Methods

Search Terms

("Motor Neuron Disease"[Mesh] OR "Amyotrophic Lateral Sclerosis"[Mesh] OR "Motor Neuron Disease" OR "Lateral Sclerosis" OR "Lateral Scleroses" OR "Anterior Horn Cell Disease" OR "Charcot Disease" OR "Amyotrophic Lateral Sclerosis" OR ALS OR "Gehrig's Disease" OR "Gehrig Disease" OR "Gehrigs Disease" OR "Guam Disease") AND (FOOTBALL[TIAB] OR SPORT[TIAB] OR SPORTS[TIAB] OR SOCCER[TIAB] OR BOXING[TIAB] OR HOCKEY[TIAB])

Inclusion and exclusion criteria table

	Include	Exclude
Population	• Adults (≥16 years) with a history of playing competitive sports	• Youth sports under the age of 16 years
Exposure	• Level of competitive play (professional, non-professional) • Sport type	• Strenuous non-competitive sport activity • Military • Non-sport trauma
Comparator	• Non-sport control • Standardized reference group	• Crude (non-standardized) population reference group
Outcome	• ALS • Mortality associated with ALS	• Other neurologic disorders
Type of studies	• Cohort study • Case control study	• Cross-sectional studies • Studies not producing an effect measure (OR, RR or standardized ratio)

Definitions of professional and non-professional sports.

Non-professional sports included sports that were labelled organized or competitive. Professional sports were all identified as professional, employed professionally, employed for ≥1 year as main occupation, or identified with a professional organization such as the A, B and C soccer league in Italy or the National Football League in America.

Excluded at Full Text

	Reason for exclusion
1. Cruz DC1, Nelson LM, McGuire V, Longstreth WT Jr. Physical trauma and family history of neurodegenerative diseases in amyotrophic lateral sclerosis: a population-based case-control study. Neuroepidemiology. 1999;18(2):101-10.	No sport specific data
2. Deapen DM, Henderson BE. A case-control study of amyotrophic lateral sclerosis. Am J Epidemiol. 1986 May;123(5):790-9.	No sport specific data
3. Gallo V1,2, et al. Physical activity and risk of Amyotrophic Lateral Sclerosis in a prospective cohort study. Eur J Epidemiol. 2016 Mar;31(3):255-66. doi: 10.1007/s10654-016-0119-9. Epub 2016 Mar 11.	No sport specific data
4. Abel EL. Football increases the risk for Lou Gehrig's disease, amyotrophic lateral sclerosis. Percept Mot Skills 2007;104(3 Pt 2):1251-1254	Crude prevalence, no standardized rate
5. Kondo K, Tsubaki T. Case-control studies of motor neuron disease: association with mechanical injuries. Arch Neurol. 1981 Apr;38(4):220-6.	No sport specific data

6. Li TM, Alberman E, Swash M. Clinical features and associations of 560 cases of motor neuron disease. J Neurol Neurosurg Psychiatry. 1990 Dec;53(12):1043-5.	Case series, no controls
7. Pupillo E1, Messina P, Logroscino G, Zoccolella S, Chiò A, Calvo A, Corbo M, Lunetta C, Micheli A, Millul A, Vitelli E, Beghi E; EURALS Consortium. Trauma and amyotrophic lateral sclerosis: a case-control study from a population-based registry. Eur J Neurol. 2012 Dec;19(12):1509-17. Epub 2012 Apr 27.	No sport specific data
8. Armon C, Kurland LT, Daube JR, O'Brien PC. Epidemiologic correlates of sporadic amyotrophic lateral sclerosis. Neurology 1991;41(7):1077-1084	No sport specific data
9. Feddermann-Demont N, Junge A, Weber KP, Weller M, Dvorak J, Tarnutzer AA. Prevalence of potential sports-associated risk factors in Swiss amyotrophic lateral sclerosis patients. Brain Behav 2017;7(4):e00630	No sport specific data
10. Gunnarsson LG, Bodin L, Soderfeldt B, Axelson O. A case-control study of motor neurone disease: its relation to heritability, and occupational exposures, particularly to solvents. Br J Ind Med 1992;49(11):791-798	No sport specific data
11. Park RM, Schulte PA, Bowman JD, et al. Potential occupational risks for neurodegenerative diseases. Am J Ind Med 2005;48(1):63-77	No sport specific data
12. Williams DB, Annegers JF, Kokmen E, O'Brien PC, Kurland LT. Brain injury and neurologic sequelae: a cohort study of dementia, parkinsonism, and amyotrophic lateral sclerosis. Neurology 1991;41(10):1554-1557	No sport specific data
13. Schulte PA, Burnett CA, Boeniger MF, Johnson J. Neurodegenerative diseases: occupational occurrence and potential risk factors, 1982 through 1991. Am J Public Health 1996;86(9):1281-1288	Not ALS specific
14. Okamoto K, Kihira T, Kondo T, et al. Lifestyle factors and risk of amyotrophic lateral sclerosis: a case-control study in Japan. Ann Epidemiol 2009;19(6):359-364	No sport specific data
15. Kurtzke JF, Beebe GW. Epidemiology of amyotrophic lateral sclerosis: 1. A case-control comparison based on ALS deaths. Neurology 1980;30(5):453-462	No sport specific data
16. Gallagher JP, Sanders M. Trauma and amyotrophic lateral sclerosis: a report of 78 patients. Acta Neurol Scand 1987;75(2):145-150	No sport specific data
17. Provinciali L, Giovagnoli AR. Antecedent events in amyotrophic lateral sclerosis: do they influence clinical onset and progression? Neuroepidemiology 1990;9(5):255-262	No sport specific data
18. Savettieri G, Salemi G, Arcara A, Cassata M, Castiglione MG, Fierro B. A case-control study of amyotrophic lateral sclerosis. Neuroepidemiology 1991;10(5-6):242-245	No sport specific data
19. Gotkine M, Friedlander Y, Hochner H. Triathletes are over-represented in a population of patients with ALS. Amyotroph Lateral Scler Frontotemporal Degener 2014;15(7-8):534-536	Wrong design, cross-sectional

Risk of Bias Evaluation

COHORT STUDIES								
Study	Participants in both cohorts came from the same population	Complete follow-up ≥80%	F/U long enough for outcomes	Objective, unbiased outcomes	Accounting for prognostic factors	RoB Rating	CoE	Comments/questions
Chio 2009	No*	Yes	Yes	Yes	Yes†	Mod high	III	*Cases from players born in Italy, controls from registries covering 15% of pop †SMRs matching on age and sex
Janssen 2017	Yes	No*	Yes	Yes	No	High	IV	*Only athletes with constant prolonged medical presence in Rochester Epidemiology Project database were included (30% of all athletes)
Savica 2012	Yes	No*	Yes	Yes	No	High	IV	*Differential f/u 86% vs 69%)
Lehman 2012	Yes	Yes	Yes	Yes	Yes†	Mod low	II	*Unclear how many players were originally included in the study †SMR matching on race, age and calendar year
Taioli 2007	Yes	Yes	Yes	Yes	Yes*	Mod low	II	*SMR matching on sex, age, calendar year
Belli 2005	Yes	Yes	Yes	Yes	Yes*	Mod low	II	*PMR matching on sex, age, calendar year

CASE-CONTROL STUDIES							
Study	Incidence cases from defined population over specified time	Control represents population from which cases come	Exposure precedes outcome	Accounting for prognostic factors	RoB Rating	CoE	Comments/questions
Beghi 2010	Unclear*	Yes	Yes	Yes	Mod high	III	*No specified time for population
Huisman 2013	Yes	Yes	Yes	Yes	Mod high	III	
Longstreth 1998	Yes	Yes	Yes	Yes	Mod high	III	
Pupillo 2014	Yes	Yes	Yes	Yes	Mod high	III	
Strickland 1996	Unclear*	Yes	Yes	Yes	Mod high	III	*No specified time for population
Valenti 2005	Yes	Yes	Yes	Yes	Mod high	III	
Vanacore 2010	Yes	Yes	Yes	Yes	Mod high	III	
Felmus 1976	Yes	No*	Yes	No	High	IV	*Controls from hospital/clinic, not from population at risk
Scarmeas 2002	Yes	No*	Yes	Yes	High	IV	*Enough that controls and ALS patients were from the same clinic? No age/sex/location matching
Veldink 2005	Yes	No*	Yes	Yes	High	IV	*Patients asked to find their own controls friends and family

Risk of bias criteria and class of evidence (CoE)

CoE	Risk of bias	Study design	Criteria
I	**Low risk** Study adheres to commonly held tenets oif high quality design, execution and avoidance of bias	Good quality cohort[1]	• Prospective design • Patients at similar point in the course of their disease or treatment • F/U rate of 80%[2] • Patients followed long enough for outcomes to occur • Accounting for other prognostic factors[3]
II	**Moderately low risk** Study has potential for some bias; does not meet all criteria for level I but deficiencies not likely to invalidate results or introduce significant bias	Moderate quality cohort	• Prospective design, with violation of one of the other criteria for good quality cohort study. • Retrospective design, meeting all the rest of the criteria in level I
III	**Moderately high risk** Study has flaws in design and/or execution that increase potential for bias that may invalidate study results	Poor quality cohort Good qualtiy case-control	• Prospective design with violation of 2 or more criteria for good quality cohort, or • Retrospective design with violation of 1 or more criteria for good quality cohort • A good case-control study[4]
IV	**High risk** Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group	Poor quality case-control	Other than a good case-control study

[1] Cohort studies follow individuals with the exposure of interest over time and monitor for occurrence of the outcome of interest.
[2] Applies to cohort studies.
[3] Authors should consider other factors that might influence patient outcomes and should control for them if appropriate.
[4] A good case-control study must have the all of the following: all incident cases from the defined population over a specified time period, controls that represent the population from which the cases come, exposure that precedes an outcome of interest, and accounting for other prognostic factors.