A Systematic Review of Potential Long-Term Effects of Sport-Related Concussion
Online Supplementary Material: Tables 1-3

Manley, G.T., Gardner, A. J., Schneider, K. J., Guskiewicz, K.M., Bailes, J., Cantu, R.C., Castellani, R.J., Turner, M., Jordan, B., Randolph, C., Dvořák, J., Hayden, K.A., Tator, C.H., McCrory, P., & Iverson, G.L. (2017). A Systematic Review of Potential Long-Term Effects of Sport-Related Concussion. *British Journal of Sports Medicine*.

Online Supplementary Table 1. MEDLINE search strategy.

Concussion Terms	Sport Terms	Long Term Outcome Terms
Post-Concussion Syndrome (MeSH) OR exp Brain Concussion(MeSH) OR concuss* OR sport* related concuss* OR Brain Injuries (MeSH) OR Brain Injury, Chronic (MeSH) OR Craniocerebral Trauma(MeSH) OR mtbi OR traumatic brain injur* OR subconcuss* OR repetitive head injur* OR repetitive head impact* OR cumulative head impact* OR cumulative head injur* OR repetitive brain trauma* OR repetitive traumatic brain injur* OR Brain Damage, Chronic (MeSH) OR brain damage OR multiple concuss* OR cumulative concuss* OR repetitive concuss*	Athletes (MeSH) OR Sports (MeSH) OR Baseball (MeSH) OR Boxing (MeSH) OR Bicycling (MeSH) OR Diving (MeSH) OR Football (MeSH) OR Hockey (MeSH) OR Racquet Sports (MeSH) OR Martial Arts (MeSH) OR Mountaineering (MeSH) OR Skating (MeSH) OR Skiing (MeSH) OR Snow Sports (MeSH) OR Soccer (MeSH) OR Wrestling (MeSH) OR athlete* OR player* OR rider* OR cyclist* OR boxer* OR skater* OR skier* OR wrestler* OR sport* OR athletic* OR football OR hockey OR skating OR rugby OR lacrosse OR soccer OR baseball OR boxing OR bmx OR bicycling OR cycling OR biking OR diving OR equestrian OR equine OR racket sport* OR racquet sport* OR tennis OR squash OR racquetball OR martial arts OR judo OR tae kwon do OR mountaineering OR climbing OR skiing OR snowboard* OR ski jump* OR ski racing OR bobsled* OR toboggan* OR wrestling OR contact sport* OR ringette OR softball OR handball	chronic traumatic encephalopath* OR cte OR Neurodegenerative Diseases (MeSH) OR neurodegenerative disease* OR neurodegenerative disorder* OR neurodegenerat* OR Dementia (MeSH) OR dementia* OR dementia pugilistica OR neurodegenerative dementia* OR punch drunk OR traumatic encephalopath* OR Alzheimer Disease (MeSH) OR alzheimer* OR Amyotrophic Lateral Sclerosis (MeSH) OR amyotrophic lateral sclerosis OR als OR Motor Neuron Disease (MeSH) OR motor neuron disease* OR Parkinson Disease, Secondary (MeSH) OR Parkinson Disease (MeSH) OR parkinson* OR Frontotemporal Dementia (MeSH) OR Septum Pellucidum (MeSH) OR septum pellucidum OR Cognition Disorders (MeSH) OR cognit* adj3 impairment OR cogniti* adj3 deficit* OR White Matter (MeSH) OR white matter tract* OR Tauopathies (MeSH) OR TDP-43 Proteinopathies (MeSH) OR tdp-43 OR tauopath* OR Endocrine System Diseases (MeSH) OR endocrine dysfunction OR Hypopituitarism (MeSH) OR hypopituitarism OR Depression (MeSH) OR depress* OR Suicide (MeSH) OR Suicide, Attempted (MeSH) OR suicid* OR Aggression (MeSH) OR aggres* OR Anger (MeSH) OR Psychotic Disorders (MeSH) OR psychos* OR Anxiety (MeSH) OR Anxiety Disorders (MeSH) OR anxiety OR Seizures (MeSH) OR seizure* OR executive dysfunction OR executive function* OR long term adj3 impairment OR long term adj3 sequelae
MeSH terms were exploded to include more specific terms MeSH terms were translated into the appropriate subject headings for other databases Keywords were the same for each database searched		

Online Supplementary Table 2. Summary of Studies.

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Clinical Studies, Including Surveys						
Clinical Kelly et al., 2014 [1] PMID: 24552537	Cross-sectional study	68 of 430 initially contacted	30-65 yrs	M	8	4
Sport/setting/level: Former NFL players (at least one season in NFL) with poor quality of life based on Short Form 36 Mental Component Score. Duration of symptoms: N/A Diagnosis of Concussion: Concussions self-reported on a survey and defined by the researchers. Length of follow-up: N/A Key Outcome Measures: Blood draws including: Luteinizing hormone, follicle-stimulating hormone, free and total testosterone to assess gonadal function; free T4, total T4, thyroid-stimulating hormone to assess thyroid function; prolactin level to assess for lactotroph dysfunction; serum and urine sodium and osmolality and urine specific gravity to assess posterior pituitary function. Growth Hormone deficiency [insulin-like growth factor 1 (IGF-1) level and glucagon] and adrenal insufficiency (adrenocorticotrophic hormone and cortisol levels); Metabolic syndrome: Fasting glucose, insulin, and lipid panel; SF-36 and International Index of Erectile Function (IIEF) Comparison group/s: N/A Results: In a sample of retired NFL players with poor QoL, 23.5% had Hormone Deficiency (HD), including 19% with GHD (using a BMI-adjusted definition), 9% with hypogonadism, and 50% had MetS. Although the cause of HD is unclear, these results suggest that GHD and hypogonadism may contribute to poor QoL, erectile dysfunction, and MetS in this population. Subjects with HD had lower mean scores on the IIEF survey (p=0.016). MetS was present in 50% of subjects, including 5 of 6 (83%) with hypogonadism, and 29 of 62 (46.8%) without hypogonadism (p=0.087). Age, BMI, median years in NFL, games played, number of concussions, and acknowledged use of performance-enhancing steroids were similar between HD and non-HD groups					
Clinical Lolekha et al., 2010 [2] PMID: 20669292	Cross sectional	704/961	Mean= 57.2 ±0.8 years	M	11	4
Sport/setting/level: Thai traditional boxers Duration of symptoms: The duration of time between the end of the boxing career and year of onset of symptoms ranged from 23 to 43 years (mean=35.6 years, SD= 7.9 years) Diagnosis of Concussion: Not Reported Length of follow-up: Not reported Key Outcome Measures: Parkinson's disease screening using two standardized screening questionnaires translated into Thai language. Individuals who were screened positive were evaluated by neurologists as well as a random sample of 10% who screened negative. Parkinsonism diagnosed based on United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria. Comparison group/s: USA 1970 census Results: 8/704 boxers (1.14%) had Parkinsonism: 5 with PD, 1 with progressive supranuclear palsy, and 2 with vascular parkinsonism. Of the 137 who screened positive, 91 (66.4%) received a neurological examination. Boxers with PD were found to have an older mean age than those without PD (71.2±5.3, 57.1±0.8 years, p = 0.003). Number of professional bouts (>100 times) was a risk factor for PD (p = 0.01), advancing age; the association of chronic repetitive head trauma and PD was restricted to later-onset cases (71.2 vs. 57.2 years), but no other related factors were associated with PD. The crude prevalence of PD in Thai boxers was 0.71% (95% CI: 0.09–1.33), with a significant increase with age.					

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Clinical (mortality, epidemiological) Lehman et al., 2016 [3] PMID: 27159317	Retrospective Cohort	3,439 players	Not reported (deceased participants)	M	18	3
Sport/setting/level: Professional American football players (NFL) (minimum 5 years of experience) Duration of symptoms: N/A Diagnosis of Concussion: Not Reported Length of follow-up: N/A Key Outcome Measures: Mortality, cause of death including cancer, heart disease, assault/homicide, and suicide. The focus of the study was suicide. Comparison group/s: United States male population database Results: Overall mortality (SMR = 0.60; 95% CI, 0.55-0.65) and mortality from cancer (SMR = 0.59; 95% CI, 0.50- 0.70), heart diseases (SMR = 0.75; 95% CI, 0.65-0.86), and assault/homicide (SMR = 0.14; 95% CI, 0.04-0.37) continue to be lower than men in the general population. The NFL cohort experienced a significantly reduced risk of death from suicide, with 12 suicide deaths observed compared with 25.6 that would be expected in a comparable sex/race/age sector of the US population (SMR = 0.47; 95% CI, 0.24-0.82).						
Clinical Murelius et al., 1991 [4] PMID: 2011947	Cross-sectional	50 25 randomly selected high match (HM) and 25 low match (LM) boxers	HM: mean age 30.5 +/- 5.1 years; LM: mean age of 32.3+/- 5.6 years	M	10	4
Sport/setting/level: Swedish former amateur boxers Duration of symptoms: n/a Diagnosis of Concussion: Based on sport exposure (Boxing vs soccer vs track and field) Length of follow-up: Minimum of one year following cessation of boxing and who boxed for 8-19 years. Key Outcome Measures: Neuropsychological tests: Interview including sport, medical and social history; neuropsychological test battery including sensory, motor, cognitive, memory tasks and Halstead-Reitan batteries. Comparison group/s: 25 soccer players "who headed the ball a lot during their career", 25 track and field athletes with no previous history of head trauma Results: High match (HM) boxers performed more poorly in finger-tapping than the other two groups with both the dominant ($p<0.05$) and non-dominant hand ($p<0.001$). In HM group, poorer performance on finger-tapping was correlated with length of boxing career and number of fights but was not correlated significantly with number of knockouts, referee stopping contest, number of groggy states or number of lost fights. For soccer players, there was significant correlation between length of soccer career and worse finger-tapping performance.						
Clinical Kerr, Marshall, Herndon et al., 2012 [5] PMID: 22922518	Prospective cohort	1,044	1,044	M	12	3
Sport/setting/level: Former NFL Duration of symptoms: N/A Diagnosis of Concussion: Concussions were self-reported on the General Health Survey as: “an injury resulting from a blow to the head followed by a variety of symptoms that may include any of the following: headache, dizziness, loss of balance, blurred vision, seeing stars, feeling in a fog or slowed down, memory problems, poor concentration, nausea, or throwing-up.” Participants were reminded that they did not need to be “knocked out” or unconscious to sustain a concussion. Length of follow-up: Nine years Key Outcome Measures: General Health Survey (GHS) in 2001 and 2010; Self-reported clinical diagnosis of depression between the baseline survey in 2001 and follow-up survey in 2010 Comparison group/s: Total number of concussions sustained during pro football career, categorized as 0, 1-2, 3-4, 5-9, and 10 or more. Results: Binomial risk regression estimated adjusted risk ratios (RR). Controlling for years since retirement and physical health composite score, the nine-year risk of self-reported clinically-diagnosed depression increased with more self-reported concussions (1-2 concussions RR=2.3, 95%CI: 1.1-4.7; 3-4 concussions RR=3.3, 95%CI: 1.7-6.7; 5-9 concussions RR=4.1, 95%CI: 2.0-8.4; 10 or more concussions RR=5.8, 95%CI: 2.8-12.2)						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Clinical Didehbani et al., 2013 [6] PMID: 23644673	Cross-sectional	30	M: 58.60; SD: 10.33; range: 41-77 years	M	9	4
Sport/setting/level: Former NFL Duration of symptoms: Not reported Diagnosis of Concussion: American Academy of Neurology (AAN) Practice Parameter guidelines for grading concussion (1997) Length of follow-up: Not reported Key Outcome Measures: Neuropsychological testing; neurological examination; Beck Depression Inventory II; DSM-IV dementia criteria Comparison group/s: 29 age-, education-, and IQ-matched controls without a history of concussion Results: The number of lifetime concussions and total scores on the BDI-II were significantly correlated (r=.43, p=.02). More athletes endorsed items on the BDI-II compared with controls. Athletes scored significantly higher on total BDI-II scores and on each of the three Buckley factors; cognitive, affective, and somatic.						
Clinical Seichepine et al., 2013 [7] PMID: 23421745	Self-referred, survey	64 (current and retired players)	mean age = 47.0 ±13.6 years	M	6	4
Sport/setting/level: American Football Duration of symptoms: n/a Diagnosis of Concussion: Concussion history established with a phone call. Length of follow-up: Divided between College and Professional players and by age <40 and 40+ Key Outcome Measures: Self-reporting study - retired players. Completed online Behaviour Rating Inventory of Executive Function, adult version (BRIEF-A) questionnaire. Comparison group/s: Age appropriate T scores based on previously published data but data for current versus retired players in this sample were not reported separately. Results: Compared to age adjusted norms, football players reported worse function than the normative sample on seven of nine scales. Athletes 40 years of age or older reported more problems (t(62)=2.7; p<0.05).						
Clinical Randolph et al., 2013 [8] PMID: 23902607	Cross-sectional survey	n=513 retirees NFL with probable MCI: n=41 Controls: n=41 matched on age, education and gender; MCI controls: n=81	64.2 (SD=5.5) for NFL retirees	M	10	4
Sport/setting/level: Retired National Football League players/USA/ Professional Diagnosis of Concussion: Not discussed Length of follow-up: Variable and not specifically mentioned but retired players were between 50-75 years Key Outcome Measures: Alzheimer's disease inventory AD8 with score of 2 or higher suggesting clinically significant cognitive impairment. Wechsler Adult Intelligence Test-III (WAIS-3), Repeatable Battery for Assessment of Neuropsychological Status (RBANS) Comparison group/s: Controls matched based on age, education, and gender; MCI controls Results: AD8: 35.1% of retirees scored 2 or higher; WAIS-3: Mean 110.8; Mean spousal AD8 score was 2.9 (similar to previous reports of patients with MCI score mean of 2.9); RBANS Total score for retired NFL sample was significantly less than control sample [F=10.4, p=0.002; Cohen's d=1.5 (effect size 0.6)]. No correlation between years played in NFL and RBANS Total Scale score (r=0.016).						
Clinical Vann Jones et al., 2013 [9] PMID: 24026299	Cross-sectional	92	Mean 67.45 (±6.96, 95% CI) years	M	12	4
Sport/setting/level: Professional Soccer (Football) United Kingdom Duration of symptoms: n/a Diagnosis of Concussion: Study of the possible long-term effects of heading the ball in soccer. Retired professional soccer players were required to complete a self-administered Test Your Memory (TYM) questionnaire. All respondents over 55 years old Length of follow-up: Mean length of playing career = 13.8 years Key Outcome Measures: Test Your Memory Questionnaire Comparison group/s: Control group were players who did not head the ball - goalkeepers - and the normative data of a large MCI Study of men in Wales Results: No association between low-risk and high-risk playing positions (HR=0.40, p=0.46) or length of career (HR=1.05; 95% CI 0.87, 1.26; p=0.59) and positive screen for MCI.						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Clinical Kerr, DeFreese, et al., 2014 [10] PMID: 26535354	Cross-sectional	797 of 3,657 initially contacted	Less than 24=43; 25 to 34=308; 35 to 44=325; 45 and over=121	421 F; 376 M	9	4
Sport/setting/level: Former collegiate athletes (mean of 14.5 years since retirement) Duration of symptoms: N/A Diagnosis of Concussion: Concussions self-reported on a survey and defined as "occurring typically, but not necessarily, from a blow to the head followed by a variety of symptoms that may include any of the following: headache, dizziness, loss of balance, blurred vision, 'seeing stars,' feeling in a fog or slowed down, memory problems, poor concentration, nausea, or throwing-up." Length of follow-up: N/A Key Outcome Measures: Veterans RAND 12-Item Health Survey (VR-12) physical health composite score (included scores of physical functioning, role physical, bodily pain, and general health) and mental health composite score (included scores of vitality, social functioning, role emotional, and mental health) Comparison group/s: Total number of concussions sustained, categorized as 0, 1-2, and 3 or more. Results: Physical Composite Scores (PCS) were lowest among those sustaining 3 or more concussions in total (ANOVA post-hoc P < .001). Mental Cognitive Scores (MCS) were not significantly different (ANOVA P = .06). A lower prevalence of depression, bipolar disorders, and attention deficit disorder than the World Health Organization US population data.						
Clinical Kerr, Evenson, et al., 2014 [11] PMID: 27747661	Cross-sectional study	797 of 3,657 initially contacted Age less than 29=212; 30-34=139; 35-39=158; 40-44=167; 45 and over=121	M=N/R Range=N/R	376:421	8	4
Sport/setting/level: Former collegiate athletes (mean of 14.5 years since retirement) Duration of symptoms: N/A Diagnosis of Concussion: Concussions self-reported on a survey and defined as "occurring typically, but not necessarily, from a blow to the head followed by a variety of symptoms that may include any of the following: headache, dizziness, loss of balance, blurred vision, 'seeing stars,' feeling in a fog or slowed down, memory problems, poor concentration, nausea, or throwing-up." Length of follow-up: mean 14.5 years since last played collegiate sport Key Outcome Measures: Depression module of the Patient Health Questionnaire (PHQ-9), with outcome dichotomized as no/mild depression (scores below 10) and moderate to severe depression (scores of 10 and above); the Short Form of the Barratt Impulsiveness scale (BIS15), with outcome maintained as continuous variable; and the 12-item Short Form of the Buss-Perry Aggression Questionnaire (BPAQ-SF), with outcome maintained as continuous variable. Comparison group/s: Total number of self-recalled concussions (sport-related and non-sport-related), were categorized as: zero (referent), one, two, or three or more concussions. Results: Binomial risk regression estimated adjusted prevalence ratios (PR). Linear regression estimated adjusted mean differences (MD). Controlling for alcohol dependence and family history of depression, the prevalence of moderate to severe depression among former collegiate athletes reporting three or more concussions in total was higher than that of those reporting zero concussions [PR=2.4; 95% Confidence Interval (CI): 1.0, 5.7]. Controlling for alcohol dependence, family history of anxiety, relationship status, obtaining a post-graduate degree, and playing primary college sport professionally, former collegiate athletes reporting two or more concussions in total had higher mean scores for impulsivity, compared to those reporting no concussions (2 concussions MD = 2.7; 95% CI: 1.2, 4.1; 3+ concussions MD = 1.9; 95% CI: 0.6, 3.2). Controlling for alcohol dependence, sex, and relationship status, former collegiate athletes reporting three or more concussions in total had a higher mean score for aggression, compared to those reporting no concussions (MD = 3.0; 95% CI: 1.4, 4.7).						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Clinical Stamm et al., 2015 [12] PMID: 25632088	Cross-sectional	42	40-69	M	10	4
Sport/setting/level: Retired National Football League (NFL) Players Duration of symptoms: N/A Diagnosis of Concussion: N/A Length of follow-up: N/A Key Outcome Measures: Wisconsin Card Sort Test (WCST), Neuropsychological Assessment Battery List Learning Test (NAB-LL), Wide Range Achievement Test, 4th Edition (WRAT-4) Comparison group/s: Pairwise comparisons with pairs matched on age; Age of First Exposure to tackle football (AFE) < 12 years old and ≥12 years old. Results: Players with AFE <12 performed significantly worse on WCST, NAB-LL, and WRAT-4 than the AFE≥12 group.						
Clinical Hume et al., 2016 [13] PMID: 27558141	Cross-sectional survey	Elite (n=103) Community-rugby (n=198)	M: 43.3; SD: 8.2	M	10	4
Sport/setting/level: Retired Elite (National or International level playing experience) and Community Rugby Union (Club or regional playing experience) Duration of symptoms: Elite: 41.3±7.5 years; Community: 44.9±8.4 years Diagnosis of Concussion: Self-reported concussions. Concussion defined as blow to the head followed by a variety of symptoms. Length of follow-up: Retirement from competition ranged from a few months to 50+ years Key Outcome Measures: Neuropsychological Assessment (CNS Vital Signs), Alcohol Use Disorders Identification Test (AUDIT), Clinical Questionnaire (physical health) Comparison group/s: Non-contact sports group (n=65), mean age 42.1±7.7 years Results: The elite-rugby group performed worse on tests of complex attention (effect size -0.67, 95 % confidence interval [CI] -1.07 to -0.26), processing speed (-0.51, - 0.89 to -0.12), executive functioning (-0.41, -0.80 to -0.02), and cognitive flexibility (-0.37, -0.74 to 0.00) than the non-contact-sport group, and worse than the community-rugby group on complex attention (-0.38, -0.71 to -0.05). The community-rugby group performed worse than the non-contact group on executive functioning (-0.51, -0.89 to -0.12) and cognitive flexibility (-0.39, -0.69 to -0.08). Rugby groups performed worse on processing speed (elite rugby: -0.51, -0.75 to -0.26; community rugby: -0.32, -0.48 to -0.17), cognitive flexibility (elite rugby: -0.26, -0.47 to -0.05; community rugby: -0.27, -0.41 to -0.13) and executive functioning (elite rugby: -0.24, -0.45 to -0.03; community rugby: -0.23, -0.37 to -0.10) than the US norms. The community-rugby group performed worse than the US norms on composite memory (-0.31, -0.48 to -0.14), while the community-rugby group and the non-contact-sport group performed slightly better than the US norms on complex attention (community rugby: 0.22, 0.08–0.35; non-contact sport: 0.40, 0.20–0.60), as did the elite-rugby group in relation to motor speed (0.38, 0.19–0.57).						
Clinical Meehan et al., 2016 [14] PMID: 26193380	Case-control	3,652	40 -70	2,032:1,624	12	3
Sport/setting/level: Division III collegiate. Divided into collision sports, contact sports, non-contact sports, non-athletes Duration of Symptoms: Not reported Diagnosis of Concussion: Self report Length of Follow-up: Not reported Key Outcome Measures: Neuro-QOL Comparison group/s: Contact, non-contact sports, and non-athletes Results: Respondents with a history of concussion had worse self-reported health on several measures. When subjects with a history of concussion were removed from the analyses in order to assess for any potential effect of sub-concussive blows alone, negative consequences of alcohol use remained higher among collision sport athletes (b-coefficient 1.957, 95% CI 0.827-3.086). There were, however, no other significant associations between exposure to collision sports during college and any other quality-of-life measures. The results suggested that, in the absence of a history of concussions, participation in collision sports at the Division III collegiate level is not a risk factor for worse long-term neurobehavioral outcomes, despite exposure to repeated sub-concussive blows.						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Clinical Montenigro et al., 2016 [15] PMID: 27029716	Retrospective convenience sample	93	47.3 (SD 13.9)	M	6	3
Sport/setting/level: Former amateur high school and collegiate football players Duration of symptoms: Not reported Diagnosis of Concussion: LEGEND participants. Self-report from a convenience sample in which participants learn of study through website and word of mouth Length of follow-up: Divided between high school and collegiate players. Average age of high school 43.6 +/- 11.6 and college 47.7 +/- 14.2 Key Outcome Measures: BTACT, BRIEF-A, CES-D, AES. Transformed continuous outcomes into dichotomous variable (normal vs. impaired) Comparison group/s: 17 high school and 76 collegiate Results: The 'cumulative head impact index' (CHII) was associated with later-life clinical outcomes. The risk of impairment increased with every 1,000 impacts. The risk of developing clinically meaningful impairments in mood, behavior, and cognition increased with two additional seasons of head impacts.						
Clinical (Mortality/Epidemiological) Baron et al., 2012 [16] PMID: 22284915	Cohort Study	3,439	Median age 57 yrs	M	11	4
Sport/setting/level: Former NFL players with a minimum of 5 years playing experience Duration of symptoms: N/A Diagnosis of Concussion: No definition reported Length of follow-up: N/A Key Outcome Measures: Mortality; mortality due to cardiovascular-related disease (with other causes presented in a comprehensive table) Comparison group/s: US population estimated Results: Overall mortality and morbidity from cancer and cardiovascular disease were significantly decreased. The rates of psychiatric illness and suicide were significantly lower in the former athletes than in men from the general population. They also reported that diseases of the nervous system and sense organs were somewhat higher than men in the general population, but the difference was not statistically significant. Of the 334 former players who had died, 12 (3.6%) had one of these diseases listed on his death certificate when it was expected, from population estimates, that the number should have been 9.7 people.						
Clinical (Mortality/Epidemiological) Lehman et al., 2012 [17] PMID: 22955124	Cohort Study	3,439	Median age 57 yrs	M	11	3
Sport/setting/level: Former NFL players with a minimum of 5 years playing experience Duration of symptoms: N/A Diagnosis of Concussion: No definition reported Length of follow-up: N/A Key Outcome Measures: Mortality; mortality due to neurodegenerative causes, multiple causes Comparison group/s: US population estimated Results: Standard mortality rate (SMR) for players was lower when compared to US population (SMR=0.53; 95% CI 0.48-0.59); 3 neurodegenerative causes of death in non-speed positions and 14 in speed positions; In speed positions, SMR was higher than the US population for dementia (SMR=6.02; 95% CI, 2.21-13.1) and ALS (SMR=6.24; 95% CI, 2.29-13.6) but not for Parkinson's Disease (SMR=2.01; 95% CI, 0.24-7.25). There was no difference in SMR compared to the US population for non-speed players. Of the 334 death certificates reviewed, the number of times neurodegenerative diseases were listed as an underlying or contributing cause of death were as follows: Alzheimer's Disease/Dementia=7, Parkinson's Disease=3, and ALS=7.						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Clinical Critchley 1957 [18] PMID: 13396257	Case Series	21	Not described	M	1	5
Sport/setting/level: Boxers (amateur and professional). Duration of symptoms: Variably described Diagnosis of Concussion: No definition reported Length of follow-up: N/A Key Outcome Measures: Clinical description of the 'principal ill effects ascribed to boxing' Comparison group/s: None Results: Variable description of self-reports of difficulty thinking, difficulty concentrating, slowness, a groggy sensation, difficulty remembering, headaches, dizziness, decreased hearing, visual disturbances, seizures, dysarthria, ataxia, tremor, imbalance, altered coordination and dysdiadochokinesis.						
Clinical Mawdsley & Ferguson, 1963 [19] PMID: 14052038	Case Series	10	Median 56; Range 33-69	M	2	5
Sport/setting/level: Boxers (4 amateur and 6 pro). They had between 80 and 600 fights during their careers. Duration of symptoms: Variably described. Some noticed the onset of neurological problems, such as slowing down and have slurred speech, while still actively fighting. Others noticed neurological deterioration years after they retired. Most appeared to have progressive courses. Diagnosis of Concussion: No definition reported Length of follow-up: N/A Key Outcome Measures: Clinical Examination and Investigations (type of investigations depended on case) Comparison group/s: None Results: Clinical evidence of dementia in 9/10; in all patients who had lumbar punctures performed the CSF was under normal pressure; in 6 cases, symmetrical dilation of lateral ventricles were observed on radiographs; a cavum septi pellucidi was seen in 6 air-encephalograms but degree of separation of the septal leaves varied.						
Clinical (epidemiological) Savica et al., 2012 [20] PMID: 22469346	Retrospective cohort	438	Median (IQR): 68.4 (31.5-75.6)	M	11	3
Sport/setting/level: American high school football Duration of symptoms: n/a Diagnosis of Concussion: Exposure to football; no diagnosis of concussion Length of follow-up: Football players at high schools in Rochester, Minnesota 1946-1956. Years of follow-up 13.7-57.5 (mean 50.2) Key Outcome Measures: Diagnosis of ALS, Parkinson's disease, or dementia as per medical records and from incidence data from general population. Comparison group/s: 140 male students from band, glee club, or choir. Also comparison with national statistics for the local population. Median age (25th, 75th percentile) 59.1 (26.7-73.4). Results: No increased risk of dementia (HR=1.58; 95% CI, 0.36-7.01; p=0.55), PD (HR=0.48; 95% CI, 0.17-1.42; p=0.19) or ALS (HR=0.52; 95% CI, 0.05-5.68; p=0.59) between former players and controls. There was no difference between former players, controls, and the general population estimates.						
Clinical Roberts et al., 1969 [21] PMID: Not Applicable	Cross-sectional cohort study	Random sample of 224 retired boxers	Not reported. Age-stratified sampling.	M	12	4
Sport/setting/level: Professional boxers who were registered professional boxers in England between 1929 and 1955. Duration of symptoms: Varied greatly from person to person. Diagnosis of Concussion: Included in descriptions of injury history. Length of follow-up: Varied from years to decades after end of boxing career. Key Outcome Measures: Clinical history, Neurological examination Comparison group/s: None Results: The first and only large study examining the clinical features of CTE in living subjects was published in 1969. From a list of 16,781 retired boxers, Roberts selected an age-stratified random sample of 250; he was able to locate and clinically examine 224 of these men. He concluded that 17% had the syndrome (11% had a mild form of the syndrome and 6% had severe problems). However, for boxers over the age of 50 who had 150+ fights, 50% had the syndrome compared to 7% who had fewer than 50 fights. He wrote that the syndrome typically seemed stable, with some possible gradual age-related worsening. Clinical worsening of a Parkinsonian-like syndrome was noted in a very small number of subjects.						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Clinical Guskiewicz et al., 2005 [22] PMID: 16239884	Cross-sectional Survey	n=2,552/3,683 (69% response rate on survey)	Mean age 53.8 (±13.4) years	M	12	3
Sport/setting/level: Retired Professional American Football Players with an average professional football career of 6.6 (±3.6) years. Duration of symptoms: N/A Diagnosis of Concussion: Retrospective recall of previous concussions by participants and defined as resulting from a blow to the head that caused an alteration in mental status and one or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering and difficulty concentrating. Length of follow-up: N/A Key Outcome Measures: General Health Questionnaire, Short-Form 36 (SF-36); questionnaire related to mild cognitive impairment (MCI) was sent to 1,754 retirees aged 50 years and older and their spouse (a subgroup of the total sample), of whom 758 (43%) retired players, and 641 (37%) retired players' spouses or close relative, responded. Comparison group/s: Individuals not reporting a previous concussion Results: 33 (1.3%) of players reported being diagnosed with Alzheimer's Disease (AD) (age-adjusted prevalence ration=1.37; 95% CI: 0.98-1.56). The number of concussions sustained and a diagnosis of AD were not associated (Fisher's exact test, p=0.24). Players had similar mental component scale (MCS) scores on the SF-36 to population norms (p>0.05). Those players with previous recurrent concussions had a lower score on the MCS than players without a history of recurrent concussion (F[3,2146]=19.29, p=0.001). There were 22 cases of diagnosed MCI. There was an association between clinical diagnosis of MCI and recurrent concussion (x^2=7.82, df=2, p=0.02).						
Clinical Guskiewicz et al., 2007 [23] PMID: 17545878	Cross-sectional Survey	n=2,552/3,683 (69% response rate on survey)	Mean age 53.8 (±13.4) years	M	12	3
Sport/setting/level: Retired Professional American Football Players with an average professional football career of 6.6 (±3.6) years. Duration of symptoms: N/A Diagnosis of Concussion: Retrospective recall of previous concussions by participants and defined as resulting from a blow to the head that caused an alteration in mental status and one or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering and difficulty concentrating. Length of follow-up: N/A Key Outcome Measures: General Health Questionnaire (including questions about diagnosed medical conditions such as depression), Short-Form 36 (SF-36) Comparison group/s: Individuals not reporting a previous concussion Results: 1,513 (60.7%) reported at least one previous concussion; 884 reported one or two concussions (36.3%) and 595 (24.4%) reported three or more concussions. 269/2552 (11.1%) reported a current diagnosis of depression. Retired players reporting three or more concussions were three times more likely to have been diagnosed with depression (prevalence ratio=3.06; 95% CI: 2.29, 4.08; adjusted prevalence ration=2.58; 95% CI: 1.90, 3.55). Individuals with a history of one or two previous concussions were 1.48 times more likely to have been diagnosed with depressions when compared to individuals with no previous history of concussion (prevalence ratio=1.48; 95% CI: 1.08, 2.02; Adjusted prevalence ratio=1.39; 95% CI 1.03, 1.96).						
Clinical Hinton et al., 2011 [24] PMID: 22030936	Cross-sectional survey	n=400 (n=214 former football players, n=136 former non-collision sport athletes, n=50 non athletes)	Mean age: 64.09 (±13.32) years	347:52	10	4
Sport/setting/level: Former Division I collision-sport collegiate football players from Mid-western university Duration of symptoms: N/A Diagnosis of Concussion: Not specifically recorded ("assumed that former football players experienced significantly more concussions and subconcussive events than the other athlete and non-athlete control groups") Length of follow-up: N/A Key Outcome Measures: Self-report survey of physical and demographic characteristics, exercise (Godin Leaisure-time Exercise Questionnaire), diet (Rapid Eating and Activity Assessment for Patients), cognitive difficulties (Cognitive Difficulties Scale), physical and mental health Comparison group/s: non-collision-sport athletes and non-athletes Results: Former football players had higher past and current BMIs. In former players but not in controls, higher total fat intake was associated with cognitive difficulties. Football was associated with worse physical and mental						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
health, however vigorous exercise was associated with higher ratings of physical and mental health.						
Imaging Studies and Mixed Imaging and Clinical Studies						
Imaging Hampshire et al., 2013 [25] PMID: 24135857	Cross sectional	13	Mean age: 54 years	M	5	4
Sport/setting/level: NFL Duration of symptoms: No diagnosis of neurological or psychiatric illness. No evidence of structural MRI abnormalities. Diagnosis of Concussion: No diagnostic criteria, self-reported 'total number of times that they had been taken out of play due to head impact' Length of follow-up: Not reported Key Outcome Measures: One Touch Spatial Planning task, an fMRI-optimised variant of the Tower of London Comparison group/s: 20 Age matched healthy volunteer controls Results: There were some differences in cognitive functioning in former NFL players. Compared to controls, former NFL players had differences in mean functional connectivity between right dorsolateral prefrontal cortex and other sub-regions of the dorsal planning network.						
Imaging Small et al., 2013 [26] PMID: 23343487	Cross sectional	5	45-73	M	7	4
Sport/setting/level: NFL/retired/professional Duration of symptoms: Not stated Diagnosis of Concussion: Mild cognitive impairment based on Mini-Mental State Examination, Hamilton Rating Scale for Depression and neuropsychological test battery. Length of follow-up: N/A Key Outcome Measures: Positron emission tomography (PET) Comparison group/s: 5 age, education, and body mass index matched controls Results: FDDNP signals were higher in players than in controls in all subcortical regions and amygdala.						
Imaging Koerte et al., 2015 [27] PMID: 25843317	Cross sectional	11	Mean age: 52±7 years	Information on sex not included	8	4
Sport/setting/level: Professional German Soccer League (1st, 2nd, or 3rd Bundesliga); "competitive" recreational non-contact controls Duration of symptoms: N/A Diagnosis of Concussion: N/A- concussion was used as an exclusion criteria Length of follow-up: N/A Key Outcome Measures: Estimated number of headers per week in the 12 months before the study; Trailmaking Test (TMT) parts A and B, Rey-Osterrieth Complex (ROCF) test, and Balance Error Scoring System (BESS); MRI, MR spectroscopy Comparison group/s: Non-contact athletes (N=14); Mean age 47±8 years matched on age, handedness, and gender Results: All participants (soccer and non-contact) performed within normal ranges for their age and there were no significant group differences; soccer players had significant higher ratios of Cho/Cr (0.21 + 0.03) compared to athlete controls (0.19 + 0.02; $p = 0.04$, $df = 17$, $t = 2.17$). mI/Cr levels were increased in the soccer players (0.89 + 0.04) compared with athlete controls (0.83 + 0.09; $p = 0.04$, $df = 20$, $t = 2.24$). No differences between NAA/Cr, total Cr, Glu, or GSH were found; generally neurochemical levels were correlated with soccer heading both within the last year and lifetime estimated. TMT B significantly correlated with GSH/Cr + PCr but no other clinical tests correlated with biochemistry.						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Imaging Lin et al., 2015 [28] PMID: 25780390	Cross sectional	5	Mean = 43.6±10.8 years	M	4	4
Sport/setting/level: American football, Wrestling, Baseball Duration of symptoms: Not reported but all reported some symptoms. Diagnosis of Concussion: Not reported Length of follow-up: Between 3-25 (mean=13.8±10.1) years since the end of their careers. Key Outcome Measures: Localized Correlated Spectroscopy (L-COSY) protocol Comparison group/s: 5 healthy, non-professional athletes; gender, age, and weight matched (mean age=45.2±12.6 years). Results: Former athletes had an increase of 31%, 32%, and 35% in the glutamine/glutamate cross peaks (2.09–3.75 ppm, 2.07–3.73 ppm and 2.14–3.74 ppm, respectively) compared to controls. The methylene group of choline at 4.05–4.05 ppm was 65% higher in former professional athletes. The cross peaks in the F2: 4.0– 4.5, F1: 1.1–1.7 region, show a higher cross peak volume in molecules assigned to covalently linked terminal fucose molecules and threonine of 60% in former professional athletes. Phenylalanine was 46% higher in former athletes.						
Imaging Gardner et al., 2016 [29] PMID: 25970145	Retrospective	17	Retired NFL= Mean age: 54.6 ± 15.8 years	M	12	4
Sport/setting/level: NFL Duration of symptoms: Not reported Diagnosis of Concussion: Not reported Length of follow-up: M: 24.5; SD: 15.5 Key Outcome Measures: Cavum septum pellucidum (CSP) grade and length; various clinical diagnosis: Alzheimer's disease, Frontotemporal lobar degeneration, Behavioral variant frontotemporal dementia; Chronic post-concussion syndrome, Mild cognitive impairment, Huntington's disease, cognitive disorder not otherwise specified, nonfluent variant of primary progressive aphasia, mild dementia not otherwise specified Comparison group/s: Age matched clinical patients with no history of TBI or football exposure (Mean age: 54.7 ± 15.8) Results: CSP was significantly higher grade ($p<0.001$) and longer in players than controls (mean length–Standard deviation [SD]: 10.6 mm–5.4 vs. 1.1 mm–1.3, $p < 0.001$). 94% (16/17) of players had a CSP graded ‡2 (at least mild) compared with 18% (3/17) of controls ($p < 0.001$). 41% (7/17) of players had a cavum vergae compared with 0% of controls ($p< 0.005$). CSP ≥2 distinguished players from controls with 94% sensitivity (95% confidence interval [CI] 71–100%) and 82% specificity (95% CI 57–96%). CSP length ≥5 mm distinguished players from controls with 82% sensitivity (95% CI 57–96%) and 100% specificity (95% CI 81–100%). Among players, CSP length was not significantly correlated with Mini Mental Status Exam score, years of football exposure (total or pro-only), age, or years since retirement from football. CSP length was not greater in players with a history of at least one concussion with LOC compared to players without any history of LOC (mean length–SD 11.6 mm–5.2 mm vs. 8.8 mm–5.6 mm, $p=0.3$). Similarly, CSP grade was not higher among players with a history of LOC compared with players without a history of LOC ($p=0.6$). Eight players were followed longitudinally for 6–36 months. All remained stably impaired (n=3) or declined cognitively/behaviorally (n = 4, including the player with CSP grade 0) except one player (CSP grade 3, age 29) who improved at 11-month follow-up.						
Imaging Multani et al., 2016 [30] PMID: 27142715	Cross-sectional	18	49.6 +/- 12 years	M	7	4
Sport/setting/level: Canadian Football League/Retired/Professional Duration of symptoms: N/A Diagnosis of Concussion: History of multiple concussions based on player recall of blow to head or body that resulted in concussion symptoms Length of follow-up: 16.2 +/- 13 years since last concussion; average CFL career length of 7.8+/-4 years Key Outcome Measures: Imaging (3 Tesla MRI using standard 8-channel head coil used to acquire structural and diffusion-weighted imaging), neuropsychological assessment (Rey Visual Learning Test, Personality Assessment Inventory, Wechsler Test of Adult Reading), concussion-related symptoms Comparison group/s: 17 healthy male controls matched on age and education; mean age 46.7 +/- 10 years Results: Increased axial diffusivity in right hemisphere in retired players in superior longitudinal fasciculus, corticospinal tract, and anterior thalamic radiations. Higher reports of neuropsychiatric and cognitive symptoms in retired CFL players than in healthy controls, and retired football players also reported an increase in symptoms since last concussion.						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Imaging Wilde et al., 2016 [31] PMID: 26414735	Cross sectional	10	Mean age = 45.7 (±9.7)	M	7	4
Sport/setting/level: Amateur and/or professional boxers (8 retired and 2 active) Duration of symptoms: N/A Diagnosis of Concussion: N/A Length of follow-up: At least 15 years experience of boxing Key Outcome Measures: Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI); Verbal Selective Reminding Test (VSRT); Serial Reaction Time Test Comparison group/s: 9 from non-contact sports (mean age = 43.4 ± 9.1) Results: Boxers recalled fewer words than controls at 30 minute delayed recall (F=10.7; p=0.006); Fractional anisotropy and apparent diffusion coefficient measured by tractography were not different between groups; Years of boxing was related to number of words recalled (r=-0.74; p=0.02), delayed recall (r=-0.83; p=0.003), and serial reaction time (r=0.66; p=0.005).						
Mixed/Imaging/Clinical Strain et al., 2015 [32] PMID: 25985094	Cross sectional	28	Mean 58.1 (13) years	M	8	4
Sport/setting/level: Retired NFL Players Duration of symptoms: N/A Diagnosis of Concussion: Self-report of concussions and classified using 1997 American Academy of Neurology guidelines for grading concussion. Length of follow-up: N/A Key Outcome Measures: California Verbal Learning Test (CVLT) second edition; Rey-Osterrieth Complex Figure Test; 60-item Boston Naming Test; Semantic Object Retrieval Test; Functional Magnetic Resonance Imaging of the Brain (FMRIB); hippocampal volume Comparison group/s: 21 healthy controls matched by education and IQ and 6 controls with MCI matched by age and gender Results: Former NFL athletes with at least one Grade 3 concussion had lower mean hippocampal volumes compared to controls at 40th (left p=0.04; right p=0.03), 60th (left p=0.009; right p=0.01) and 80th (left p=0.001, right p=0.002) age percentiles. Players with over 120 games had a lower mean left hippocampal volume than controls in 60th (p=0.02) and 80th (p=0.001) age percentiles.						
Mixed/ Imaging/Clinical Koerte et al., 2016 [33] PMID: 26414478	Cross-sectional	72	Mean age: 54±8 years (NFL group)	M	9	4
Sport/setting/level: Former NFL players and collegiate non-contact athletes Duration of symptoms: Mood, cognitive, or behavioral symptoms for at least 6 months prior to enrollment Diagnosis of Concussion: NA; only looking at football vs. non-contact, no direct analysis or control for concussion history; however, controls were excluded if they had a history of concussion Length of follow-up: N/A Key Outcome Measures: Neuropsychological Assessment Battey (NAB) List Learning, NAB Map Reading; NAB Naming, Rey-Osterrieth Complex Figure; Trailmaking Test, Parts A and B; Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol; Wide Range Achievement Test 4th Ed (WRAT-4) Reading Test; Wisconsin Card Sort Test (WCST); Hamilton Depression Rating Scale (HAM-D); Brown-Goodwin Lifetime History of Aggression, Barratt Impulsivity Scale (BIS); Modified Scale for Suicidal Ideation (MSSI); Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A), Beck Depression Inventory (BDI); Beck Hopelessness Inventory (BHI); Buss-Durkee Hostility Inventory (BDHI) self-completed in paper form; Magnetic Resonance Imaging; rating of cavum septi pellucidi (CSP) Comparison group/s: Non-contact athletes (N=14) with 4 years experience (at least 2 years in college or beyond); Mean age 57±7 years Results: NFL players generally had lower cognitive functioning scores and higher behavioral symptom and problem scores than non-contact controls; no group differences on length of septum pellucidum but symptomatic NFL players had greater presence of CSP, length of CSP, and length of CSP/septum pellucidum; few relationships exist between CSP length and mood, cognitive, and behavioral outcomes.						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Mixed/ Imaging/Clinical Koerte et al., 2016 (2) [34] PMID: 26286826	Cross-sectional	15 soccer players	mean age: 49.3 ± 5.1 years	M	6	4
Sport/setting/level: Former Professional German Soccer Players Duration of symptoms: N/A Diagnosis of Concussion: Self report of number of headers per week in the past 12 months prior to study x total years of soccer; Two soccer players were described as sustaining childhood mTBI due to MVC Length of follow-up: N/A Key Outcome Measures: Trail Making Test (TMT) parts A and B, Rey Complex Figure, Barrett Impulsivity Score (BIS), and the Balance Error Scoring System (BESS); cortical thickness (measure via 3T MRI) Comparison group/s: Former professional non-contact sport athletes (N=15) matched on age, gender, and handedness; mean age 49.6 ± 6.4 years (non-contact controls) Results: Soccer players performed significantly worse on the delayed memory portion of the RCF (mean T score 47.7 [14.7] versus 56.9 [8.8], p=0.04) but no other group differences were present and all individuals scored within normal range for their age; soccer players showed significantly decreased cortical thickness with age compared to controls; within soccer players lifetime heading estimates correlated with cortical thickness in the right hemisphere parietal and occipital lobes; TMT A positively correlated with cortical thickness in a cluster located in the right inferolateral-parietal cortex.						
Mixed/Imaging/Clinical Ford et al., 2013 [35] PMID: 23679098	Cross-sectional	Retired NFL: 27	Retired NFL: M=63.4 (5.9); Controls: M=62.2 (6.3)	M	9	4
Sport/setting/level: NFL Duration of symptoms: Not reported Diagnosis of Concussion: Self-reported (no definition specified) Length of follow-up: Not reported Key Outcome Measures: Neural activity during memory tasks using event-related fMRI; Neuropsychological Assessment; Mini-Mental State Exam (MMSE); Wechsler Adult Intelligence Scale-3 (WAIS-3); Controlled Oral Word Association Test (COWA); Trail Making Test Part B (Trails B); Boston Naming Test (BNT); Wechsler Test of Adult Reading (WTAR); Geriatric Depression Scale (GDS) Comparison group/s: 14 age- and education-matched controls with no history of concussion (mean age 62.2 ±6.3 years; all male) Results: There was no significant difference in performance on memory tasks between the low (0, 1, or 2) and high (3 or more) concussion groups. Concussion history was not associated with any behavioral memory measures. The two groups of former players demonstrated different neural recruitment patterns during relational memory retrieval, suggesting that multiple concussions may be associated with functional inefficiencies in the relational memory network. The number of previous concussions correlated with functional activity in the medial temporal lobe and inferior parietal lobe.						
Mixed/Clinical/Imaging Hart et al., 2013 [36] PMID: 23303193	Cross-Sectional	34	Athletes=M: 61.8; range: 41-79 years	34	4	4
Sport/setting/level: NFL Duration of symptoms: Not reported Diagnosis of Concussion: American Academy of Neurology (AAN) Practice Parameter guidelines for grading concussion (1997) as self-reported by the players. Length of follow-up: Not reported Key Outcome Measures: Neurological assessment, neuropsychological tests (Wechsler Abbreviated Scale of Intelligence; Trail Making Test Parts A and B; Boston Diagnostic Aphasia Examination; Controlled Oral Word Association Test; Boston Naming Test; Rey-Osterrieth Complex Figure Test; California Verbal Learning Test-II; Semantic Object Retrieval Test; Beck Depression Inventory-II), & 3-T MRI (Fluid-Attenuated Inversion Recovery, Hemosiderin Scan, Diffusion Tensor Imaging, Arterial Spin Labeling). Comparison group/s: Controls=n=26; Mean age: 60.1 years (95% CI: 54.6-64.1); range: 41-79 years, age-, education-, and estimated IQ-matched, healthy controls, without a history of concussion, no history of playing college or professional football, no cognitive complaints, and no neurological or psychiatric disorder. Results: No significant correlation between neuropsychological measures and concussions or years in the NFL. All but 2 of the 34 players had sustained at least 1 concussion (range, 1-13 concussions), with a mean of 4.0 concussions during their life span.						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Mixed/Imaging/Clinical Goswami et al., 2016 [37] PMID: 25721800	Cross-sectional	19	50 (SD=12); range=34-74	M	11	4
Sport/setting/level: Retired Canadian Football League/Canada/Professional Duration of symptoms: Not reported Diagnosis of Concussion: Self-reported; operationally defined in accordance with CISG 2012 (Zurich) Length of follow-up: Variable and not specifically mentioned but retired players were between 34-74 years Key Outcome Measures: Cognition, cortical thickness, Probabilistic Tractography, resting state *f*MRI, Comparison group/s: n=17, age and education matched controls with no history or suspicion of head trauma. Results: The athlete group had faster reaction times and made more errors compared to the control group, indicative of reduced response inhibition ($p < 0.05$); had significantly higher mania and aggression scores on the PAI than the controls group ($p < 0.05$), although levels were not considered clinically significant; cortical thinning of the anterior temporal lobe (ATL) and orbitofrontal cortex (OFC) thickness correlated with errors and aggression. Cortical thickness of the left ATL was reduced in the athletes as compared to controls (3.2 mm in athletes vs. 3.5 mm in controls; $p < 0.05$, corrected for multiple comparisons, 228 significant vertices based on a cluster threshold of 108). Cortical thickness of the mOFC bilaterally was negatively correlated with SART error rate ($r = -0.514$, $p = 0.035$ for left, and $r = -0.517$, $p = 0.034$ for right). Athletes had increased functional connectivity in the left ATL with the left mOFC compared to controls ($p < 0.05$).						
Mixed/Imaging/Clinical Casson et al. (2014) [38] PMID: 25177413	Cross-sectional	45	45.6 (SD=8.9); range=30-60	M	8	3
Sport/setting/level: Retired NFL Players/USA/Professional Duration of symptoms: Not reported Diagnosis of Concussion: Self-reported Length of follow-up: Variable and not specifically mentioned but retired players were between 30-60 years Key Outcome Measures: MRI; SWI, DTI, cognitive and neurological examinations, clinical interview, blood tests, and APOE genotyping Comparison group/s: None Results: Of the 9 self-reported cognitive and memory questions: 23 retired players endorsed 0-2 symptoms, 11 retired players endorsed 2-5 symptoms, and 11 retired players endorsed 6-9 symptoms. Of the 9 self-reported depression and anxiety questions: 19 retired players endorsed 0-1 symptoms, 14 retired players endorsed 2-3 symptoms, and 12 retired players endorsed 4-8 symptoms. Seventeen subjects (37.8%) had at least one allele 4. Two of these had 2 copies of allele 4, while 2 were paired with an allele 2 and 13 were paired with an allele 3. Nine subjects fulfilled the criteria for either major depression or other depression on the PHQ. Eight of these 9 subjects also scored 14 or higher on the BDI. Two cases were found with abnormally enlarged ventricles and thin corpus callosum, 34 retired players had a CSP; 4 retired players had evidence of microbleeds on SWI; the number of concussions was associated with imaging abnormalities. None of the players had dementia (defined as impairments on 2 or more spheres of cognition that interfere with activities of daily living).						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Pathology Studies						
Corsellis et al., 1973 [39] PMID: 4729191	Retrospective Case Series	15	Mean: 69 years; range 57-91 years at time of death	M	3	5
Sport/setting/level: Former boxers (3 amateurs and 12 Professional) Duration of symptoms: Variably described Diagnosis of Concussion: No definition reported Length of follow-up: N/A Key Outcome Measures: Neuropathology, Clinical history per family member's recall Comparison group/s: None Results: Carefully described the gross and microscopic neuropathology believed to be unique to dementia pugilistica in 15 boxers whose brains were stored in a brain bank (e.g., neurofibrillary degeneration, neuronal loss, 'scarring' of the cerebellar tonsils, and fenestrated cavum septum pellucidum). 2/15 boxers suffered intraventricular haemorrhage and died. Of the remaining 13 brains, septal cavum was identified in 12/13 brains; maximum coronal widths ranged from 1-8mm; in 10/15 brains; Purkinje cell loss was noted in addition to thinning of granular layer and partial demyelination of the affected folia; Parkinsonian syndrome was identified in 4/15 cases based on hospital records; senile plaques were absent.						
Roberts et al., 1990 [40] PMID: 2191084	Case Series	20	22-83 (63.6 +/- 12.1)	M	1	5
Sport/setting/level: Boxers (5 amateur and 15 professional) Duration of symptoms: Variably described Diagnosis of Concussion: No definition reported Length of follow-up: N/A Key Outcome Measures: Neuropathology, Clinical history per family member's recall Comparison group/s: AD cases (n=20) and age-matched controls (n=20) Results: Re-examined the brains from the Corsellis series and additional cases and discovered, using modern immunohistochemistry techniques, that nearly all had extensive beta amyloid deposition similar to what is seen in Alzheimer's disease (AD). Large numbers of diffuse plaques in all case of dementia pugilistica. Substantial tangle formation showed extensive β-protein immunoreactive deposits (plaques).						
Pathology McKee et al., 2010 [41] PMID: 20720505	Case series	12	42-85 (65.4 +/- 15.9)	M	4	4
Sport/setting/level: 7 professional football, 4 professional boxers, 1 professional hockey player Duration of symptoms: Ranged between 2-8 years Diagnosis of Concussion: Diagnosis of concussion made by examining medical records, and interviews with next of kin. Criteria for concussion not explicitly stated. Length of follow-up: N/A (autopsy study) Key Outcome Measures: Pathology, including tauopathy, TDP43 proteinopathy Comparison group/s: Age and gender matched ALS controls, and controls without neurologic disease Results: The brains of all 9 athletes with CTE-no MND showed the pathological changes of CTE, consisting of numerous tau-positive NFTs, neuropil neurites, and astrocytic tangles in the frontal, temporal, and insular cortices, diencephalon, basal ganglia, and brainstem. "The TDP- 43-positive short threadlike and ring-shaped neurites (RNs), filamentous neuronal inclusions (FNIs), and ring-shaped glial inclusions (RGIs) were found in the frontal and temporal cortex and insula. The TDP-43-positive RNs and RGIs were frequent in the subcortical white matter, and TDP-43-positive FNIs and RNs were common in the brainstem, including the substantia nigra pars compacta, oculo-motor, inferior olivary, dorsal medullary, and hypoglossal nuclei. The TDP-43-positive neurites were found in the amygdala, hippocampus, caudate, putamen, thalamus, and hypothalamus."						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Pathology Omalu et al., 2011 [42] PMID: 21358359	Case series	17	16-52 (Mean 36 years)	M	6	4
Sport/setting/level: 14 professional (8 NFL, 4 wrestlers, 1 boxer, 1 mixed martial artist), 3 high school football Duration of symptoms: Not reported Diagnosis of Concussion: Concussion history and diagnostic criteria not specifically commented upon Length of follow-up: N/A (autopsy study) Key Outcome Measures: Pathology - tauopathy, amyloid beta-opathy Comparison group/s: None Results: CTE pathology found in 10 of 14 professional athletes and 1 of 3 high school athletes. The authors noted four histologic phenotypes, based on relative abundance of phosphorylated-tau in cerebral cortex, subcortical structures, and brainstem, and presence or absence of diffuse β-amyloid plaques.						
Pathology Hazrati et al., 2013 [43] PMID: 23745112	Case series	6	61-87 years	M	3	4
Sport/setting/level: Professional Canadian Football Duration of symptoms: 3-17 years Diagnosis of Concussion: Not reported Length of follow-up: N/A (autopsy study) Key Outcome Measures: Neuropathology, Clinical Interview Comparison group/s: None Results: 3/6 cases had post-mortem neuropathological findings of CTE. Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD) were evident in the other three cases. CTE cases also had co-morbid pathologies of vascular disease, Alzheimer's disease, and cancer.						
Pathology McKee et al., 2013 [44] PMID: 23208308	Case series	85	Mean 54.1 +/- 23.3 (range 14-98 years)	84:1	6	4
Sport/setting/level: Athletes, Veterans, Civilians Duration of symptoms: Range from no symptoms to several decades of symptoms (exact data not provided) Diagnosis of Concussion: Post-mortem interview of next of kin by neuropsychologist Length of follow-up: N/A (autopsy study) Key Outcome Measures: Neuropathology, including tauopathy, TDP-43 proteinopathy, amyoid beta-opathy, Clinical Interview Comparison group/s: 18 cognitively normal age- and gender-matched control subjects without known history of mild traumatic brain injury Results: Staging scheme proposed (I - IV). The number of years played (Spearman's test, $r = 0.805$, $p = 0.0001$), years since retirement (Spearman's test, $r = 0.753$, $p = 0.0001$), and age at death (Spearman's test, $r = 0.806$, $p = 0.0001$) were significantly correlated with pathological stage of CTE. Family reported number of concussions (Spearman's test, $r = 0.259$, $p = 0.184$), years of education (Spearman's test, $r = 0.258$, $p = 0.134$), lifetime steroid use (Wilcoxon–Mann–Whitney test, $p = 0.731$) and position played (Kruskall–Wallis test, $p = 0.407$) were not significantly related to CTE stage. Of the 68 individuals diagnosed with CTE, the proportion of the sample carrying at least one ApoE e4 allele was not significantly different than that observed in the general population (Chi-square goodness of fit, $p = 0.334$). Brain weight significantly smaller in stage IV compared to other stages ($p < 0.001$)						

Article Type Lead Author, Study Year	Study Design	Sample Size	Age (range, mean +/- SD)	Sex (m:f)	Risk of Bias	Level of Evidence
Pathology Bieniek et al., 2015 [45] PMID: 26518018	Case-control	264	78 (mean for cases), 74 (mean for controls)	132M:66F in "controls" (no exposure to contact sports).	9	4
Sport/setting/level: High school, collegiate, semi-professional, amateur, and professional sports identified, including football, boxing, baseball, basketball, rugby, soccer, martial arts, hockey, rodeo, wrestling Duration of symptoms: No symptoms related to CTE were identified Diagnosis of Concussion: Concussion history in the medical records commented upon in only three subjects, with no reference to criteria Length of follow-up: N/A (autopsy study) Key Outcome Measures: Tauopathy consistent with CTE, as determined by "screening" at Mayo Jacksonville, and confirmed via 50 micron sectioning at Boston University Comparison group/s: Groups with or without contact sport history were compared for evidence of pathology consistent with CTE Results: This large study of individuals with neurodegenerative disease found CTE pathology in 31.8% of former athletes (22.2% of boxers and 37.2% of former football players) and 0% of those who were not former athletes. In 33 cases who had a history of a single TBI, none had CTE pathology.						
Pathology Ling et al. (2015) [46] PMID: 26497674	Case Series	268	Mean 81 years	NR	6	4
Sport/setting/level: Only 11 cases had a history of participation in sports: rugby, soccer, cricket, lacrosse, judo, and squash. Duration of symptoms: N/A Diagnosis of Concussion: Not described Length of follow-up: N/A Key Outcome Measures: Medical records, pathology Comparison group/s: Controls over the age of 60 (n=47) Results: Screened 268 cases and identified pathology consistent with recent descriptions of CTE in 32 (11.9%), M:F=19:13. A prior history of TBI, with or without loss of consciousness, was present in 93.8%, a minority had participated in sports (34%), and 18.8% were military veterans. The rate of CTE pathology in control subjects over the age of 60 was 12.8%. The rates of CTE pathology present in those with neurodegenerative diseases were as follows: progressive supranuclear palsy=24%, Parkinson's disease=16%, Alzheimer's disease=10%, corticobasal degeneration=7.4%, frontotemporal lobar degeneration=4.2%, and multiple system atrophy=2%. Remarkably, of the 32 cases with CTE pathology, 13 were women (40.6%). The extent to which this pathology was associated with any clinical symptoms was unknown, and the authors assumed that they were likely asymptomatic from this pathology. However, Ling and colleagues used the pathological criteria for CTE proposed by McKee and colleagues [44], not the NIH consensus criteria*, so it is not known how many women would have met consensus-based criteria. *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.						
Pathology Koga et al., 2016 [47] PMID: 27543120	Retrospective cohort	139 cases of multiple system atrophy	MSA group 67 +/- 8 yrs	84:55	9	4
Sport/setting/level: 4 of 8 with CTE pathology with history of contact sports Duration of symptoms: N/A Diagnosis of Concussion: Concussion history not specifically defined in the MSA cohort Length of follow-up: N/A Key Outcome Measures: Tauopathy consistent with CTE in the presence of co-morbid multiple system atrophy Comparison group/s: None Results: 139 autopsy-confirmed cases of multiple system atrophy were examined for pathological evidence of CTE. Using the consensus criteria, CTE pathology was identified in 8 cases (6%). All 8 were male. Only 4 of 8 had exposure to contact sports (three in football and one in basketball). The authors were careful to differentiate cases of ARTAG (10 cases) from CTE in this study, and noted that ARTAG pathology in past studies might have been mistaken for CTE pathology.						

Note: AAN: American Academy of Neurology; AFE: age of first exposure to tackle football; AES: Apathy evaluation scale; ApoE: Apolipoprotein; ALS: amyotrophic lateral sclerosis; ATL: anterior temporal lobe; AUDIT: Alcohol Use Disorders Identification Test; BDI-II: Beck Depression Inventory – 2nd edition; BIS: Barratt Impulsiveness scale; BMI: body mass; BPAQ-SF: Short Form of the Buss-Perry Aggression Questionnaire; BTACT: Brief Test of Adult Cognition by Telephone; BRIEF: Behavior Rating Inventory of Executive Function – Adult Version; CES-D: Centre for Epidemiology Studies – Depression Scale; CFL: Canadian Football League; Cho: Choline; CI: confidence interval; CISG: Concussion in sport group;

Cr: Creatine; CSP: cavum septum pellucidum; CTE: chronic traumatic encephalopathy; CV: cavum vergae; CVD: cardiovascular disease; df: degrees of freedom; DLPFC: dorsolateral prefrontal cortex; DP: dementia pugilistica; DSM-IV: Diagnostic and Statistical Manual - 4th Edition; DTI: Diffusion Tensor Imaging; F: female; FDDNP: 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile; fMRI: Functional Magnetic Resonance Imaging; FMRIB: Functional Magnetic Resonance Imaging of the Brain; FPC: frontopolar cortex; GHD: gamma hydroxybutyrate; GHS: General Health Survey; Glu: glutamate; GSH: glutathione; HD: hormone deficiency; ID#: reference number; IGF-1: insulin-like growth factor 1; IIEF: International Index of Erectile Function; L-COSY: localized correlated spectroscopy; LEGEND: longitudinal examination to gather evidence of neurodegenerative disease; LOC: loss of consciousness; MCS: Mental Cognitive Scores; MCI: mild cognitive impairment; MD: mean differences; MetS: Pituitary hormonal and metabolic syndrome; mI: myo-Inositol; MND: Motor Neurone Disease; NAA: N-acetyl-asparate; N/A: not applicable; NFL: National Football League; NFT: neurofibrillary tangles; NR: not reported; M: male; MRS: magnetic resonance spectroscopy; MSA: multiple systems atrophy; OFC: orbitofrontal cortex; PC: parietal cortex; PD: Parkinson's disease; PET: Positron emission tomography; PHQ: patient health questionnaire; PR: prevalence ratios; QoL: quality of life; RBANS: Repeatable Battery for the Assessment of Neuropsychological States; ROIs: regions of interest; RR: risk ratios; SD: standard deviation; SF-36: short form 36; SMR: standardized mortality ratios; SWI: susceptibility weighted imaging; TDP-43: TAR DNA-binding protein 43; yrs: years.

Online Supplementary Table 3. Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies.

		Reporting										External Validity			Internal Validity-Bias							Internal Validity-Confounding (Selection Bias)						Power	
First Author and Year	PMID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total
Clinical Studies (24)																													M=9.7
Kelly et al. (2014)[1]	24552537	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	--	8
Lolekha et al. (2015)[2]	20669292	1	1	1	0	1	1	1	0	1	1	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0	--	11
Lehman et al. (2016)[3]	27159317	1	1	1	0	1	1	1	0	1	1	1	1	0	0	0	1	1	1	0	1	1	1	0	0	1	1	--	18
Murelius et al. (1991)[4]	2011947	1	1	1	0	1	1	1	0	0	0	0	1	0	0	0	1	0	1	0	1	0	0	0	0	0	0	--	10
Kerr et al. (2012)[5]	22922518	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	1	1	0	0	1	1	0	0	1	0	--	12
Didehbani et al. (2013)[6]	23644673	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	--	9
Seichepine et al. (2013)[7]	23421745	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	6
Randolph et al. (2013)[8]	23902607	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	--	10
Vann Jones et al. (2013)[9]	24026299	1	1	1	0	1	1	0	0	0	1	1	1	0	0	0	0	0	1	0	1	1	0	0	0	1	0	--	12
Kerr, DeFreese et al. (2014)[10]	26535354	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	--	9
Kerr, Evenson et al. (2014)[11]	27747661	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	--	8
Stamm et al. (2015)[12]	25632088	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1	0	--	10
Hume et al. (2016)[13]	27558141	1	1	1	0	1	1	1	0	0	1	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	--	10
Meehan et al. (2016)[14]	26193380	1	1	1	0	1	1	1	0	0	1	1	0	0	0	0	1	0	1	0	1	0	0	0	0	1	0	--	12
Montenigro et al. (2016)[15]	27029716	1	1	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	--	6
Baron et al. (2012)[16]	22284915	1	1	1	0	1	1	1	0	0	1	1	0	0	0	0	0	0	1	0	1	1	0	0	0	0	0	--	11
Lehman et al. (2012)[17]	22955124	1	1	1	0	1	1	1	0	0	1	1	0	0	0	0	0	0	1	0	1	1	0	0	0	0	0	--	11
Critchley (1957)[18]	13396257	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	1
Maudsley & Ferguson (1963) [19]	14052038	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	2
Savica et al. (2012)[20]	22469346	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	1	1	0	1	1	1	0	0	0	0	--	11
Roberts et al. (1969)[21]	N/A	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	1	1	0	1	1	1	0	0	1	0	--	12
Guskiewicz et al., (2005)[22]	16239884	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	--	12
Guskiewicz et al., (2007)[23]	17545878	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	1	1	0	0	1	0	--	12
Hinton et al., (2011)[24]	22030936	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	1	0	0	1	0	1	0	0	0	0	--	10
Imaging & Imaging/Clinical Studies (14)																													M=7.4
Hampshire et al. (2013)[25]	24135857	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	--	5
Small et al. (2013)[26]	23343487	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	7
Koerte et al. (2015)[27]	25843317	1	1	0	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	--	8
Lin et al. (2015)[28]	25780390	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	4
Gardner et al. (2016)[29]	25970145	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	--	12
Multani et al. (2016)[30]	27142715	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	7
Wilde et al. (2016)[31]	26414735	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	--	7
Strain et al. (2015)[32]	25985094	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	--	8
Koerte, Huf et al. (2016)[33]	26414478	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	0	--	9
Koerte, May et al. (2016)[34]	26286826	1	1	0	0	1	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	--	6
Ford et al. (2013)[35]	23679098	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0	0	0	0	--	9
Hart et al. (2013)[36]	23303193	1	0	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	4
Goswami et al. (2016)[37]	25721800	1	1	1	0	1	1	0	0	0	1	1	1	0	0	0	0	0	1	0	1	0	0	0	0	1	0	--	11
Casson et al. (2014)[38]	25177413	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	1	0	0	0	0	--	8
Pathology Studies (9)																													M=5.2
Corsellis et al. (1973)[39]	4729191	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	3
Roberts et al. (1990)[40]	2191084	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	1
McKee et al. (2010)[41]	20720505	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	4
Omalu et al. (2011)[42]	21358359	1	1	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	6
Hazrati et al. (2013)[43]	23745112	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	3
McKee et al. (2013)[44]	23208308	1	1	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	--	6
Bieniek et al. (2015)[45]	26518018	1	1	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	--	9
Ling et al. (2015) [46]	26497674	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	--	6
Koga et al. (2016)[47]	27543120	1	1	1	0	1	1	0	0	0	1	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	--	9

Note: Power was not rated due to the diverse research designs and the lack of clarity in the literature on how to apply the Downs and Black power criteria to these types of studies.

Appendix: Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies.

Reporting (1-10)

1. Hypothesis/aim/objective
2. Main outcomes clearly described
3. Characteristics of the patients
4. Interventions
5. Distributions of principal confounders
6. Main findings
7. Estimates of variability main outcomes
8. Adverse events
9. Patients lost to follow-up
10. P values

External Validity (11-13)

11. Representativeness of subjects who were asked to participate
12. Representativeness of subjects who were prepared to participate
13. Representativeness of the staff, places, and facilities where the patients were treated

Internal Validity-Bias (14-20)

14. Attempt to blind study subjects to the intervention
15. Attempt to blind those measuring the main outcomes
16. Did researchers use "data dredging" and acknowledge it
17. Adjusting analyses for different lengths of follow-up of patients, or the time-period between the intervention and outcome
18. Appropriate statistical tests
19. Reliable compliance with the intervention(s)
20. Valid/reliable/accurate main outcome measures

Internal Validity Confounding-Selection Bias

21. Recruitment of subjects from the same population (in the different intervention groups or the cases and controls)
22. Subjects in different intervention groups or were the cases and controls recruited over the same period of time
23. Randomization to interventions
24. Randomised intervention assignment double-blinded until recruitment was complete and irrevocable
25. Adequate adjustment for confounding in the statistical analyses
26. Accounting for losses of patients to follow-up

Power

27. "Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? (Size of smallest intervention group: <n1 = 0; n1-n2 = 1; n3-n4 = 2; n5-n6 =3; n7-n8 = 4; n8+ = 5)" (quote from the original article)

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