

Prevalence of Chronic Traumatic Encephalopathy (CTE) in Individuals Without Repetitive Head Impact: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION**Support** - None.**Review Stage at time of this submission** - Preliminary searches.

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: INPLASY202620070

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 February 2026 and was last updated on 23 February 2026.

INTRODUCTION

Review question / Objective The primary objective of this systematic review and meta-analysis is to establish the baseline neuropathological prevalence of Chronic Traumatic Encephalopathy (CTE) in individuals without a history of repetitive head impacts (RHI). To achieve this, the study utilizes the absence of contact sport participation as a proxy for non-exposure to RHI. The review aims to synthesize data from confirmed non-RHI cohorts to determine a baseline prevalence rate of CTE pathology, while simultaneously comparing these findings against intermediate cohorts (where exposure history is undocumented) and known RHI-exposed populations. Ultimately, this review seeks to

characterize the rarity of CTE in the absence of RHI and identify the impact of diagnostic outliers in current neuropathological literature.

Rationale Current understanding of CTE prevalence is heavily influenced by selection bias inherent in brain bank research, where symptomatic individuals or their families are more likely to pursue organ donation. This bias has led to high reported prevalence rates within RHI-exposed groups, yet the field lacks a baseline for CTE in the general, non-exposed population. Without establishing the baseline prevalence of CTE pathology, it is difficult to accurately quantify the specific risk increase attributable to repetitive impacts versus singular traumatic brain injuries or other etiologies. By defining a baseline prevalence

in non-RHI cohorts, this study provides a critical control data set that is essential for validating RHI as the primary driver of CTE and for refining the diagnostic specificity of the disease in epidemiological research.

Condition being studied Chronic traumatic encephalopathy (CTE).

METHODS

Search strategy A systematic search will be performed in PubMed and Embase from database inception through February 23, 2026, following PRISMA 2020 guidelines. The search strategy will combine controlled vocabulary (MeSH in PubMed and Emtree in Embase) with free-text terms including: “chronic traumatic encephalopathy,” “CTE,” “prevalence,” “epidemiology,” “incidence,” “frequency,” “cohort,” “cross-sectional,” “autopsy,” and “neuropathology.” No exposure restrictions will be applied during the search phase to identify both exposed and unexposed populations, including control or community-based cohorts without a history of repetitive head injury (RHI). Results will be limited to human studies and English language publications. Following the initial database query, two authors will independently screen all titles and abstracts. All references will be manually and independently screened by two authors to ensure the search included all relevant articles. To prevent data duplication, all identified studies will be independently reviewed to identify the study that included the largest number of cases. Studies with overlapping cohorts will be excluded from the final analysis.

Participant or population The review addresses individuals who have undergone neuropathological evaluation and have a documented absence of RHI exposure. Specifically, the population consists of subjects from community-based cohorts, forensic autopsy registries, and neurodegenerative disease brain banks who have no history of participation in contact sports (e.g., American football, ice hockey, rugby, soccer, or boxing). To ensure a true baseline prevalence, cohorts with known high-risk exposures, such as military combat with blast exposure or chronic epilepsy, will be excluded to minimize confounding neurotrauma. Eligible participants include both males and females across all age groups, provided that neuropathologic diagnosis was performed using standardized criteria (e.g., NINDS/NIBIB consensus criteria) to identify the presence or absence of CTE pathology.

Intervention This is a systematic review of prevalence, therefore, no clinical intervention is being evaluated. The primary focus of this review is the status of non-exposure to RHI. Exposure status is defined by the absence of documented participation in contact sports, which serves as a proxy for lack of RHI. The review evaluates cohorts that represent the general community to establish a baseline rate of CTE.

Comparator Where available, secondary narrative comparisons will be made against excluded cohorts with a documented history of contact sport participation and those who have no documentation, to quantify the relative difference in CTE prevalence.

Study designs to be included This review includes observational studies reporting neuropathological prevalence data for CTE. Eligible designs primarily consist of cross-sectional studies, prospective and retrospective cohort studies, and large-scale case series from brain banks and autopsy registries.

Eligibility criteria Inclusion criteria consist of observational cohort studies reporting neuropathological evaluations of CTE in subjects with no documented history of RHI. Additional exclusion criteria include: (1) case reports, narrative reviews, and theoretical models; (2) studies focusing on cohorts with significant confounding neurotrauma histories, specifically chronic epilepsy or military populations with documented blast exposure; (3) studies published in languages other than English; and (4) duplicate or overlapping cohorts. In the event of overlapping data within the same brain bank or registry, only the study reporting the largest sample size will be included to prevent data inflation. No restrictions will be placed on participant age, sex, or year of publication.

Information sources The information for this review will be primarily derived from electronic searches PubMed (MEDLINE) and Embase databases. To ensure a comprehensive identification of relevant studies, a manual screening of the reference lists of all included articles and major review papers will be performed to identify secondary sources. Additionally, authors of several studies may be contacted directly to provide clarification on cohort characteristics or provide specific neuropathological data not explicitly detailed in the original manuscripts.

Main outcome(s) The primary outcome of the review is the pooled prevalence of

neuropathologically confirmed CTE in subjects without a documented history of RHI. This prevalence rate will be reported with 95% confidence intervals using the Wilson score method.

Data management Data will be managed and organized using a standardized extraction template. Two reviewers will independently extract all relevant variables, with a third reviewer acting as an arbiter to resolve any discrepancies through consensus. Extracted data will be stored in a secure electronic database.

Quality assessment / Risk of bias analysis Two authors will independently evaluate the methodological quality and risk of bias for all included studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence Studies. Discrepancies between reviewers will be resolved through discussion and consensus with a third author. A priori criteria are established to classify study quality. Studies are categorized as "low risk", "moderate risk" and "high risk" depending on the 9-item tool. These risk of bias categorizations will be used to narratively contextualize the strength of the evidence, though studies will not be automatically excluded from the primary meta-analysis based solely on a high-risk designation.

Strategy of data synthesis Statistical analyses will be performed using R version 4.4.1. A random-effects meta-analysis model will be used to calculate the pooled prevalence estimate. The PLOGIT method will be applied prior to pooling to stabilize variance and account for rare events and small sample sizes. For studies with zero cases, a continuity correction of 0.5 will be applied. Additionally, potential publication bias will be visually assessed using a funnel plot and statistically evaluated utilizing the Egger test. Between-study heterogeneity will be assessed using the I^2 statistic, τ^2 (calculated via maximum likelihood estimation), and Cochran's Q test. Additionally, 95% prediction intervals (PIs) will be calculated to estimate the range of true prevalence expected in future similar studies. Publication bias will be evaluated using visual inspection of funnel plots and Egger's regression test.

Subgroup analysis To investigate the impact of exposure misclassification, secondary qualitative comparisons will be drawn between the primary 'confirmed non-RHI' cohort and 'ambiguous' or 'exposed' cohorts.

Sensitivity analysis Sensitivity analyses will be conducted using a leave-one-out method to assess the robustness of the pooled prevalence estimate and identify influential studies. We define potential outliers as any single study whose exclusion results in a reduction of statistical heterogeneity (I^2) greater than 10%. If such outliers are identified, the pooled prevalence will be reported both with and without the outlier to demonstrate the impact on the final estimate.

Language restriction English.

Country(ies) involved United States.

Keywords Chronic traumatic encephalopathy; CTE; Prevalence; Epidemiology; Neuropathology; Autopsy; Repetitive head impacts; Contact sports; Meta-analysis, Systematic review.

Dissemination plans The primary dissemination plan for this review will be the submission of the final manuscript to a peer-reviewed journal. Additionally, abstract findings may be presented at relevant national or international scientific conferences.

Contributions of each author

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