the NFLPA, all outside the submitted work.

INPLASY registration number: INPLASY202690091

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 September 2026 and was last updated on 22 September 2026.

INTRODUCTION

Review question / Objective The primary objective of this study is to systematically evaluate interventions and exposure-reduction strategies in American football that may reduce repetitive head impacts (RHI) exposure and estimate their potential impact on reducing risk and severity of chronic traumatic encephalopathy (CTE). This systematic review and meta-analysis will examine interventions designed to reduce the frequency and/or magnitude of football-related RHI. The systematic review will address the following question: Among American football players, how effective are interventions aimed at reducing football-related RHI exposure, and what are their potential implications for CTE risk and severity?

Rationale Participation in American football can expose athletes to repeated concussive and nonconcussive head impacts, collectively referred to as RHI, which has been linked to CTE. Although RHI exposure has been associated with CTE, the extent to which reducing specific football-related exposures, including years played, age at first exposure, playing position, level of play, and cumulative head impact exposure, may reduce CTE risk and severity remains unclear and has not been systematically quantified. Additionally, evidence regarding potential preventive strategies, including rule changes, limits on contact, and safety equipment, is dispersed across study types and data sources. This systematic review and meta-analysis will synthesize the available evidence on football-related factors associated with neuropathologically confirmed CTE and

evaluate strategies that may reduce CTE risk. A clearer understanding of these factors may help inform future research, clinical recommendations, and sport safety policies.

Condition being studied Chronic traumatic encephalopathy (CTE).

METHODS

Search strategy A systematic search will be conducted in PubMed (MEDLINE) and Embase through September 21, 2026, in accordance with PRISMA 2020 guidelines. The search strategy will combine controlled subject headings, including MeSH terms in PubMed and Emtree terms in Embase, with relevant keywords. The search algorithm used will be: ("Chronic Traumatic Encephalopathy" OR "CTE") AND ("American football" OR "football player*" OR "football athlete*" OR "professional football" OR "college football" OR "collegiate football" OR "high school football" OR "youth football") AND ("Repetitive Head Impact*" OR "RHI" OR "head impact*" OR "head trauma" OR "Traumatic Brain Injur*" OR "TBI" OR "concussion*" OR "subconcuss*" OR "nonconcuss*" OR "years played" OR "duration of play" OR "career duration" OR "age at first exposure" OR "age of first exposure" OR "playing position" OR "player position" OR "level of play" OR "cumulative exposure" OR "cumulative head impact*" OR "head impact exposure" OR "impact frequency" OR "impact magnitude" OR "contact exposure" OR "contact practice*" OR "rule change*" OR "equipment" OR "helmet*" OR "protective equipment"). Titles and abstracts will be screened to identify potentially eligible studies, followed by a full-text review. Studies that involve non-football and non-sport-related RHI populations, do not evaluate risk factors or preventive interventions, or focus on neurodegenerative diseases other than CTE will be excluded.

Participant or population This systematic review includes individuals with a history of American football participation. For studies evaluating CTE outcomes, participants must have undergone postmortem neuropathologic evaluation for CTE using standardized diagnostic criteria. Studies evaluating interventions or exposure-reduction strategies may include living American football players when they provide quantitative estimates of changes in RHI exposure. Studies with mixed populations will be included only when football-specific findings are reported separately.

Intervention Interventions and exposure-reduction strategies intended to reduce RHI exposure will be included, such as reducing years played, delaying age at first exposure, limiting contact practices, modifying rules or techniques, and using protective equipment.

Comparator Comparators may include observed or modeled differences in RHI exposure. Observed comparisons may include higher versus lower RHI exposure, greater versus fewer years of play, earlier versus later age at first exposure, participation before versus after a rule change, usual versus modified contact practices or playing techniques, and use of different protective equipment. When an intervention or exposure-reduction strategy has not been directly evaluated in relation to CTE, its estimated effect on RHI exposure may be used to model a counterfactual exposure scenario. For example, reductions in cumulative head-impact exposure associated with a rule change or protective equipment may be integrated with available exposure-response data to estimate the corresponding reduction in CTE risk.

Study designs to be included This review may include cohort studies, case-control studies, cross-sectional studies, autopsy or brain-bank registry, quasi-experimental, pre-post, and randomized or nonrandomized intervention studies. Relevant data from league, institutional, safety, and technical reports may also be included when they provide quantitative estimates necessary to characterize changes in RHI exposure associated with an intervention or exposure-reduction strategy.

Eligibility criteria Studies must provide data relevant to either (1) the association between football-related RHI exposure and neuropathologically confirmed CTE presence or severity, or (2) the effect of an intervention or exposure-reduction strategy on RHI exposure among American football players. Studies evaluating CTE outcomes must use postmortem neuropathologic assessment according to standardized diagnostic criteria. Studies evaluating preventive interventions or exposure-reduction strategies must provide quantitative estimates of their effects on RHI exposure that can inform subsequent modeling of CTE risk reduction.
Studies of other-sport or non-sport RHI populations (e.g., military populations or victims of abuse), case reports, and studies without relevant quantitative exposure or outcome data will be excluded. For overlapping cohorts from the same source population, the study providing the most

complete or relevant data for a given analysis will be prioritized.

Information sources PubMed and Embase will be searched through September 21, 2026. Search results will be imported to Covidence for duplicate removal and screening. Reference lists and citation records of included studies will also be manually reviewed, and relevant literature will be included. Relevant league, institutional, safety, and technical reports may also be identified through targeted searches and included when they provide quantitative estimates necessary to characterize changes in RHI exposure associated with an intervention or exposure-reduction strategy.

Main outcome(s) The primary outcome will be the estimated reduction in risk of neuropathologically confirmed CTE associated with reductions in football-related RHI exposure or implementation of RHI-reduction strategies. CTE outcomes will include both presence and neuropathological severity. Where interventions or preventive strategies have not been directly evaluated in relation to CTE, their effects on RHI exposure will be integrated with available exposure-response data to estimate the corresponding reduction in CTE risk.

Additional outcome(s) There are no additional outcomes to report.

Data management Two reviewers will independently screen studies and extract data using a standardized data extraction template in Covidence. Disagreements will be resolved through discussion or consultation with a third reviewer. Reasons for exclusion at the full text stage will be documented.

Quality assessment / Risk of bias analysis Two reviewers will independently assess methodological quality and risk of bias using the appropriate Joanna Briggs Institute (JBI) critical appraisal tool according to study design. Each source will be categorized into “low risk”, “moderate risk”, and “high risk,” and disagreement will be resolved through consultation with a third reviewer.

Strategy of data synthesis Statistical analyses of data will be conducted in R using RStudio Version 2026.07.0. Studies evaluating associations between football-related RHI exposure and CTE and studies evaluating interventions or exposure-reduction strategies will initially be synthesized separately. Meta-analysis will be performed when at least two studies are sufficiently comparable in exposures or interventions, outcomes, and effect measures.

For CTE presence, adjusted OR (Odds Ratio), RR (Risk Ratio), and HR (Hazard Ratio) will be pooled separately on the logarithmic scale using generic inverse variance methods. Estimates may be inverted as necessary so that values below 1.00 represent lower CTE risk. Relative reductions will be calculated as 100 x (1- effect estimate) and described according to the underlying measure as adjusted risk, odds, or hazard reductions. Unadjusted estimates will be synthesized separately or included only in sensitivity analyses. For CTE severity, proportional ORs will be pooled when comparable ordinal severity measures are available. When studies instead report associations with individual neuropathological severity categories or stages, estimates for comparable categories will be synthesized separately. Continuous exposures may be evaluated using dose-response meta-analysis when sufficient data are available.

Studies evaluating interventions or exposure-reduction strategies will be synthesized according to the RHI exposure measure reported. Binary outcomes will be summarized using RRs, with ORs analyzed separately. Count or rate outcomes will be summarized using rate ratios, and continuous outcomes will be summarized using mean differences when measurement scales are consistent or standardized mean differences when scales differ.

Where sufficient compatible data are available, estimated changes in RHI exposure associated with interventions or exposure-reduction strategies will be integrated with available RHI–CTE exposure-response estimates to model the corresponding relative reduction in CTE risk. Interventions will be classified according to whether their reported effects on RHI are directly compatible with the exposure metric used in the CTE exposure-response model, can be translated to a compatible metric using prespecified assumptions, or cannot be reliably translated. Selection of the RHI-CTE exposure-response model will be based on compatibility with the RHI metric reported or estimable for each intervention. The most specific available exposure metric will be prioritized (e.g., cumulative head-impact force or acceleration measures over impact frequency or duration-based proxies). When multiple compatible exposure-response models are available, the most recently published and comprehensive model using the most specific applicable RHI metric will be prioritized. Less specific exposure proxies will be used when more direct measures cannot be estimated. Interventions requiring exposure-metric conversion will be evaluated using sensitivity

analyses when feasible, while interventions that cannot be reliably mapped to the CTE exposure-response model will be synthesized with respect to their effects on RHI but will not be used to estimate CTE risk reduction. Modeled estimates will be reported separately from associations directly observed between exposures or interventions and neuropathologically confirmed CTE.
The primary analysis will use a random-effects model, with between-study variance estimated using restricted maximum likelihood and 95% confidence intervals calculated using the Knapp-Hartung adjustment. Statistical heterogeneity will be assessed using Cochran's Q test, I2 statistic, and Tau2. Pooled and modeled estimates will be.

Subgroup analysis When sufficient data are available, subgroup analysis will be conducted to evaluate potential sources of heterogeneity. For intervention studies, subgroup analyses may examine differences according to intervention type, level of play, and characteristics of the RHI exposure being modified. Additional subgroup analyses may be conducted according to study design or other methodological characteristics when sufficient data are available. Differences between subgroups will be evaluated using tests for subgroup differences or mixed-effects meta-regression.

Sensitivity analysis Leave-one-out analyses will be conducted to assess the influence of individual studies on heterogeneity and pooled estimates. When applicable, sensitivity analysis will also exclude studies at high risk of bias, estimates that include imputed data, and influential statistical outliers. Analyses may additionally be restricted to adjusted estimates and, for CTE outcomes, studies using the NINDS/NIBIB neuropathological consensus criteria. For analyses involving overlapping cohorts, sensitivity analyses will evaluate whether results are robust to the selection of alternative eligible estimates or publications from the same source population. For modeled CTE risk reductions, sensitivity analyses will evaluate alternative assumptions used to translate intervention-related changes in RHI into the exposure metric used in the CTE exposure-response model, when applicable. Robustness will be assessed based on changes in effect direction, magnitude, precision, and overall interpretation of estimates compared with those from the primary analyses.

Language restriction English.

Country(ies) involved United States.

Other relevant information No other relevant information to report.

Keywords Chronic Traumatic Encephalopathy; Repetitive Head Impacts; American football; Prevention; Intervention; Systematic Review; Meta-analysis.

Dissemination plans This systematic review and meta-analysis will be submitted to a peer-reviewed journal. Findings may also be presented at relevant national or international conferences.

Contributions of each author

Author 1 - Charlotte B Luster - Conception or design of the work; acquisition, analysis, or interpretation of data using defined statistical methods; reviewing it critically for important intellectual content; final approval of the version to be published.
Email: cluster@mgh.harvard.edu
Author 2 - Mousa El-Sururi - Conception or design of the work; acquisition, analysis, or interpretation of data using defined statistical methods; reviewing it critically for important intellectual content; final approval of the version to be published.
Email: mel-sururi@mgb.org
Author 3 - Christopher J Nowinski - Acquisition, analysis, or interpretation of data using defined statistical methods; drafting the work; registering the protocol; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy.
Email: nowinski@concussionandcte.org
Author 4 - Ria L Arabandi - Acquisition, analysis, or interpretation of data using defined statistical methods; drafting the work; registering the protocol; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy.
Email: rarabandi@mgb.org
Author 5 - Michael J Mastrodicasa - Acquisition, analysis, or interpretation of data using defined statistical methods; drafting the work; registering the protocol; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy.
Email: michael.mastrodicasa@bcm.edu

Author 6 - Evan D Feigel - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: efeigel@mgh.harvard.edu
Author 7 - Brandon Williams - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: bwilliams40@mgb.org
Author 8 - Bobak Abdolmohammadi - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: babdolmo@bu.edu
Author 9 - William H Torp - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: wtorp@mgb.org
Author 10 - Craig A Rovito - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: crovito@mgh.harvard.edu
Author 11 - Eric J Connors - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: econnors3@mgh.harvard.edu
Author 12 - Christine B Baugh - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: christine.baugh@cuanschutz.edu
Author 13 - Michael L Alosco - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: malosco@bu.edu
Author 14 - Ann C McKee - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: amckee@bu.edu
Author 15 - Jesse Mez - Acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; responsible for any part of the work appropriately investigated and resolved.
Email: jessemez@bu.edu
Author 16 - Daniel H Daneshvar - Conception or design of the work; acquisition, analysis, or interpretation of data for the work; reviewing it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy.
Email: ddaneshvar@mgh.harvard.edu