Industrial Injuries Advisory Council Information Note
Neurodegenerative diseases in professional sportspersons
May 2016

1. A series of recent high-profile news articles have reported recent studies that have found that a career as a professional sportsperson can be linked with neurodegenerative disease[1]. In consequence, the Industrial Injuries Advisory Council (IIAC) has been considering the case within the Industrial Injuries Disablement Benefit (IIDB) Scheme for prescribing motor neurone disease (also known as amyotrophic lateral sclerosis (ALS)), Parkinson's disease (PD), and Alzheimer's disease (AD), the most prevalent form of dementia, among professional sportspersons. This Information Note sets out recent evidence and the Council's current position, and updates an earlier report on injuries in professional sportsmen and sportswomen (Position Paper 15, 2005).

2. ALS is a fatal neurodegenerative disease of unknown aetiology that is characterised by rapidly progressive paralysis, leading ultimately to death within three to five years of symptom onset. The annual incidence of ALS is approximately 2 per 100,000, slightly higher in men than in women, and increasing rapidly after the age of 40 and reaching a peak at 70 to 74 years for men and 65 to 69 years for women (Logroscino *et al.*, 2010). In the US, ALS is known as Lou Gehrig's disease, after a famous American baseball player who died of the disease at a relatively young age (Pearce *et al.*, 2015).

3. PD is a progressive disease of the nervous system characterised by tremor, facial and general muscular rigidity, and difficulty with fine movements and walking. It is rare in people below the age of 50, in whom genetic predisposition or environmental causation might be suspected. Thereafter its incidence increases with age, affecting on average about 85 people per 100,000 over the age of 65. Men are much more likely to be afflicted than women. A few rare genetic causes have been described and a family history of the disease is a known risk factor. Other risk factors have been described

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[1] For example, see http://www.dailymail.co.uk/sport/concussion/article-2780920/Brian-Moore-calls-commentators-head-injuries-seriously-former-England-rugby-star-Gary-Neville-join-Mail-Sunday-s-concussion-campaign.html

including work with pesticides, obtaining water from wells and head trauma (Dick *et al.*, 2007; Horsfall *et al.*, 2013). In contrast smoking appears to afford some protection while of course increasing risks of many other more common diseases. .

4. Dementia describes a clinical condition in which there is serious impairment of brain function causing practical difficulties in daily living. Pathological studies of patients with this disease show brain shrinkage and features that sometimes allow a diagnosis of AD or arteriosclerotic vascular disease. In life, early evidence of these conditions comes from psychological testing to detect impairment of several brain functions. There are great difficulties in studying environmental risk factors, partly on account of the forgetfulness characteristic of the disease and partly from the variety of psychological functions that may be studied. While, in retrospect, it is possible to characterise dementia as progressive, far from everyone who notices memory problems at an older age will progress to functional dementia. Nevertheless, as with PD, a number of risk factors have been identified. These include age (particularly above age of 75 years (Matthews *et al.*, 2005)), smoking, family history, and episodes of serious acute medical illness. A strong hint that lifestyle factors are important comes from the repeated observations that the incidence of dementia in the elderly is now declining in several countries including the UK, mirroring the fall in incidence of coronary heart disease and suggesting that similar vascular protective factors related to diet, exercise and perhaps cardioprotective drugs may be at play.

5. Over the years, there have been a number of small studies and anecdotal reports indicating that long-term risks of neurodegenerative disease may be increased by sports involving repeated head trauma. The short-term and long-term effects of boxing have been known since the 1920s. In the last 5 years or so, associations of sports-related head trauma with PD and ALS, as well as more general cognitive impairments, have begun to be investigated (Pearce *et al.*, 2015).

6. Recently, biologically plausible mechanisms for these associations have also been proposed; and investigations on them have been extended beyond boxing into other professional sports involving repeated concussions, such as American football, ice hockey and rugby. Evidence is also beginning to

emerge on risks in association football, where the occurrence of concussion is rare relative to the other sports, but where repeated low level trauma to the head from heading a football is commonplace (Pearce *et al.*, 2015).

7. It should be noted that before recommending prescription within the IIDB Scheme for diseases that i) are not specific to occupation, and ii) in which cases caused by occupation cannot reliably be distinguished in the individual claimant from those that would arise irrespective of occupation, IIAC normally seeks convincing research evidence that risks of disease from a given exposure are more than doubled (relative risk (RR) more than 2) relative to a suitable comparator. The aim is to identify an exposure or circumstances in which attribution to work can be established on the balance of probabilities in the individual claimant of Benefit. This standard was applied in considering the evidence on neurodegenerative diseases in professional sportspersons.

8. Interpretation of the evidence on neurodegenerative disease and work as a professional sportsperson is complicated by the difficulty of defining the relevant exposure – for example, whether a single event of head trauma or repeated events, and whether accompanying concussion is a necessary requirement. This may be further complicated by exposure to other potential risk factors for disease. In addition, certain of the disorders, such as ALS are rare, making it more difficulties studies to rule out findings arising from chance alone. A further consideration, with prescription in mind, is to identify and define qualifying exposures (those sufficient to at least double risks), in a way that would be feasible to corroborate and apply within the high volume IIDB Scheme.

The epidemiological evidence

9. The Council has taken the studies cited on neurodegenerative disease in sportspersons in a recent article by Pearce et al (Pearce *et al.*, 2015) as a starting point for its review, but then supplemented these with a literature review. The full list of studies considered in this Note are summarised in a concluding Appendix and a brief summary of them appears below.

10. In all, they represent nine research reports. Three of these looked at AD in former American football players (two cross-sectional studies and one cohort study); seven reports (covering four cohort studies and three case-control

studies) looked at ALS in former association footballers, former American footballers and in population-based case-control studies; and one cohort study looked at PD in former American footballers. Study populations overlapped in some reports (notably of ALS in Italian professional footballers), such that each study is unlikely to have provided additional independent evidence.

Alzheimer's Disease

11. In Position Paper 15, the Council considered among other things whether the heading of footballs could cause chronic cumulative injury leading to dementia. Evidence was limited to a few small cross-sectional studies of retired elderly footballers and, no high quality studies were found with dementia as their clinical end point. A wide range of psychometric tests had been employed, and some reports involving brain scans occasionally found brain atrophy (shrinkage). Collectively, however, the available studies had several much discussed and accepted limitations including small sample size, the relative youth of those studied, the difficulty of finding appropriate comparators and the problem of accounting for baseline (pre-morbid) differences from other comparative groups. These limitations have been extensively discussed by others.

12. A search of studies appearing since Position Paper 15 was published indicates no new important evidence that would change the previous appraisal of prescription for AD in soccer players.

13. Instead, three reports of AD have been identified in American football players, none of which indicated a doubling of the risk. A RR (prevalence ratio) of 1.37 was found in a study of retired professional American football players compared to the US population (Guskiewicz *et al.*, 2005). A cohort mortality study of 3,439 former professional American football players found a RR of 1.80, but this was based on only two cases, and the statistical uncertainty was large, being compatible with markedly lower or elevated risks (Lehman *et al.*, 2012). In a third study, the rate of dementia was no different to that expected in the general population, again based on only two cases (Hart *et al.*,

2013).

Amyotrophic Lateral Sclerosis/ Motor Neurone Disease

14. Regarding ALS, three reports, based on Italian professional association football players, had overlapping time periods and sampling frames. A cohort investigation of some 24,000 soccer players from the top three leagues of Italian professional football who played between 1960 and 1996 reported the proportional mortality ratio (PMR) for ALS to be 11.6. Analysis was based on only eight deaths, but the findings were statistically significant (Belli and Vanacore, 2005). A cohort study of 7,235 professional footballers from the top two Italian leagues (1970 to 2001) also found a significantly elevated standardised mortality ratio (SMR), of 6.5, based on five deaths (Chio *et al.*, 2005). For midfield football players the SMR was 12.2, based on 4 deaths; for players with a career of five years or more, the SMR was 15.2, based on three deaths. All of these findings were statistically significant. Mortality risks were higher in the midfield players than in the backs. Finally, a third cohort study of Italian football players playing between 1975 and 2003, likely to have been based on many cases in common to the report by Chio *et al.*, found a significantly elevated SMR for ALS of 18.2, based on four cases of ALS (Taioli, 2007).

15. Separately, a population-based case-control study compared 300 cases of probable or definite ALS diagnosed at specialist centres in Italy with neighbourhood controls. The odds ratio (OR) for competitive practice of soccer (which may have been amateur and professional) was 0.67. This finding was based on only three exposed cases but the reduction in relative risk was statistically significant (Valenti *et al.*, 2005).

16. A few other reports on ALS and sporting activity have involved a mix of athletes, and not only soccer players. In a case-control study which recruited subjects from Ireland, Italy and the UK, three cases but no controls reported professional sports activity (two cases being association footballers and one an athlete) (Beghi et al, 2010). In a large population-based case-control study involving over 14,000 fatal cases of ALS from 24 A states, the OR in men who were professional athletes (of any kind) was 1.81. The finding was based on six exposed cases and was not statistically significant, despite the study's

large sample size (Vancacore *et al.*, 2010). The earlier-mentioned study of the cohort of 3,439 former professional American football players (Guskiewicz *et al.*, 2005) found a significantly elevated SMR of 4.0, based on six cases.

<u>Parkinson's disease</u>

17. Following the initial account of a "peculiar [punch drunk] condition among prize fighters", professional boxing has become linked with a syndrome of marked mental deterioration and Parkinsonian features, including tremor.

18. As reported in Position Paper 15, the syndrome (which became known as dementia pugilistica or chronic traumatic brain encephalopathy) cannot be distinguished reliably in life from other forms of Parkinsonism or dementia. This precludes its prescription on the basis of unique clinical features.

19. Despite the passage of time, epidemiological evidence on risk of dementia pugilistica in boxers relative to other workers remains elusive. Numerous studies of boxers exist, but these have generally focussed on abnormal EEGs (electroencephalogram; electrical traces of brain activity), neurological, neuropsychological and pathological signs, and not on clinically overt dementia or PD. As in 2005, there remains insufficient evidence to indicate a more than doubled risk of a dementia- or Parkinson-like syndrome in boxers.

20. The only new epidemiological study on PD identified within the scope of this review was that mentioned above, by Lehman *et al.*, 2012, in former professional American football players. This investigation found an SMR of 2.1, based on only two deaths; the findings would also be compatible with a reduced risk, given the statistical uncertainty in the data.

Summary and discussion

21. Several epidemiological studies of neurodegenerative disease in sportspersons have reported a more than doubling of relative risks. However, evidence in relation to dementia and PD is sparse and insufficient to support prescription.

22. More evidence exists for an increased risk of ALS in in professional sportsmen and sportswomen. Most of this evidence derives from the Italian football league, where investigations were originally initiated in the context of a drug doping scandal. It seems likely (although not documented clearly) that

most of cases described in the three main studies were common to all reports, making for less independent evidence than might appear to exist. In these studies risks were markedly elevated, beyond that expected by chance. However, other evidence, from the Italian general population, found a significantly lower risk of ALS among soccer competitors; while other reports, involving a mix of athletes from different settings and countries, tended to support but did not clearly establish an elevation in risk. No study outside the Italian football league has strongly suggested an increase in risk in professional soccer players.

23. While it is hypothesised that risks of dementia and PD in sportspeople could arise from repeated head trauma, and some evidence exists for this, no evidence has been found so far to suggest that repeated head trauma can increase the risk of ALS, the pathology for which is located partly in the brain but also in the nerves supplying muscles in the periphery of the body. Studies of ALS in footballers and other professional athletes have described risks by occupational title but not conducted analyses relating to head injury or any other specific exposures or aspects of the work. It has been suggested by some researchers that a diet enriched with branched-chain amino acids (a common dietary supplement among athletes) may contribute to the higher risk sometimes reported in athletes, but this is likewise unproven.

24. Given the various limitations in the evidence base, the Council is unable to recommend prescription for ALS in professional sportspersons.

This information note contains technical terms which are explained in a glossary

References

Beghi E, Logroscino G, Chio A, Hardiman O, Millul A, Mitchell D, Swingler R, Traynor BJ. Amyotrophic lateral schlerosis, physical exercise, trauma and sports: results of a population-based case-control study. Amyotrop Lateral Schler 2010; 11: 289-92.

Belli S and Vanacore N. Proportionate mortality of Italian soccer players: Is amyotrophic lateral sclerosis and occupational disease? Eur J Epidemiol 2005; 20: 237-42.

Chio A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. Brain 2005; 128: 472-6.

Dick FD, De Palma G, Ahmadi A, et al. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. Occup Environ Med 2007; 64: 666-672.

Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C, Jordan BD. Association between recurrent concussion and late-life cognitive impairment in retired professional footballers. Neurosurgery 2005; 2005; 57: 719-726.

Hart J Jr, Kraut MA, Womack KB, Strain J, Didebhani N, Bartz E, Conover H, Mansinghani BS, Lu H, Cullum CM. Neuroimaging of cognitive dysfunction and depression in aging retired NFL players: a cross-sectional study. JAMA Neurol 2013; 70: 326-35.

Horsfall L, Petersen I, Walters K, Schrag A. Time trends in incidence of Parkinson's disease diagnosis in UK primary care. J Neurol 2013; 260: 1351-7.

Industrial Injuries Advisory Council. Sporting Injuries. Position Paper 15, London, Corporate Document Services, 2005.

Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. Neurology 2012; 79: 1970-4.

Logroscino G, Traynor BJ, Hardiman O, Chio A, Mitchell D, Swingler RJ, Millul A, Benn E, Beghi E, EURALS. Incidence of amyotrophic lateral sclerosis in Europe. J Neurol Neurosurg Psychiatry 2010; 81(4): 385-90.

Matthews F, Brayne C, Medical Research Council Cognitive Function and Ageing Study Investigators. The Incidence of Dementia in England and Wales: Findings from the Five Identical Sites of the MRC CFA Study. PLoS Med 2005; 2(8): e193.

Pearce N, Gallo V, McElvenny D. Head trauma in sport and neurodegenerative disease: an issue whose time has come? Neurobiology of Aging 2015; 36: 1383-9.

Taioli E. All causes mortality in male professional soccer players. Eur J Publ Health 2007; 17: 600-4.

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: 223-5.

Vanacore N, Cocco P, Fadda D, Dosemeci M. Job strain, hypoxia and risk of amyotrophic lateral sclerosis: results from a death certificate study. Amyoptrophic lateral sclerosis 2010; 11: 430-4.

Glossary

Types of study

Case control study: A study which compares people who have a given disease (cases) with people who do not (non-cases, also called controls) in terms of exposure to one or more risk factors of interest. Have cases been exposed more than non-cases? The outcome is expressed as an **Odds Ratio**, a form of **Relative Risk**.

Cohort study: A study which follows those with an exposure of interest (usually over a period of years), and compares their incidence of disease or mortality with a second group, who are unexposed or exposed at a lower level. Is the incidence rate higher in the exposed/more exposed workers than the unexposed/less exposed group? Sometimes the cohort is followed forwards in time ('prospective' cohort study), but sometimes the experience of the cohort is reconstructed from historic records ('retrospective' or 'historic' cohort study). The ratio of risk in the exposed relative to the unexposed can be expressed in various ways, such as a **Relative Risk**, or **Standardised Mortality Ratio.**

Cross-sectional study: A study which classified people at a point in time as having a given disease (or characteristic) or not (controls), and then compares them in terms of exposure to one or more risk factors of interest. Is disease more frequent in those with exposure than in those without? The outcome can be expressed as an **Odds Ratio**, **Prevalence Ratio** or **Relative Risk**.

Measures of association

Statistical significance and P values: Statistical significance refers to the probability that a result as large as that observed, or more extreme still, could have arisen simply by chance. The smaller the probability, the less likely it is that the findings arise by chance and the more likely they are to be 'true'. A 'statistically significant' result is one for which the chance alone probability is suitably small, as judged by reference to a pre-defined cut-point. (Conventionally, this is often less than 5% ($P<0.05$)).

Relative Risk (RR): A measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. *A value greater than 1.0 indicates a positive association between exposure and disease.* (This may be causal, or have other explanations, such as bias, chance or **confounding**.)

Odds Ratio (OR): A measure of the strength of association between exposure and disease. It is the odds of exposure in those with disease relative to the odds of exposure in those without disease, expressed as a ratio. For rare exposures, odds and risks are numerically very similar, so the OR can be thought of as a **Relative Risk**. A value greater than 1.0 indicates a positive association between exposure and disease. (This may be causal, or have other explanations, such as bias, chance or **confounding**.)

Prevalence Ratio (PR): The ratio of the prevalence of disease in one group to that in another (e.g. in the exposed group vs. the unexposed). A value greater than 1.0 indicates a positive association between exposure and disease. (This may be causal or have other explanations, such as bias, chance or **confounding**.)

Standardised Mortality Ratio (SMR): A measure of the strength of association between exposure and mortality; a form of **Relative Risk** in which the outcome is death. The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard).

Proportional Mortality Ratio (PMR): A measure of the strength of association between exposure and mortality; another form of **Relative Risk** in which the outcome is death. The PMR is the proportion of deaths in the study population attributed to a specific cause divided by the proportion of deaths in the general population attributed to that same specific cause.

Standardised rate ratio (SRR): A measure of the strength of association between

exposure and rate of disease; a form of **Relative Risk**. The rate ratio is the ratio of the disease rate in one group (an exposed group) to that in a suitable comparator (unexposed) group. Standardisation is a method that allows the two rates to be compared when the groups differ in other characteristics that affect disease rates such as age, sex, calendar period, geographical region or socioeconomic status. By convention, SMRs and PMRs are usually multiplied by 100. Thus, an SMR (or PMR) of 200 corresponds to a RR of 2.0. For ease of understanding in this report, SMRs and PMRs are quoted as if RRs, and are *not* multiplied by 100. Thus, a value greater than 1.0 indicates a positive association between exposure and disease.

Other epidemiological terms

Confidence Interval (CI): The **Relative Risk** reported in a study is only an *estimate* of the true value in the underlying population; a different sample may give a somewhat different estimate. The CI defines a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. The commonly chosen 95%CIs give a range in which there is a 95% chance that the true value will be found (in the absence of bias and confounding). *Small studies generate much uncertainty and a wide range, whereas very large studies provide a narrower band of compatible values.*

Confounding: Arises when the association between exposure and disease is explained in whole or part by a third factor (confounder), itself a cause of the disease, that occurs to a different extent in the groups being compared.

For example, smoking is a cause of lung cancer and tends to be more common in blue-collar jobs. An apparent association between work in the job and lung cancer could arise because of differences in smoking habit, rather than a noxious work agent.

Studies often try to mitigate the effects of ('control for') confounding in various ways such as: restriction (e.g. only studying smokers); matching (analyzing groups with similar smoking habits); stratification (considering the findings separately for smokers and non-smokers); and mathematical modelling (statistical adjustment).

Appendix: studies of neurodegenerative disease in sportspersons (the meaning of abbreviations is given in the glossary)

Alzheimer's Disease

Reference, Study Period	Study Type	Exposure Assessment	Relative risk (95% Confidence Interval (CI), number of cases observed)	Additional information
Guskiewicz *et al.*, 2005 Questionnaire administered in 2001-2	Cross-sectional questionnaire survey of 2,552 retired professional American football players age 50 or over who played at least two seasons (members of the National Football League Retired Players Association)	The questionnaire asked about number of head concussions (defined as injury resulting from a blow to the head that caused an alteration in mental status and one of several defined symptoms. However, risk of AD was not related to the 'dose' of head injury.	33 (1.3%) of retired players diagnosed with AD by a physician. The overall age-adjusted prevalence ratio compared to US male population for AD was 1.37 (0.98 to 1.56)	69% response rate. 1,513 (61%) reporting having 1 or more concussions during their playing career (817 experienced a loss of consciousness and 787 memory loss), and 597 (24%) reported having 3 or more concussions. Recall of concussion may have been problematic. No data were available on other risk factors for AD.
Lehman *et al.*, 2012 Mortality to 2007	Cohort mortality study of 3,439 National (American) Football League players with at least 5 pension-credited playing seasons from 1959-1988	Players were placed into 2 strata based on characteristics of position played: non-speed players (linemen) and speed players (all other positions except punter/kicker).	Standardised mortality ratio (SMR) (underlying cause) 1.80 (0.22 to 6.50, n = 2) SMR (contributory cause) 3.86 (1.55 to 7.95, n = 7) SMR (contributory cause, non-speed) 1.51 (0.04 to 8.41, n = 1) SMR (contributory cause, speed) 6.02 (2.21 to 13.1 contributory cause, speed vs non-speed) 5.96 (0.72 to 49.6)	Analysis allowed statistically for age, race, calendar year. No data were available on concussions or other risk factors for AD.

Reference, Study Period	Study Type	Exposure Assessment	Relative risk (95% Confidence Interval (CI), number of cases observed)	Additional information
Hart *et al.*; 2013 Late 2000s	Cross-sectional study of 34 retired professional football players aged 41 to 79 recruited from North Texas, with 85 healthy age-, education-, and IQ-matched controls	Each player received a complete neurologic and neuropsychologic evaluation. Their American (NFL) football experience ranged from 2 to 15 years. 18 played offence and 16 played defence. Concussion history was obtained retrospectively.	2 (6%) of 34 former NFL players had dementia, which was not different than expected in the general population of the same age.	Controls were excluded if they had a history of concussion or played college or professional American football. The study sample comprised volunteers so its representativeness is uncertain.

Amyotrophic Lateral Sclerosis/Motor Neurone Disease

Reference, Study period	Study Type	Exposure Assessment	Relative risk (95%CI, number of cases observed)	Additional information
Belli and Vanacore, 2005 1960-1996	Cohort mortality study of about 24,000 Italian soccer players from the top 3 leagues of Italian professional football, 375 of whom had died.	Professional footballer vs. not.	Proportional Mortality Ratio (PMR) ALS, 11.6 (6.7 to 20.0, n = 8)	This study was conducted in the frame of an Italian public enquiry into the possible long term effects of doping. The proportion of deaths in study population due to ALS was 2.29% compared to the national data of 0.07%.
Chio *et al.*, 2005 1970-2001	Cohort study of 7,235 male professional footballers engaged by a football team from the Italian first or second division and played at least one official match.	Playing position (goalkeeper, back, midfielder, forward) ; number of years as a professional footballer.	SMR 6.5 (2.1 to 15.1, n = 5). The SMR was significantly increased for onset before age 49, but not for older subjects SMR midfield 12.2 (3.3 to 21.2, 4) SMR back 4.1 (0.1 to 23.1, 1) SMR < 5 years worked, 3.4 (0.4 to 12.7, 2) SMR > 5 years worked, 15.2 (3.1 to 44.4, 3)	Overlap with Belli and Vancore, 2005 and Taiolo 2007. Non-Italian nationals were excluded.
Taioli, 2007 1975-2003	Cohort study of professional soccer players in the Italian A and B professional leagues enrolled for at least one season between 1975 and 2003 (enumeration list and sampling procedures unstated).	Position played, date and age of first appearance in an Italian or foreign championship, total official games played, and last year played in A or B league.	SMR 18.2 (5.0 to 46.6, n = 4) No significant variation across calendar years.	Overlap with earlier studies. Used US data to calculate mortality rates.
Valenti *et al.*,	Italian case-control study:	Physical activity/sport(s)	Odd Ration (OR) for competitive	

2005 2002-2003	300 cases of probable or definite ALS at 10 reference centres vs. 300 age- and sex-matched neighbourhood controls.	practiced; sports associations and federations to which subjects belonged; traumas incurred in direct relation to sports activity that involved discontinuation of the activity for 30 days or more and trauma location (including cranium).	practice of soccer, 0.67 (0.06 to 0.82, 3 exposed cases) Findings were not presented in relation to head injuries.	
Beghi *et al.*, 2010 Late 2000s	Case-control study: 61 newly diagnosed cases from centres in Ireland, Italy and the UK in the EURALS consortium vs. 112 age- and sex-matched controls.	A detailed history of each sport was collected, including type, date of commencement and cessation and degree of physical activity required (mild, moderate, strenuous) and hours per month. Sports were classified as amateur, organised or professional.	3 patients and 0 controls reported professional sports activity, 2 soccer layers, 1 athlete (p<0.04).	The report focussed on physical exercise and not on trauma to the brain.
Vanacore *et al.*, 2010 1984-1998	Population-based case-control study: 14,628 deaths vs. 58,512 controls from 24 states in the USA, frequency matched on age, sex and broad geographic area.	Usual occupation was recorded on death certificate, but no further details such as duration of employment or concurrent disease were available.	OR male professional athlete, 1.81 (0.50 to 6.77, 6 exposed cases)	Analysis allowed for for marital status, socioeconomic status, and urban vs. rural residence.
Lehman *et al.*, 2012	See above.	See above .	SMR (underlying cause) 4.04 (1.48 to 8.79, n = 6) SMR (contributory cause) 4.31 (1.73 to 8.87, n = 7) SMR (contributory cause, non-speed) 1.71 (0.04 to 9.50, n = 1) SMR (contributory cause, speed) 6.24 (2.29 to 13.6, n = 6) Standardised Rate Ratio (SRR) (contributory cause, speed vs non-speed) 3.88 (0.47 to 32.2)	See above.

Parkinson's Disease

Study	Study Type	Study population	Relative risk (95%CI, number of cases observed)	Additional comment
Lehman *et al.*, 2012	See above.	See above.	SMR (contributory cause) 2.14 (0.26 to 7.75, n = 2) SMR (contributory cause) 1.69 (0.35 to 4.94, n = 3) SMR (contributory cause, non-speed) 1.53 (0.04 to 8.53, n = 1) SMR (c contributory cause, speed) 2.01 (0.24 to 7.25 n = 2) SRR (contributory cause, speed vs non-speed) 1.19 (0.11 to 13.2)	See above.