2-1-2019

Contact Sports as a Risk Factor for Amyotrophic Lateral Sclerosis: A Systematic Review.

Ronen Blecher
Swedish Neuroscience Institute, Swedish Medical Center, Seattle, Washington, USA

Michael A Elliott
Swedish Neuroscience Institute, Seattle, WA, USA

Emre Yilmaz
Swedish Medical Center, Swedish Neuroscience Institute

Joseph R Dettori

Rod J Oskouian
Swedish Neuroscience Institute, Swedish Medical Center, Seattle, Washington, USA

See next page for additional authors

Authors
Ronen Blecher, Michael A Elliott, Emre Yilmaz, Joseph R Dettori, Rod J Oskouian, Akil P Patel, Andrew Clarke, Mike Hutton, Robert McGuire, Robert Dunn, John DeVine, Bruce Twaddle, and Jens R Chapman

Global Spine Journal
2019, Vol. 9(1) 104-118
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2192568218813916
journals.sagepub.com/home/gsj

Contact Sports as a Risk Factor for Amyotrophic Lateral Sclerosis: A Systematic Review

Ronen Blecher, MD, PhD[1,2], Michael A. Elliott, MD[1], Emre Yilmaz, MD[1], Joseph R. Dettori, PhD[3], Rod J. Oskouian, MD[1], Akil Patel, MD[1], Andrew Clarke, FRCS (Orth)[4], Mike Hutton, FRACS (Orth)[4], Robert McGuire, MD[5], Robert Dunn, MBBA[6], John DeVine, MD[7], Bruce Twaddle, BHB, MBChB, FRACS[8], and Jens R. Chapman, MD[1]

Abstract

Study Design: Systematic review.

Introduction: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease, ultimately resulting in paralysis and death. The condition is considered to be caused by a complex interaction between environmental and genetic factors. Although vast genetic research has deciphered many of the molecular factors in ALS pathogenesis, the environmental factors have remained largely unknown. Recent evidence suggests that participation in certain types of sporting activities are associated with increased risk for ALS.

Objective: To test the hypothesis that competitive sports at the highest level that involve repetitive concussive head and cervical spinal trauma result in an increased risk of ALS compared with the general population or nonsport controls.

Methods: Electronic databases from inception to November 22, 2017 and reference lists of key articles were searched to identify studies meeting inclusion criteria.

Results: Sixteen studies met the inclusion criteria. Sports assessed (professional or nonprofessional) included soccer (n = 5), American football (n = 2), basketball (n = 1), cycling (n = 1), marathon or triathlon (n = 1), skating (n = 1), and general sports not specified (n = 11). Soccer and American football were considered sports involving repetitive concussive head and cervical spinal trauma. Professional sports prone to repetitive concussive head and cervical spinal trauma were associated with substantially greater effects (pooled rate ratio [RR] 8.52, 95% CI 5.18-14.0) compared with (*a*) nonprofessional sports prone to repetitive concussive head and cervical spinal trauma (pooled RR 0.60, 95% CI 0.12-3.06); (*b*) professional sports not prone to repetitive head and neck trauma (pooled RR 1.35, 95% CI 0.67-2.71); or (*c*) nonprofessional sports not prone to repetitive concussive head and cervical spinal trauma (pooled RR 1.17, 95% CI 0.79-1.71).

[1] Swedish Neuroscience Institute, Seattle, WA, USA
[2] Sackler Faculty of Medicine, Tel Aviv University, Israel
[3] Spectrum Inc, Tacoma, WA, USA
[4] Princess Elizabeth Orthopaedic Centre, Exeter, UK
[5] University of Mississippi, Jackson, MS, USA
[6] University of Cape Town, Cape Town, South Africa
[7] Georgia Health, Augusta, GA, USA
[8] Auckland City Hospital, Auckland, New Zealand

Corresponding Author:
Jens R. Chapman, Swedish Neuroscience Institute, Swedish Medical Center, 550 17th Avenue, Seattle, WA 98122, USA.
Email: jens.chapman@swedish.org

Conclusions: Our review suggests that increased susceptibility to ALS is significantly and independently associated with 2 factors: professional sports and sports prone to repetitive concussive head and cervical spinal trauma. Their combination resulted in an additive effect, further increasing this association to ALS.

Keywords
amyotrophic lateral sclerosis (ALS), motor neuron disease, risk factor, association, sports, athletes, meta-analysis, systematic review, football, soccer

Introduction

Amyotrophic lateral sclerosis (ALS, also known as "Lou Gehrig disease") is a progressive neurodegenerative disease, considered to be caused by a complex interaction between environmental and genetic factors.[1] The pathological hallmark consists of progressive neurodegeneration of upper and lower motor neurons, ultimately leading to paralysis and death. As a clinical entity, ALS has remained primarily associated with the field of neurology, however spine surgeons may also encounter these patients given that early clinical presentations can mimic a number of spinal disorders, especially such that present as weakness in presence of a compressive cervical spondylosis. The incidence of ALS in Western countries is estimated to be between 1 and 3 per 100 000 per year per person-years.[2] About 90% of cases are sporadic with negative family history whereas in the remaining 10% are familial.[3] Advanced genetic technologies in recent years has led to the identification of around 25 ALS-related genes[4,5] and to the generation of ALS-specific animal models, mimicking the human condition.[6,7] Nonetheless, a unified pathogenic mechanism that would adjoin all known clinical and genetic findings is still lacking. There is also evidence that environmental factors play a role in the pathogenesis of sporadic ALS and may trigger the onset of disease for those with known genetic mutations. Indeed, various exposures that have been linked with ALS include smoking,[8] heavy metals,[9] and pesticides.[10] Of note, a recent growing body of evidence also supports a role for increased physical activity[11,12] and musculoskeletal trauma.[13] Interestingly, various sports such as American football[14] and soccer[15] have also been shown to carry an increased risk of developing ALS, further strengthening a possible mechanical etiology. These contact sports, which in the most advanced competitive implementations combine both vigorous physical activity and carry the risk of potential repetitive head and cervical spine trauma with the resultant risk in the form of traumatic brain injury in varying degrees of severity. Yet analysis of how the level of competitiveness (professional vs nonprofessional) or the type of sport (contact vs noncontact) affect this risk remains unanswered. We hypothesized that not all sports, but only those at the highest competitive levels that involved repetitive head and cervical spine trauma result in an increased risk of ALS compared with the general population or nonsport controls. To test this hypothesis, our systematic review sought to answer the following key questions (KQ).

Clinical Questions

KQ 1: Is there an increased risk of ALS or mortality associated with ALS among those who play organized competitive sports?

KQ 2: Does the risk vary by higher levels of competitive play (professional vs nonprofessional)?

KQ 3: Does the risk vary by whether the sport is prone to repetitive concussive head and cervical spinal trauma?

KQ 4: Within different levels of competitive play, does the risk vary by whether the sport is prone to repetitive concussive head and cervical spinal trauma?

Materials and Methods

Study Design

Systematic review.

Information Sources

PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to November 22, 2017; Google Scholar and bibliographies of included articles and systematic reviews.

Eligibility Criteria

The inclusion criteria were (*a*) adults $\geq$16 years with a history of playing competitive organized sports, (*b*) comparison of a nonsport control or standardized reference group, and (*c*) comparative cohort and case-control study designs. The exclusion criteria were (*a*) youth sports under the age of 16 years; (*b*) strenuous noncompetitive sport activity, military activity, nonsport trauma; (*c*) crude (nonstandardized) population reference group; (*d*) other neurologic disorders as outcomes; and (*e*) studies not producing an effect measure (odds ratio, rate ratio, standardized ratio, etc), cross-sectional studies, reviews, or case reports.

Outcomes

Incidence of ALS or mortality associated with ALS.

Exposures

Any organized competitive sport either professional or nonprofessional. We defined the following sports a priori as those deemed to expose players to repetitive concussive head and cervical spinal trauma: American football, soccer, hockey, boxing, rugby.

Controls

Controls consisted of the general population or individuals with no history of engaging in organized competitive sports.

Data Collection Items and Process

Data was extracted by a single individual and verified independently by a second investigator. Two individuals independently evaluated the risk of bias and disagreements were resolved through discussion.

Risk of Bias

Risk of bias (RoB) was assessed against preset criteria for prognostic studies. From the RoB, study class of evidence (CoE) was derived. RoB criteria and CoE assessment for each included article can be found in the supplemental material.

Analysis

Several types of measurements enable the assessment of how a certain exposure (in our study contact sports) may be associated with a certain disease (ALS). "Mortality ratio" and "incidence ratio" are the observed number of deaths or patients with a disease in the exposed group, respectively, divided by that in the unexposed group. An assessment of this association over a period of time is termed "Hazard ratio." Another way of estimating risk is calculating "odds ratio" in which an exposure is associated with a known health outcome (ALS) and is usually performed in case-control studies. Proportional mortality ratio (PMR) calculates the ratio of a specific-cause mortality to the overall mortality. Standardized mortality or incidence ratios, hazard ratios, odds ratios, proportional mortality ratios, and rate ratios were treated as equivalent measures of risk and referred to as the rate ratio (RR). Each of these measures compare the occurrence of ALS in the exposed versus control populations. After undergoing a logarithmic transformation, studies were pooled and weighted according to the reciprocal of their variances (calculated as the square of their standard error, which if not available, was sourced from reported confidence intervals). Results were then transformed back to their original units and presented with 95% confidence intervals along with P values derived from t tests. A random effects model was assumed to address heterogeneity. I^2 statistics were calculated with the null hypothesis that there were no differences in the effect sizes across studies and that chi-square distribution was followed. Effect estimates were stratified in order to analyze different patient population characteristics. The same methods used to pool and test at the study level further extend to pool and test at the subgroup level. A sensitivity analysis consisted of removing any study with a high risk of bias, class of evidence IV. All meta-analysis calculations and plots were done using Cochrane's Revman v.5.3.

Results

Study Selection

Sixteen studies met the inclusion criteria, 12 assessing the incidence of ALS[16-27] and 4 the mortality associated with ALS[14,28-30] (Table 1). Three studies were judged to have moderately low risk of bias, CoE II[14,28,29]; 8 moderately high risk of bias,[16,17,19,21,22,25,26,30] CoE III; and 5 high risk of bias,[18,20,23,24,27] CoE IV. Four studies evaluated professional soccer,[16,17,28,29] 1 professional American football,[14] 1 professional basketball,[17] 1 professional cycling,[17] 3 professional general sports (not specified),[21,22,30] 1 nonprofessional soccer,[26] 2 nonprofessional American football,[20,23] 1 nonprofessional marathon or triathlon,[19] 1 nonprofessional skating,[19] and 8 nonprofessional general sports (not specified).[16,18,21,22,24-27] Figure 1 shows the inclusion/exclusion of articles from the search. CoE rating and a list of excluded articles can be found in the supplemental material.

Is there an increased risk of ALS or mortality associated with ALS among those who play organized competitive sports?

- Organized competitive sports was associated with an increased risk of ALS compared with controls (24 comparisons from 16 studies,[14,16-30] pooled RR 1.80, 95% CI 1.13-2.88, $I^2 = 83\%$) (Figure 2). Substantial heterogeneity was present in the analysis. Exclusion of the poorest quality studies (CoE IV) did not change the results or reduce heterogeneity (11 studies,[14,16,17,19,21,22,25,26,28-30] pooled RR 1.82, 95% CI 1.02-3.25, $I^2 = 87\%$).

Does the risk vary by higher levels of competitive play (professional vs nonprofessional)?

- When stratified by levels of competitive play, professional sports was associated with greater effects (10 comparisons, 8 studies,[14,16,17,21,22,28-30] pooled RR 4.07, 95% CI 1.99-8.32, $I^2 = 70\%$) compared with nonprofessional sports (14 comparisons, 11 studies,[16,18-27] pooled RR 1.13, 95% CI 0.79-1.62, $I^2 = 60\%$), test for subgroup differences, $P = .002$ (Figure 2).

Does the risk vary by whether the sport is prone to repetitive concussive head and cervical spinal trauma?

- Sports prone to repetitive concussive head and cervical spinal trauma was associated with greater effects (8 studies,[14,16,17,20,23,26,28,29] pooled RR 5.98, 95% CI 3.03-11.80, $I^2 = 56\%$) than sports not prone to repetitive concussive head and cervical spinal trauma (16 comparisons, 11 studies,[16-19,21,22,24-27,30] pooled RR 1.17, 95%

Table 1. Characteristics of Included Studies Assessing Risk of Amyotrophic Lateral Sclerosis (ALS) in Athletes.

Author Country CoE	Design Effect	Sport	Outcome Definition	Controls	Study Participants	Funding
Beghi 2010 Italy, UK, Ireland, Scotland CoE III	Case control Odds ratio	Professional soccer Nonprofessional general sports	Probable or possible ALS via El-Escorial criteria	Non-ALS patients from general practitioner, matched on age and sex	N = 173 (ALS = 61 vs controls = 112) Mean age, years: 63.7 vs 62.3 Male professional: 100% vs 100% Male nonprofessional: 56% vs 57% Mean BMI: 25.3 vs 26.1 Strenuous physical work: 13% vs 4% Mean duration of work-related exercise, years: 10.7 vs 7.3 Mean duration of sport-related exercise, years: 9.6 vs 5.2 Traumatic events: 48% vs 53% Smoker: 53% vs 57% Drinks alcohol: 48% vs 43%	Grants from the Istituto Superiore di Sanita and the American ALS Association. Research was supported in part by the Intramural Research Program of the National Institute of Aging. COI: Authors report no conflicts of interest
Belli 2005 Italy CoE II	Cohort Standardized proportional mortality rate	Professional soccer (A, B and C league)	Death associated with ALS	National death registry, matched on age, sex, cause and calendar year	N = 350 (ALS = 8 vs other = 342) Mean age at death, years: 50.8 Male: 100%	NR COI: NR
Chiò 2009 and 2005 Italy CoE III	Cohort Standardized incidence ratio	Professional: Soccer (1st or 2nd division) Basketball (major league series A1 or A2) Cycling (team engaged in ≥1 official race)	Definite, probable or lab-supported probable ALS using medical record, death certificate, patient or relative interview	Population registries, matched on age and sex	N = 10 999 (soccer cohort = 7325 vs basketball cohort = 1973 vs road cyclist cohort = 1701) Mean age, years: 41.7 vs 36.2 vs 60.1 Male: 100% vs 100% vs 100% Mean age of onset, years: 43.4 vs NA vs NA Bulbar onset: 63% vs NA vs NA	Grants from the Italian Ministry of Health (2005 Research Programme on Drugs and Illegal Activities in Sports; and Finalized Research on Neurodegenerative Disorder) and from the Fondazione Vialli e Mauro per la Ricerca e lo Sport ONLUS COI: Authors declare no conflict of interest
Felmus 1976 USA CoE IV	Case control Odds ratio	Nonprofessional general sports (high school or college varsity letter sports	ALS diagnosis from clinical exam, history, labs, EMG, muscle biopsy, consensus of >1 neurologist	Non-ALS patients from neurology service, matched on age and sex	N = 75 (ALS = 25 vs diseased control = 25 vs health controls = 25) Mean age, years: 51.0 vs 53.7 vs 50.5 Male: 64% vs 64% vs 64% *ALS patients only:* Mean age of onset, years: 46.3	NR COI: NR
Huisman 2013 Netherlands	Case control Adjusted odds ratio	Nonprofessional, marathon, triathlon, or	Probable or possible new ALS via El-Escorial criteria	Non-ALS individuals from Dutch Health Care	N = 2802 (ALS = 636 vs controls = 2166) Median age, years: 63 vs 62	Prinses Beatrix Fonds (PB 0703), VSB Fonds, H Kersten and M Kersten, The Netherlands ALS Foundation,

(continued)

Table 1. (continued)

Author Country CoE	Design Effect	Sport	Outcome Definition	Controls	Study Participants	Funding
CoE III		ice skating		Registry, matched on age and sex	Male: 62% vs 58% Median BMI: 24.1 vs 25.6 Smoker: 21% vs 13% Drinks alcohol: 75% vs 85% *ALS patients only:* El Escorial classification: Definite: 18% Probable: 45% Probable lab supported: 18% Possible: 19% Site of onset: Bulbar: 32% Spinal: 68%	and the JR van Dijk and the Addessium Foundation. The research leading the studies results has received funding from the European Community's Health Seventh Framework Programme COI: van den Berg received travel grants and consultancy fees from Baxter and serves on the advisory board for Biogen and Cytokinetics. Veldink received travel grants from Baxter
Janssen 2017 USA CoE IV	Cohort Risk ratio	Nonprofessional football (high school)	ALS from medical records confirmed by 1 investigator	Non-football high school athlete	N = 486 (football players = 190 vs non–football players = 296) Age range, years: 62 to 78 Male: 100% Head trauma: 18% vs 5%	Rochester Epidemiology Project (Grant number R01-AG034676) COI: Dr Boeve has received personal fees from the Scientific Advisory Board of the Tau Consortium and Isis Pharmaceuticals and grants from GE Healthcare, the National Institutes of Health, the Mangurian Foundation, Cephalon Inc, FORUM Pharmaceuticals, and C2N Diagnostics, all outside the present work. Dr Mielke serves as a consultant for Lysosomal Therapeutics Inc and holds a grant from the Michael J. Fox Foundation, both outside the present work.
Lehman 2012 USA CoE II	Cohort Standardized mortality rate	Professional football (with $\geq$5 NFL playing seasons)	Death associated with ALS on National Death Index and State vital statistics	National death registry, matched on age, sex, cause and calendar year	N = 3439 Median age, years: 57 Median age at death, years: 54 Male: 100% Median number of credited seasons as of 1988/1989 season: 8	NR COI: Authors declare no conflicts of interest
Longstreth 1998 USA CoE III	Case control Adjusted odds ratio	Professional general sports (employed professionally) Nonprofessional general sports	Progressive motor neuron disease of upper and lower motor neurons, and a diagnosis of ALS by neurologist	Non-ALS patients from Washington State counties and Medicare eligibility lists, matched on age and sex	N = 522 (ALS = 174 vs controls = 348) Age: 18 to 44 years: 13% vs 13% 45 to 54 years: 16% vs 19% 55 to 64 years: 28% vs 22%	Grant from the National Institute of Neurological Disorders and Stroke (R01 NS27889) COI: NR

(continued)

Table 1. (continued)

Author Country CoE	Design Effect	Sport	Outcome Definition	Controls	Study Participants	Funding
		(during high school)			65 to 74 years: 30% vs 33% ≥75 years: 13% vs 13% Male: 55% vs 55%	
Pupillo 2014 Italy, France, England, Ireland, Serbia CoE III	Case control Adjusted odds ratio	Professional general sports (employed for ≥1 year as main occupation) Nonprofessional general sports (participate in sport association or official competition for ≥1)	Probable or possible new ALS via El-Escorial criteria	Non-ALS patients from general practitioner, matched on age and sex	N = 1818 (ALS = 652 vs controls = 1166) Median age, years: 66 vs 67 Male: 57% vs 57% Median BMI: 23.9 vs 25.7 Previous traumatic injury: Yes: 46% vs 42% No: 54% vs 58% Not specified: <1% vs <1% Smoker: 48% vs 47% (not specified: 0% vs <1%) Drinks alcohol: 40% vs 37% (not specified: <1% vs <1%) *ALS patients only:* El Escorial cateogry: Definite: 46% Probable: 42% Possible: 12% Site of onset: Spinal: 64% Bulbar: 33% Generalized: 3% Symptom duration: <12 months: 37% 12 to 24 months: 38% >24 months: 25%	Grant from the American ALS Association (grant 1542), grant from the European Community's Health Seventh Framework Program 2007 to 2013 (grant agreement 259 867), and the Italian Drug Agency COI: E.P.: grants/grants pending, Italian Drug Agency, Italian Ministry of Health, UE. P.M.: grants/grants pending, Italian Drug Agency, Italian Ministry of Health, EISAI, Lombardy Region, Sanofi-Aventis. A.Ch: grants/grants pending: European Union, Italian Ministry of Health; scientific advisory boards, Biogen Idec, Cytokinetics. O.H.: grants/grants pending, Health Research Board, Merck Serono; consultancy, Biogen Idec, Novartis. E.B.: board membership, Viropharma, EISAI; travel expenses, UCBPharma, GSK; speaking fees, UCB-Pharma, GSK, Viropharma; paid educational presentations, GSK; grants/grants pending, Italian Drug Agency, Italian Ministry of Health, American ALS Association; consulting, GSK.
Savica 2012 USA CoE IV	Cohort Hazard ratio	Nonprofessional football (high school)	ALS confirmed by medical record review	Non-football high school band, glee club, choir members, matched on age and sex	N = 578 (football players = 438 vs non–football players = 140) Median age, years: 68.4 vs 59.1 Male: 100% vs 100%	Grant from the National Institutes of Health (R01 AG034676), the Rochester Epidemiology Project COI: NR
Scarmeas 2002 USA CoE IV	Case control Adjusted odds ratio	Nonprofessional general sports (varsity high school or college)	MND (82.4% ALS), results same for ALS	Non-ALS neurologic patients from same clinic from which the ALS patients were obtained	N = 431 (ALS = 279 vs controls = 152) Age: NR Male: NR BMI: Obese (≥30): 10% vs 21% Overweight (25-29.9): 35% vs 33%	NR COI: NR

(continued)

Table 1. (continued)

Author Country CoE	Design Effect	Sport	Outcome Definition	Controls	Study Participants	Funding
					Normal/under (≤24.9): 55% vs 46% Previous varsity athlete: 40% vs 26%	
Strickland 1996 USA CoE III	Case control Adjusted odds ratio	Nonprofessional general sports (varsity high school or college)	Clinical ALS patients undefined	Non-ALS neurologic patients from same clinic from which the ALS patients were obtained	N = 75 (ALS = 25 vs clinic controls = 25 vs community controls = 25) Mean age, years: 56.2 vs 55.2 vs 56.1 Male: NR *ALS patients only:* Mean time since diagnosis, months: 27 (1 to 84)	Grants from the Muscular Dystrophy Association, Inc and the Kent Hrbek Celebrity Tournament for ALS COI: NR
Taioli 2007 Italy CoE II	Cohort Standardized mortality rate	Professional soccer (A and B leagues)	Death associated with ALS	General US population obtained from 2 publications, matched on age, sex and calendar year	N = 5389 (players alive at study end = 5146, players with partial follow-up = 180, players deceased at study end = 63) Mean age at enrollment, years: 18.4 Mean age at end of follow-up, years: 38 Mean length of professional career, years: 8	Grant from the Italian Ministry of Health (03/232) COI: The authors declare no conflict of interest
Valenti 2005 Italy CoE III	Case control Adjusted odds ratio	Nonprofessional soccer and general sports (competitive)	Probable or possible ALS via criteria of World Federation of Neurology	Healthy controls from the same living location, matched on age and sex	N = 600 (ALS = 300 vs controls = 300) *ALS patients only:* Mean age, years: 60 Male: 64%	Funding NR COI: Luigi Frati is the chairman and Tullio Manzoni and Marco Valenti are members of CONI's Anti-Doping Scientific Committee. Emma Altobelli, Fiorenzo Conti, and Francesco E. Pontieri are consultants to the Committee. None of the Committee members is employed by CONI
Vanacore 2010 USA CoE III	Case control Adjusted odds ratio	Professional general sports	Death associated with ALS on death certificate	Deceased from causes other than ALS, matched on age, sex and geography	N = 73 140 (ALS = 14 628 vs controls = 58 512) Mean age at death, years: 67.3 Male: 52% vs 53% Socioeconomic status: Low: 25% vs 43% Medium: 51% vs 37% High: 24% vs 20% Physical activity:	NR COI: Authors declare no conflicts of interest

(continued)

Table 1. (continued)

Author Country CoE	Design Effect	Sport	Outcome Definition	Controls	Study Participants	Funding
					Low: 42%vs 39% Moderate: 39% vs 42% High: 15% vs 18% Undefined: 4% vs 2%	
Veldink 2005 Netherlands CoE IV	Case control Adjusted odds ratio	Nonprofessional general sports	Definite, probable or possible ALS via El Escorial	Non-ALS friends of patients, matched on age and sex	N = 473 (ALS = 219 vs controls = 254) Median age, years: 59 vs 59 Male: 67% vs 57% Median BMI: 25 vs 25 Smoker: Never: 34% vs 40% Ever: 40% vs 43% Current: 26% vs 17% Drinks alcohol: Never: 24% vs 17% Ever/current: 76% vs 83% *ALS patients only:* El Escorial category: Possible: 18% Probable: 58% Definite: 24% Site of onset: Spinal: 75% Bulbar: 25%	Grant from ZonMw, The Netherlands Organization for Health Research and Development COI: NR

Abbreviations: ALS, amyotrophic lateral sclerosis; BMI, body mass index; CoE, class of evidence; COI, conflict of interest; EMG, electromyogram; MND, motor neuron disease; NFL, National Football League; NR, not reported.

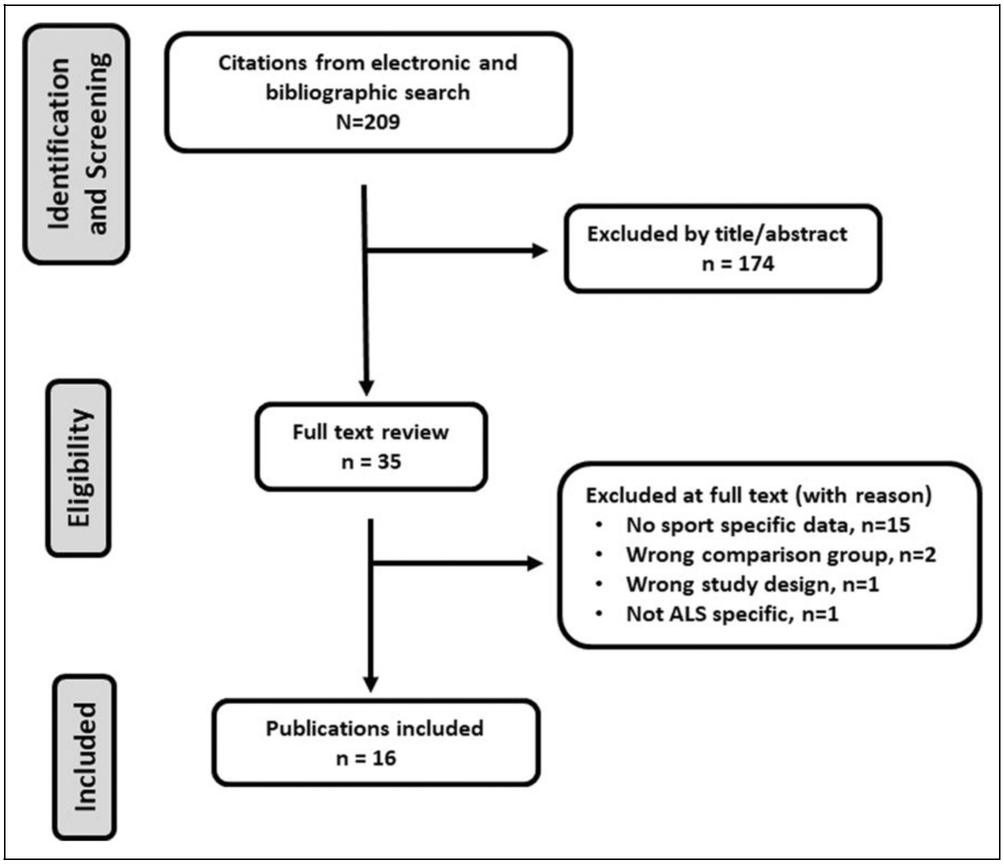

Figure 1. Flow diagram showing results of literature search and study selection.

CI 0.84-1.63, $I^2 = 57\%$), test for subgroup differences, $P = .000$ (Figure 3).

Within different levels of competitive play, does the risk vary by whether the sport is prone to repetitive concussive head and cervical spinal trauma?

- Professional sports prone to repetitive concussive head and cervical spinal trauma was associated with substantially greater effects (5 studies,[14,16,17,28,29] pooled RR 8.52, 95% CI 5.18-14.0, $I^2 = 34\%$) compared with (*a*) nonprofessional sports prone to repetitive concussive head and cervical spinal trauma (3 studies,[20,23,26] pooled RR 0.60, 95% CI 0.12-3.06, $I^2 = 0\%$); (*b*) professional sports not prone to repetitive concussive head and cervical spinal trauma(5 comparisons, 4 studies,[17,21,22,30] pooled RR 1.35, 95% CI 0.67-2.71, $I^2 = 0\%$); or (*c*) nonprofessional sports not prone to repetitive concussive head and cervical spinal trauma (11 comparisons, 9 studies,[16,18,19,21,22,24-27] pooled RR 1.17, 95% CI 0.79-1.71, $I^2 = 69\%$), test for subgroup differences, $P = .000$ (Figure 4).
- Among professional sports prone to head and neck trauma, 2 studies evaluated the risk by player position. In 1 professional soccer study,[17] midfielders had a greater risk of ALS mortality, standardized morbidity ratio [SMR] 10.5, 95% CI 3.9-22.9) compared with forwards (SMR 6.6, 95% CI 0.2-36.8) and backs (SMR 2.4, 95% CI 0.1-13.4). In 1 study of American professional football,[14] speed positions (fullback, halfback, defensive back, quarterback, wide receiver, running back, linebacker, and tight end) were more likely to die from ALS than nonspeed positions (defensive and offensive linemen), SMR 6.24, 95% CI 2.29-13.6 vs 1.71, 95% CI 0.04-9.50, respectively).
- A list of professional contact sports athletes publicized as diagnosed with ALS and a case example are presented in Table 2 and Figure 5, respectively.

Discussion

The recent development of various genetic analysis tools has significantly advanced our understanding of some of the molecular pathways that lead to motor neuron death in ALS patients.[4,5] Furthermore, certain genetic variants have been associated with specific clinical characteristics, providing better estimates of the rate of disease progression and survival.[31] However, possible triggers for the disrupted molecular pathways have remained obscure.

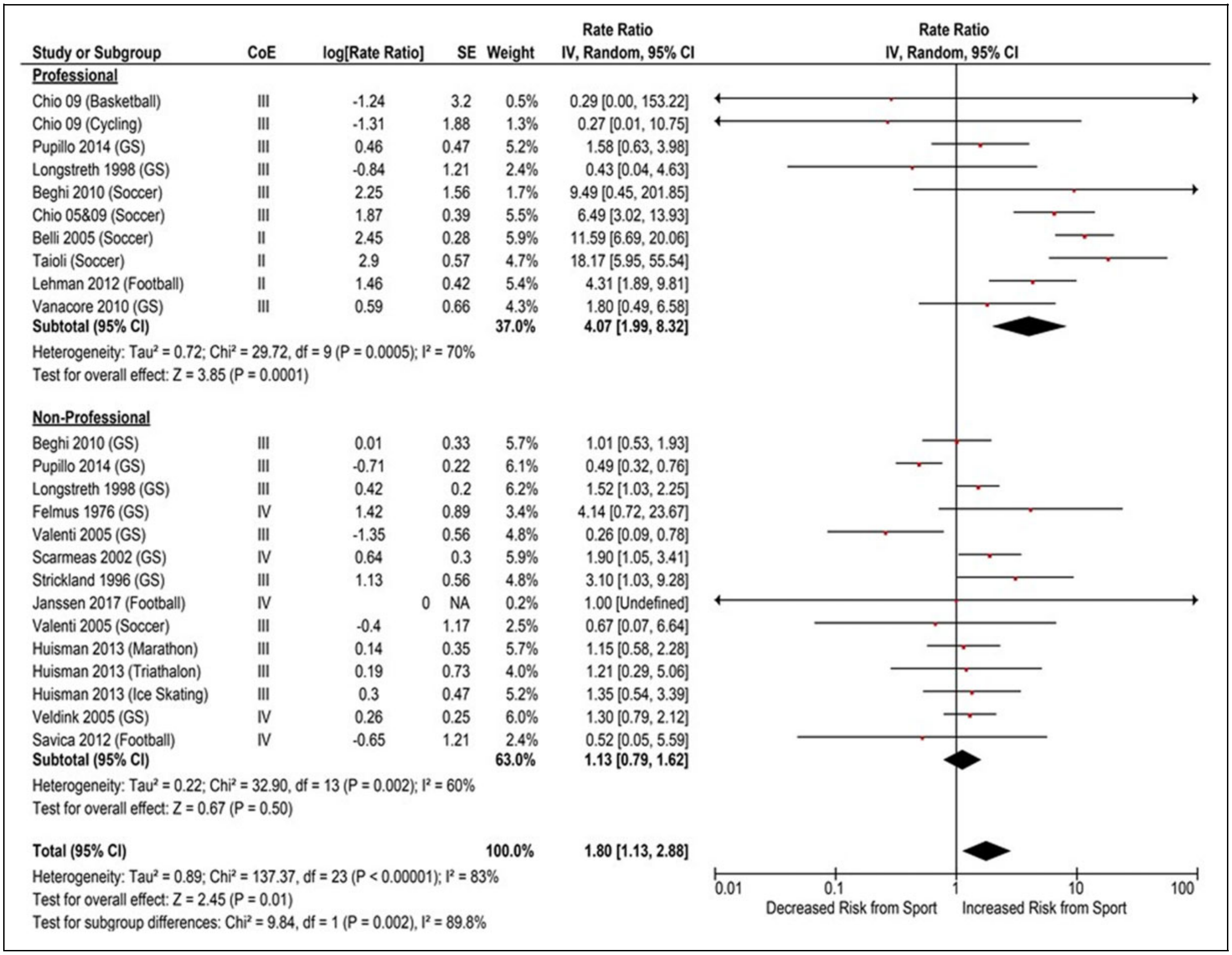

Figure 2. Forest plot of the association between competitive organized sports and the risk of amyotrophic lateral sclerosis, stratified by levels of competitive play (professional or nonprofessional).

The associations of physical activity[13,19,32] and sports-related trauma[26,33] to ALS have been widely debated. Our review provides evidence that increased susceptibility to ALS may lie in a certain combination of both factors. Competitive organized sports, which usually include high levels of physical activity and sports that include high probability to sustain concussive head and neck trauma were both found to independently increase the risk to develop ALS. When combined together, as is the case with professional American football and soccer, the effect was additive, reaching a rate ratio of 8.52 (Figure 4).

This finding may have several important implications. First, increased awareness among athletes who engage in contact sports as well as by their managing environment, regardless of competitive level, cannot be overemphasized. Precautions aimed at decreasing the likelihood to sustain blunt concussive head or neck trauma, accurate medical documentation and periodic health monitoring may all prove to be life-saving, as is the case with an increased awareness regarding traumatic brain injuries in sports. This is also of potentially increased importance for other professional contact sports lacking similar ALS incidence reports, such as rugby or hockey. In light of these findings additional further formal data-gathering through organizations such as the National Football League and Rugby Union, as is been done with the more recent focus on traumatic brain injury, might also be in order. Second, in light of the accumulated genetic data, future ALS-directed genetic analysis of athletes at-risk may assist in developing appropriate risk-stratification prevention strategies. Third, ALS has been previously associated with chronic traumatic encephalopathy due to some shared clinical and pathological characteristics.[34] Our findings, that sports prone to cervical and head concussive trauma also appear to increase the risk for ALS, highlights an additional region where trauma may play an important role in the pathogenesis of ALS. Cervical cord neuropraxia, also known as transient quadriplegia, is an injury to the spinal cord, usually caused by head collisions with the neck being either hyperflexed or hyperextended.[35,36] This injury, which results in

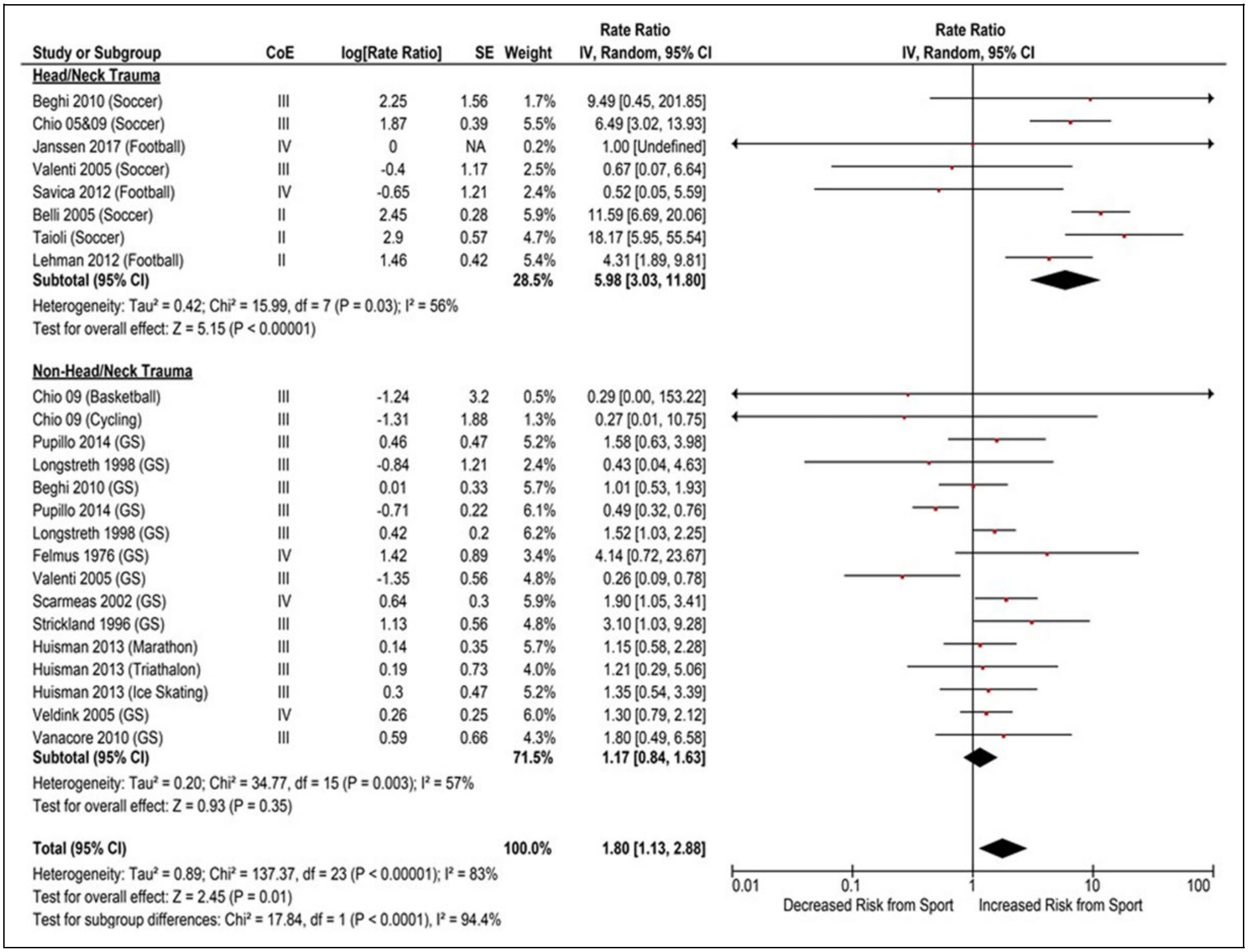

Figure 3. Forest plot of the association between competitive organized sports and the risk amyotrophic lateral sclerosis, stratified by whether the sport is prone to repetitive concussive head and cervical spinal trauma.

a brief disturbance of limb sensation and/or motor function, commonly lasts less than 24 hours after which the athlete usually displays complete recovery. Whereas usually viewed as a benign condition, our study raises the questions regarding the longer term effects of this type of injury. Our findings warrant further investigation to begin to understand the potential role of brain and spinal trauma in the pathogenesis of ALS.

For spine surgeons and sports physicians who are tasked to assess athletes in contact sports with chronic exposure to head and neck impact trauma with extremity weakness in presence of spinal spondylosis and stenosis the real challenge arises to be aware of the potential of motor neuron disease as an underlying disorder beyond compressive spondylotic myelopathy and radiculopathy.

This systematic review has several limitations. First, there is a significant amount of heterogeneity among the included studies. We attempted to account for this heterogeneity through sensitivity and stratified analyses. Second, a majority of the studies included in this review were judged to have high or moderately high risk of bias due to study design (phase 1 prognostic studies identifying associations between a number of potential prognostic factors and a health outcome[37]). However, among the subgroup of studies that evaluated professional athletes in sports that are prone to head or neck trauma, 3 of 5 studies were judged to have moderately low risk of bias,[14,28,29] giving us more confidence in the pooled estimate of this subgroup. Third, there is heterogeneity of the diagnostic criteria for ALS among studies. Some used the El Escorial criteria,[16,19,22,26,27] some used study specific criteria,[17,18] and still others used undefined criteria.[20,21,23-25] Furthermore, some studies enrolled cases based on death certificates.[14,28-30] While there is some evidence that death certificate diagnosis of ALS is adequate for analytic studies,[38] the variation of the diagnosis on death certificates can be substantial among geographical regions.[39] Fourth, there is substantial variation in sports exposure in our review. Our finding is in keeping with a recent review article by Lacorte et al,[40] where a general sports exposure

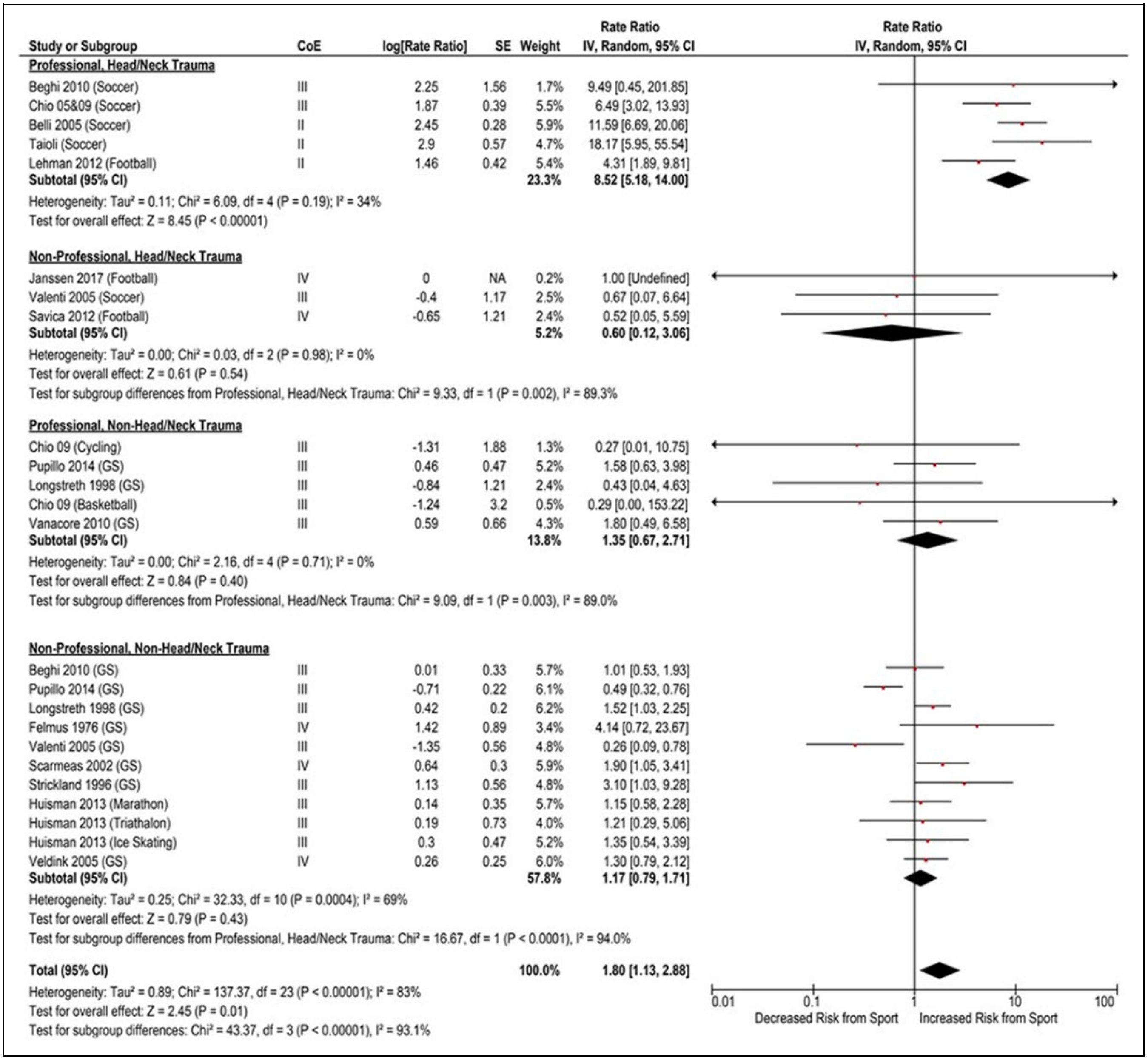

Figure 4. Forest plot of the association between competitive organized sports and the risk of amyotrophic lateral sclerosis, stratified by level of competitive play and whether the sport is prone to repetitive concussive head and cervical spinal trauma.

identified as "physical activity" was identified as an independent risk factor for ALS, but without more specific focus on sports well known to be associated with recurrent head impact trauma. We attempted to control for exposure duration and intensity by stratifying professional versus nonprofessional sports, and by sports prone to head or neck versus no head or neck trauma. However, there were several studies that included any sports activity as a single category that we labeled general sports not defined, which may or may not include sports subject to head or neck trauma.[16,18,21,22,24-27,30] From a larger systems perspective, this review would seem to invite a more formal evaluation of professional sports exposing its players to repetitive blunt head and neck trauma, such as professional American football, Rugby Union, soccer and ice hockey, possibly also motor racing sports with repetitive impact potential. Despite some case reports of high-profile athletes succumbing to ALS and growing awareness of the deleterious effects of chronic traumatic encephalopathy, so far there have been few if any formal longitudinal or postmortem investigations into a possible association of ALS and high-impact contact sports. Perhaps this systematic review will inspire a more formal investigation on this topic.

Table 2. Professional Contact Sport Athletes Publicized as Diagnosed with ALS.

Athlete	Sport	Years Active	Age (Years) ALS/ MND Diagnosis	Clinical Outcome	Reference[a]/Comments
Lee Bertie	Soccer (Scotland)	9 seasons	Diagnosed age 34	Died age 39	https://www.eveningtelegraph.co.uk/fp/wife-tragic-footballer-lee-bertie-thanks-nhs-staff/
Stefano Borgonovo	Soccer (Italy)	14 seasons	Age 44, 13 years after retirement	Died age 49	https://en.wikipedia.org/wiki/Stefano_Borgonovo https://www.revolvy.com/topic/Stefano%20Borgonovo
O. J. Brigance	Football (CFL and NFL)	11 seasons	Age 37, 5 years after retirement	Died age 48	https://en.wikipedia.org/wiki/O._J._Brigance
Marian Cisovsky	Soccer (Slovakia)	18 pro seasons	Diagnosed age 35	Impaired	https://en.wikipedia.org/wiki/Marián_Čišovský
Dwight Clark	Football (USA)	9 seasons Pro	Diagnosed age 60	Impaired	https://en.wikipedia.org/wiki/Dwight_Clark
John Cushley	Soccer (Scotland)	17 seasons	Diagnosed age 64	Died age 65	https://en.wikipedia.org/wiki/John_Cushley
Neale Daniher	Australian Rules football	11 seasons	Diagnosed age 54	Impaired	https://en.wikipedia.org/wiki/Neale_Daniher
Danny Delport	Rugby (South Africa, Zimbabwe)	10 years	Diagnosed age 55	Died age 62	http://www.espn.com/rugby/story/_/id/15 340 114/former-natal-sharks-rhodesia-winger-danny-delport-diagnosed-mnd
Pete Frates	Baseball (USA)	8 seasons pro and semi - pro	Diagnosed age 27	Impaired	https://petefrates.com https://www.bostonglobe.com/metro/2014/08/15/stricken-with-als-pete-frates-closely-linked-ice-bucket-challenge-shows-will-live/m2Abeu4SIGROfg0aBICTCM/story.html
Henry Louis Gehrig	Baseball (USA)	17 pro seasons	Age 36, Last professional season	Died age 38	https://www.lougehrig.com
Steve Gleason	NFL Football (USA)	6 pro seasons	Diagnosed age 34	Impaired	https://en.wikipedia.org/wiki/Steve_Gleason http://www.teamgleason.org
Patrick Grange	Soccer (USA)	6 seasons semi – and pro	Diagnosed age 27	Died age 29 age 29	https://www.nytimes.com/2014/02/27/sports/soccer/researchers-find-brain-trauma-disease-in-a-soccer-player.html
James Augustus "Catfish" Hunter	Baseball (USA)	15 pro seasons	Diagnosed age 51	Died age 53	https://en.wikipedia.org/wiki/Catfish_Hunter
Jimmy Johnstone	Soccer (Scotland)	19 seasons	Diagnosed age 57, 22 years after retirement	Died age 62	https://en.wikipedia.org/wiki/Jimmy_Johnstone
Marthinus Linee	Rugby (South Africa)	9 seasons	Diagnosed age 44	Died age 45	https://en.wikipedia.org/wiki/Tinus_Linee
Adriano Lombardi	Soccer (Italy)	27 seasons	Unknown	Died age 62	https://en.wikipedia.org/wiki/Adriano_Lombardi
Glenn Montgomery	NFL Football (USA)	7 pro seasons	Diagnosed age 30	Died age 31	https://en.wikipedia.org/wiki/Glenn_Montgomery
Krzysztof Nowak	Soccer (Poland)	9 pro seasons	Diagnosed age 27	Died age 29	https://en.wikipedia.org/wiki/Krzysztof_Nowak https://web.archive.org/web/20 140 720 115 053/https://www.vfl-wolfsburg.de/en/info/social/gesundheit/the-krzysztof-nowak-foundation.html
John Proudfoot	CFL (Canadian Football)	11 seasons	Diagnosed age 58	Died age 61	https://en.wikipedia.org/wiki/Tony_Proudfoot
Don Revie	Soccer (England)	18 pro seasons	Diagnosed age 60	Died age 62	https://en.wikipedia.org/wiki/Don_Revie
Fernando Ricksen	Soccer (Netherlands)	9 seasons	Diagnosed age 37	Impaired	https://www.dailyrecord.co.uk/news/scottish-news/footballs-new-brain-bombshell-shock-11 227 657
Ayan Sadakov	Soccer (Bulgaria)	18 pro seasons	Diagnosed age 53	Died age 55	https://en.wikipedia.org/wiki/Ayan_Sadakov
Ed Sadowski	Baseball (USA)	6 pro seasons	Unknown	Died age 62	https://en.wikipedia.org/wiki/Ed_Sadowski
Washington Cesar Santos	Soccer (Brazil)	15 pro seasons	Unknown	Died age 54	https://en.wikipedia.org/wiki/Washington_César_Santos

(continued)

Table 2. (continued)

Athlete	Sport	Years Active	Age (Years) ALS/ MND Diagnosis	Clinical Outcome	Reference[a]/Comments
Tim Shaw	NFL Football (USA)	5 pro seasons	Diagnosed age 29	Impaired	https://abcnews.go.com/Health/nfl-player-reveals-als-diagnosis-ice-bucket-challenge/story?%20id=25 051 474
Gianluca Signorini	Soccer (Italy)	19 pro seasons	Diagnosed 38	Died Age 41	https://en.wikipedia.org/wiki/Gianluca_Signorini
Steve Smith	NFL Football	9 seasons as pro	Diagnosed at age 28	N. app.	https://en.wikipedia.org/wiki/Steve_Smith_(running_back)
Orlando Thomas	NFL Football	7-year career as pro	Diagnosed age 35	Died age 42	http://time.com/3 577 408/nfl-orlando-thomas-lou-gehrigs-disease/
Kevin Turner	NFL Football (USA)	8 seasons as pro	Diagnosed age 41	Died age 46	http://www.espn.com/nfl/story/_/id/15 059 587/kevin-turner-46-dies-long-battle-als
Joost van der Westhuizen	Rugby	10 seasons	Diagnosed age 39	Died age 45	https://www.sport24.co.za/Rugby/Ex-Natal-player-struck-down-with-MND-20 150 126
Ryan Walker	Rugby (South Africa)	7 pro seasons	Diagnosed age 33	Impaired	http://ryanwalker.co.za
Doddie Weir	Rugby (Scotland)	10 seasons	Diagnosed age 46	Impaired	https://en.m.wikipedia.org/wiki/Doddie_Weir

Abbreviations: ALS, amyotrophic lateral sclerosis; CFL, Canadian Football League; MND, motor neuron disease; NFL, National Football League
[a]All references were accessed May 6, 2017 through bing.com searches.

Mr. Steve Gleason had spent a life-long career in U.S. American football. In high school, he played both on defense and offense, as well as high level baseball. during college, he continued playing football as well as baseball for 4 years until he signed a contract with a National Football League team, where he played a total of 83 games as a safety, which is a high speed high contact type defensive position for 8 seasons. At the age of 34, 3 years after retirement, he began to experience twitching in his arms, shoulder and back followed by progressive limb weakness. Today, 6 years after having been diagnosed with Amyotrophic Lateral Sclerosis, he is wheelchair-bound, breathes with a ventilator and communicates with a computer-assisted eye-tracking device. His nonprofit foundation is currently supporting ALS patients and their families by providing adaptive technology, increase awareness and promote research.

Figure 5. A representative case example.

Conclusions

Our study raises a number of questions warranting further investigation. In the debate of whether physical activity and sports are related to ALS, we found that professional athletes who engage in sports prone to blunt head or cervical spine concussive injuries such as football and soccer are at an increased risk to develop ALS. This finding has implications in both prevention strategies and in the basic research of ALS pathogenesis.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Emre Yilmaz, MD https://orcid.org/0000-0002-1492-1201

Supplemental Material

The supplemental material is available in the online version of the article.

References

1. Brown RH Jr, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med*. 2017;377:1602.
2. Robberecht W, Philips T. The changing scene of amyotrophic lateral sclerosis. *Nat Rev Neurosci*. 2013;14:248-264.
3. Mulder DW, Kurland LT, Offord KP, Beard CM. Familial adult motor neuron disease: amyotrophic lateral sclerosis. *Neurology*. 1986;36:511-517.
4. Peters OM, Ghasemi M, Brown RH Jr. Emerging mechanisms of molecular pathology in ALS. *J Clin Invest*. 2015;125:1767-1779.
5. Therrien M, Dion PA, Rouleau GA. ALS: recent developments from genetics studies. *Curr Neurol Neurosci Rep*. 2016;16:59.
6. Gurney ME, Pu H, Chiu AY, et al. Motor neuron degeneration in mice that express a human Cu, Zn superoxide dismutase mutation. *Science*. 1994;264:1772-1775.
7. Yang C, Danielson EW, Qiao T, et al. Mutant PFN1 causes ALS phenotypes and progressive motor neuron degeneration in mice by a gain of toxicity. *Proc Natl Acad Sci U S A*. 2016;113:E6209-E6218.
8. Wang H, O'Reilly EJ, Weisskopf MG, et al. Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of 5 prospective cohorts. *Arch Neurol*. 2011;68:207-213.
9. Ingre C, Roos PM, Piehl F, Kamel F, Fang F. Risk factors for amyotrophic lateral sclerosis. *Clin Epidemiol*. 2015;7:181-193.

10. Malek AM, Barchowsky A, Bowser R, Youk A, Talbott EO. Pesticide exposure as a risk factor for amyotrophic lateral sclerosis: a meta-analysis of epidemiological studies: pesticide exposure as a risk factor for ALS. *Environ Res*. 2012;117: 112-119.
11. Fang F, Hallmarker U, James S, et al. Amyotrophic lateral sclerosis among cross-country skiers in Sweden. *Eur J Epidemiol*. 2016; 31:247-253.
12. Gotkine M, Friedlander Y, Hochner H. Triathletes are over-represented in a population of patients with ALS. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014; 15:534-536.
13. Pupillo E, Messina P, Logroscino G, et al. Trauma and amyotrophic lateral sclerosis: a case-control study from a population-based registry. *Eur J Neurol*. 2012;19:1509-1517.
14. Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. *Neurology*. 2012;79:1970-1974.
15. Chiò A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain*. 2005;128(pt 3):472-476.
16. Beghi E, Logroscino G, Chiò A, et al. Amyotrophic lateral sclerosis, physical exercise, trauma and sports: results of a population-based pilot case-control study. *Amyotroph Lateral Scler*. 2010;11: 289-292.
17. Chiò A, Calvo A, Dossena M, Ghiglione P, Mutani R, Mora G. ALS in Italian professional soccer players: the risk is still present and could be soccer-specific. *Amyotroph Lateral Scler*. 2009;10: 205-209.
18. Felmus MT, Patten BM, Swanke L. Antecedent events in amyotrophic lateral sclerosis. *Neurology*. 1976;26:167-172.
19. Huisman MH, Seelen M, de Jong SW, et al. Lifetime physical activity and the risk of amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 2013;84:976-981.
20. Janssen PH, Mandrekar J, Mielke MM, et al. High school football and late-life risk of neurodegenerative syndromes, 1956-1970. *Mayo Clin Proc*. 2017;92:66-71.
21. Longstreth WT, McGuire V, Koepsell TD, Wang Y, van Belle G. Risk of amyotrophic lateral sclerosis and history of physical activity: a population-based case-control study. *Arch Neurol*. 1998;55: 201-206.
22. Pupillo E, Messina P, Giussani G, et al. Physical activity and amyotrophic lateral sclerosis: a European population-based case-control study. *Ann Neurol*. 2014;75:708-716.
23. Savica R, Parisi JE, Wold LE, Josephs KA, Ahlskog JE. High school football and risk of neurodegeneration: a community-based study. *Mayo Clin Proc*. 2012;87:335-340.
24. Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and varsity athletics in ALS. *Neurology*. 2002; 59:773-775.
25. Strickland D, Smith SA, Dolliff G, Goldman L, Roelofs RI. Physical activity, trauma, and ALS: a case-control study. *Acta Neurol Scand*. 1996;94:45-50.
26. Valenti M, Pontieri FE, Conti F, Altobelli E, Manzoni T, Frati L. Amyotrophic lateral sclerosis and sports: a case-control study. *Eur J Neurol*. 2005;12:223-225.
27. Veldink JH, Kalmijn S, Groeneveld GJ, Titulaer MJ, Wokke JH, van den Berg LH. Physical activity and the association with sporadic ALS. *Neurology*. 2005;64:241-245.
28. Belli S, Vanacore N. Proportionate mortality of Italian soccer players: is amyotrophic lateral sclerosis an occupational disease? *Eur J Epidemiol*. 2005;20:237-242.
29. Taioli E. All causes of mortality in male professional soccer players. *Eur J Public Health*. 2007;17:600-604.
30. Vanacore N, Cocco P, Fadda D, Dosemeci M. Job strain, hypoxia and risk of amyotrophic lateral sclerosis: results from a death certificate study. *Amyotroph Lateral Scler*. 2010;11:430-434.
31. Li HF, Wu ZY. Genotype-phenotype correlations of amyotrophic lateral sclerosis. *Transl Neurodegener*. 2016;5:3.
32. Gallo V, Vanacore N, Bueno-de-Mesquita HB, et al. Physical activity and risk of amyotrophic lateral sclerosis in a prospective cohort study. *Eur J Epidemiol*. 2016;31:255-266.
33. Piazza O, Siren AL, Ehrenreich H. Soccer, neurotrauma and amyotrophic lateral sclerosis: is there a connection? *Curr Med Res Opin*. 2004;20:505-508.
34. Thomsen GM, Ma AM, Ko A, et al. A model of recurrent concussion that leads to long-term motor deficits, CTE-like tauopathy and exacerbation of an ALS phenotype. *J Trauma Acute Care Surg*. 2016;81:1070-1079.
35. Asan Z. Spinal concussion in adults: transient neuropraxia of spinal cord exposed to vertical forces. *World Neurosurg*. 2018; 114:e1284-e1289.
36. Dailey A, Harrop JS, France JC. High-energy contact sports and cervical spine neuropraxia injuries: what are the criteria for return to participation? *Spine (Phila Pa 1976)*. 2010;35(21 suppl): S193-S201.
37. Hayden JA, Côté P, Steenstra IA, Bombardier C; QUIPS-LBP Working Group. Identifying phases of investigation helps planning, appraising, and applying the results of explanatory prognosis studies. *J Clin Epidemiol*. 2008;61:552-560.
38. Chiò A, Magnani C, Oddenino E, Tolardo G, Schiffer D. Accuracy of death certificate diagnosis of amyotrophic lateral sclerosis. *J Epidemiol Community Health*. 1992;46:517-518.
39. Marin B, Couratier P, Preux PM, Logroscino G. Can mortality data be used to estimate amyotrophic lateral sclerosis incidence? *Neuroepidemiology*. 2011;36:29-38.
40. Lacorte E, Ferrigno L, Leoncini E, Corbo M, Boccia S, Vanacore N. Physical activity, and physical activity related to sports, leisure and occupational activity as risk factors for ALS: a systematic review. *Neurosci Biobehav Rev*. 2016;66:61-79.