Specialist Medical Review Council

REASONS

Section 196W

Veterans' Entitlements Act 1986

Re: Statements of Principles Nos. 67 & 68 of 2013

in respect of motor neurone disease

Request for Review Declaration No. 31

1. In relation to the Repatriation Medical Authority (RMA) Statements of Principles **Nos. 67 and 68 concerning motor neurone disease** made under subsections 196B of the *Veterans' Entitlements Act 1986* (the VEA), the Council under subsection 196W(5) of the VEA:

   DECLARES that there is insufficient sound medical-scientific evidence on which the RMA could have relied to include in the Statements of Principles the following factors:

   - having a moderate to severe traumatic brain injury more than one year before the clinical onset of motor neurone disease; and
   - having received at least 250 blows to the head while participating in a high impact contact activity, where these blows occurred more than one year before the clinical onset of motor neurone disease.

   And accordingly:

DECLARES that Statement of Principles No. 68 of 2013 should not be amended to include those factors; AND

DIRECTS the RMA to amend Statement of Principles No. 67 of 2013 by removing factors 6. (b) and (c).

DECLARES that there is no sound medical-scientific evidence on which the RMA could have relied to amend the Statements of Principles to include the following factor(s):

- smoking at least ten pack-years of cigarettes, or the equivalent thereof in other tobacco products coupled with having received at least 250 blows to the head while participating in a high contact activity, where the smoking and blows to the head occurred more than one year before the clinical onset of motor neurone disease.

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REASONS FOR DECISIONS

INTRODUCTION

1. The Specialist Medical Review Council (the Council) is an independent statutory body established by the VEA. In general terms, upon receipt of a valid application the Council is to review as relevant:

   - the contents of Statement/s of Principles in respect of a particular kind of injury, disease or death; or
   - a decision of the RMA not to determine, not to amend, Statement/s of Principles in respect of a particular kind of injury, disease or death.

2. In conducting a review, the Council must review all of the information (and only that information) that was available to the RMA when it made the decision under review. This is information which was actually used by the RMA as opposed to information which was generally available but not accessed by the RMA. A list of the information that was available to the RMA is listed in **B1 of Appendix B**.

3. Fundamental to Statements of Principles (SoPs), and so to a Council review, is the concept of sound medical-scientific evidence (SMSE), as that term is defined in section 5AB(2) of the VEA[1].

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[1] The sound medical-scientific evidence is a subset of the available information. It comprises those articles which the Council considers:

a) are relevant to the matters within the proposed scope of review, and

b) satisfy the definition in the VEA of 'sound medical-scientific evidence'.

Sound medical-scientific evidence is defined in section 5AB(2) of the VEA as follows:

"Information about a particular kind of injury, disease or death is taken to be sound medical-scientific evidence if:

a) the information:

(i) is consistent with material relating to medical-science that has been published in a medical or scientific publication and has been, in the opinion of the Repatriation Medical Authority, subjected to a peer review process; or

(ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and

b) in the case of information about how that kind of injury, disease or death may be caused – meets the applicable criteria for assessing causation currently applied in the field of epidemiology.

The latter requirement is held to mean 'appropriate to be taken into account by epidemiologists'.

4. The SMSE relevant to this application (the relevant SMSE) is listed in the **reference list** at the end of this document**.**

5. The information to which the Applicant referred, being information which the RMA advised was new information, that is, information which was not available to the RMA at the relevant times, and so was not considered by the Council in reaching its review decision is listed in **B2 of Appendix B**.

6. **Appendix A** sets out further details regarding the composition of the Council for this review and the legislation relating to the making of SoPs.

SCOPE OF THIS REVIEW

7. The SMRC received an application seeking review of the decision made by the RMA in June 2017, following an investigation, not to amend to SoPs Instrument No. 68 of 2013 as already determined in respect of motor neurone disease.

8. The Applicant contended that there was SMSE on which the RMA could have relied to amend SoPs No. 68 in respect to **motor neuron disease**, and to include factors for:

    - having a moderate to severe traumatic brain injury more than one year before the clinical onset of motor neurone disease;

    - having received at least 250 blows to the head while participating in a high impact contact activity, where these blows occurred more than one year before the clinical onset of motor neurone disease; and/or

    - smoking at least ten pack-years of cigarettes, or the equivalent thereof in other tobacco products coupled with having received at least 250 blows to the head while participating in a high contact activity, where the smoking and blows to the head occurred more than one year before the clinical onset of motor neurone disease.

9. The Council, when reviewing the SMSE, must determine whether or not there is SMSE on which the Authority could have relied to determine a SoPs under subsection 196B(2), or a SoPs under subsection 196B(3), in respect of that kind of injury, disease or death.

10. The Council, when reviewing the SMSE, must determine whether or not there is SMSE which indicates a reasonable hypothesis connecting the particular injury, disease or death to the relevant service.

11. In a reasonable hypothesis, the evidence 'points to' as opposed to merely 'leaves open' a link between injury, disease or death and the relevant service. In a reasonable hypothesis, the link is not 'obviously fanciful, impossible, incredible or not tenable or too remote or too tenuous.'[2]

12. If Council is of the opinion that a reasonable hypothesis has been raised, the Council proceeds also to determine whether a connection exists to relevant service on the balance of probabilities,[3] i.e. whether the connection is more probable than not.

13. In these Reasons the association for both the reasonable hypothesis test and the balance of probabilities test are respectively referred to as the 'relevant association'.

14. The Council exercises its scientific judgement in weighing the evidence about the relevant association.

COUNCIL'S DECISION ON THE SCOPE OF REVIEW

15. The Council wrote to both the Applicant and the Commissions advising its decision on the proposed scope of the review and inviting comment. No comments were received on the proposed scope of the review and therefore the Council decided that, consistent with its role, it will have particular regard to whether there was SMSE on which the RMA could have relied to amend SoPs No. 68 of 2013 in the following ways:

    the possible inclusion of a factor or factors as contended, for:

    - having a moderate to severe traumatic brain injury more than one year before the clinical onset of motor neurone disease;

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2 See the full Federal Court decision in *Repatriation Commission v Bey* (1997) 79 FCR 364 which cited with approval these comments from Veterans' Review Board in *Stacey* (unreported 26 June 1985), all of which were in turn cited with approval in the Moore J decision at [33].

3 Relevant service in balance of probabilities statements of principles refers to non-operational service having regard to the various definitions applying to types of 'service' as defined in the VEA and the MRCA.

- having received at least 250 blows to the head while participating in a high impact contact activity, where these blows occurred more than one year before the clinical onset of motor neurone disease; and/or

- smoking at least ten pack-years of cigarettes, or the equivalent thereof in other tobacco products coupled with having received at least 250 blows to the head while participating in a high contact activity, where the smoking and blows to the head occurred more than one year before the clinical onset of motor neurone disease.

16. Pursuant to s.196W(3A), in reviewing SoP No.68 (the balance of probabilities SoP), the Council 'must' also review SoP No.69 (the reasonable hypothesis SoP) to the extent of the scope of review that has been identified by the Council and notified to the Applicant and Commissions.

Submissions

17. The Council took into account all submissions made to it.

Applicant

18. The Applicant provided a written submission to the SMRC on 9 January 2018.

19. The Applicant elected not to make an oral submission complementing his written submission.

20. In summary, in respect to the medical science, the Applicant submitted that there is sufficient SMSE supporting the contention on the balance of probabilities that head injury is a factor in the onset of motor neuron disease. The Applicant also contended that the literature supports the contention that smoking, coupled with brain injury or blows to the head, is a factor in the onset of motor neuron disease.

Commissions

21. The Repatriation Commission and the Military Rehabilitation and Compensation Commission (the Commissions) made a written submission to the Council received on 15 December 2017.

22. In the submission by the Commissions contented that the evidence concerning one or several head injuries and risk of motor neuron disease is inconsistent and inconclusive

and that more recent and better quality evidence has strengthened the case against a causal association. The Commissions concluded that the evidence that was available to the RMA does not warrant any amendment to instrument No. 68 of 2013 to include any new factor or factors relating to head injury or blows to the head.

COUNCIL'S DECISIONS ON THE RELEVANT SOUND MEDICAL-SCIENTIFIC EVIDENCE

23. The Council considered that the SMSE to be assessed in the review should comprise information:

    - that was available to the RMA at the relevant times;
    - which was sent by the RMA to the Council under section 196K of the VEA;
    - which was considered by the Council to be SMSE as defined in section 5AB(2) of the VEA being information which:

        a) epidemiologists would consider appropriate to take into account; and

        b) in the Council's view 'touches on' (is relevant to) matters within the scope of review.

24. The Council's final decision on the SMSE for the review was that it should comprise the information listed **reference list** at the end of this document.

25. Information which the RMA advised was not available to it at the relevant times was not taken into account by the Council for the purposes of the review, as it could only be considered as 'new information'.

COUNCIL'S EVALUATION OF THE SOUND MEDICAL-SCIENTIFIC EVIDENCE

26. When evaluating the SMSE, the Council focussed on information relevant to the scope of the review and the **reference list** at the end of this document**.**

27. In forming its decisions on the SMSE, the Council brings to bear its scientific expertise and judgement. The Bradford Hill criteria and other tools or criteria appropriate to be taken into account by epidemiologists were applied to the articles as it considered appropriate.

28. The Council also considered any methodological limitations or flaws (including such things as statistical power, control of confounders, bias, exposure assessment methods etc.) in the various articles.

29. For ease of reference, the Bradford Hill criteria (noting that these are not exhaustive) are:
    - strength of association
    - consistency across investigation
    - specificity of the association
    - temporal relationship of the association
    - biological gradient
    - biological plausibility
    - coherence
    - experiment
    - analogy

30. The Council noted that these criteria are not necessary conditions of a cause and effect relationship. They act to provide some circumstantial evidence of such a relationship.

31. The Council considered that while **animal studies** may sometimes support the biological plausibility of an association, the results from animal studies may not be generalisable to humans. At best such studies are used as initial research to generate hypotheses, which may indicate a need for further studies on human subjects or to demonstrate possible biological mechanisms. For this reason, the Council focussed on studies that involved human subjects rather than animals for this review.

32. While the Council considered, it did not focus its evaluation on those articles that:
    - were reviews of available information that the Council has evaluated in these reasons for decisions;
    - did not provide data that the Council could draw conclusions about **motor neuron disease**.

COUNCIL'S CONCLUSIONS ON THE RELEVANT SOUND MEDICAL-SCIENTIFIC EVIDENCE

33. In reaching a decision about the existence or otherwise of a reasonable hypothesis the Council must consider and evaluate all of the SMSE. In the situation where there is a

single piece of evidence, such as a single study or paper, in support of a reasonable hypothesis, on its own that may be enough to support the hypothesis. However, this information should be considered with other SMSE in identifying whether the SMSE indicates the relation to the medical condition. It is therefore important that the Council considers all information in context.

34. From the information that was available to the RMA at the relevant time, the Council considered all studies important to the scope of this review. In considering the matters within the scope of the review, the Council closely analysed these studies, both individually and collectively, taking into consideration both quantitative and qualitative evidence in its evaluations.

MOTOR NEURON DISEASE

35. In the SoPs Nos. 67 and 68 of 2013, the RMA defined "motor neuron disease" as a progressive neurodegenerative disease with clinical signs of lower and upper motor neurone damage in the absence of other disease processes that explain the clinical signs.

36. The Council notes that motor neuron disease includes a number of subgroups such as amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy and primary lateral sclerosis.

37. The Council also observed that diagnosis of motor neuron disease is often difficult with no gold-standard diagnostic test or criteria and significant differential. In the available papers, the definition of disease was not always consistent between studies and may have been influenced by the health of the participants or accuracy of the death certificate used to determined cases. In addition, studies from many decades ago are more likely to have inaccurate diagnoses of motor neurone disease due to the lack of diagnostic tools such as CT and MRI. Medical records were not always available to investigators to validate the diagnosis or presence and temporal relationship of potentially causative factors. Patient health and early death may have biased both case ascertainment and identification of causative factors.

COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE NEW FACTOR(S)

Moderate to Severe Traumatic Brain Injury

38. The Council reviewed a number of papers[1-26] that included studies of sports trauma,[2, 5, 15, 18] military personnel,[1, 8, 12, 14, 19, 20, 22] and traumatic injury.[3-5, 7, 9-11, 13, 16, 17, 21, 23-26]

Sports Trauma

39. The Council considered studies based on sports trauma[2, 5, 15, 18] were not convincing and were generally of poor quality. Limitations included small sample sizes and potential bias due to self-report, poorly defined exposure criteria, and poor ascertainment of disease. None of the studies of sportspeople was specifically able to determine the number or severity of head injuries received. All except one[18] used the general population as control groups, which may not be an appropriate comparison group for a highly active and physical fit group of sports players and there were potential confounders such as suggested drug and supplement use.

Military Personnel

40. Some of the available studies based on military personnel did not have any information on head injuries or repeated blows to the head[8, 12, 20, 22] so were not considered informative for the question under consideration. Two other studies examined head injuries but this was self-reported.[1, 19] One further study[14] was able to look at hospital admissions for head injury during service but had only eight cases with head injuries and may not have had accurate diagnoses of motor neurone disease.

Other Trauma

41. The Council considered several other studies which aimed to examine the association between head injury and motor neurone disease.[3-5, 7, 9-11, 13, 16, 17, 21, 23]

42. The Council noted that these papers[1-23] were hampered by one or more of the following:

    - Cases were derived from a single or limited number of centres, i.e. they not population based.
    - Small sample size, particularly the number of exposed cases.
    - Poorly defined diagnostic criteria for disease and exposure, or a reliance on death certificates or self-reporting to identify cases and exposures.

- Poor ascertainment of disease with possible misdiagnosis and/or confusion with chronic traumatic encephalitis.
- Timing of head injury in relation to diagnosis, with reports of head injury just prior to diagnosis of motor neurone disease when motor neurone disease may have also been present and contributory (reverse causality) i.e. a fall associated with motor neuron disease that causes a head injury prior to diagnosis.
- Issues with selection of controls, for example the use of friends or spouses as cases controls, or other convenience controls including patients with other diseases, such as multiple sclerosis.
- Low response rates.
- Selection bias where individuals may be excluded from participating due to being unwell and unable to respond or censored by early death, resulting in the inclusion of participants with less severe forms of the disease.
- Recall bias due to self-reporting of disease and exposures and the reliance on questionnaires completed by family members.

43. The Council considered that three papers, by Turner et al,[26] Peters et al[24] and Seals et al,[25] provided the best quality evidence.

44. Turner et al[26] conducted a large cohort study using the Oxford Record Linkage Study data and identified over 100 000 people who had an admission for one or more days for a head injury. Follow-up for amyotrophic lateral sclerosis found a total of 55 cases and an overall adjusted rate ratio (ARR) of 1.5 (95% confidence interval (CI) 1.1-2.1). When examining different time intervals, the only significant finding was for head injury within one year of diagnosis of amyotrophic lateral sclerosis (ARR 4.6, 95% CI 2.1-9.9). The Council considered that this finding was convincing evidence for reverse causality in the year prior to diagnosis of amyotrophic lateral sclerosis.

45. Peters et al[24] conducted a case-control study nested within a Swedish cohort of 5 764 522. They identified 4004 cases of amyotrophic lateral sclerosis and randomly selected 20 020 controls matched for age and gender. The study found a statistically significant association, but only if the head injury (determined by hospitalisation for head injury) was within one year of amyotrophic lateral sclerosis diagnosis (odds ratio (OR) 3.9, 95%

CI 2.6-6.1). Beyond one year there was no association between head injury and amyotrophic lateral sclerosis. The Council considered that this finding was convincing evidence for reverse causality in the year prior to diagnosis of amyotrophic lateral sclerosis.

46. Seals et al[25] conducted a case-control study nested within the Danish Patient Register and identified 3650 cases of amyotrophic lateral sclerosis, each matched with 100 controls by age and gender. They looked for any trauma (head trauma alone, other trauma, or combination of head and other trauma) in the inpatient records since 1977 and prior to 1995. After 1995 both inpatient and outpatient records were used. Head injury alone at any time was associated with amyotrophic lateral sclerosis (OR 1.51, 95% CI 1.11-2.06), however, when excluding head injury within five years before the diagnosis date the association was reduced to OR 0.85 (95% CI 0.56-1.30). When head injury was combined with 'other injury' at any time the association was significant (OR 1.55, 95% CI 1.26-1.91) and remained statistically significant when excluding injury within five years of diagnosis (OR 1.40, 95% CI 1.09-1.80). Figure 2[25(p299)] strongly supports the findings of Turner et al[26] and Peters et al[24] that the association between head injury and amyotrophic lateral sclerosis is raised only in the year prior to, and the year after, diagnosis of amyotrophic lateral sclerosis (although the authors do not draw that conclusion).

47. In the three papers the Council has identified as being of the highest available quality reverse causality is demonstrated, and explains any association determined in those papers. Reverse causality is likely to explain association between head injury and amyotrophic lateral sclerosis reported in other studies where there is insufficient detail to identify it.

48. The Council identified a systematic review and meta-analysis by Wang et al.[27] The 2016 meta-analysis by Wang and colleagues[27] reported an association between previous head trauma and amyotrophic lateral sclerosis with an odds ratio = 1.27 (95% CI 1.02-1.57). However, the review did not undertake any quality assessment of the included studies or otherwise exclude low quality studies. Many of the included studies had used inconsistent or broad definitions of head injury or self-report of head injury, were not population-based, had inappropriate comparison groups, or had unclear definitions of amyotrophic lateral sclerosis. Of the three high quality studies that the Council

identified (Turner et al,[26] Peters et al[24] and Seals et al[25]), Turner et al[26] and Seals et al,[25] were cited in the meta-analysis but their results were incorrectly reported.

49. The Council identified three reviews[28-30] and an editorial[31] that examined the association between traumatic brain injury and the development of motor neurone disease and noted the reviews[28-30] provided conflicting results and the editorial was an opinion piece.

Summary and Conclusions

50. The Council considered that the most informative studies that provided the highest-quality data between moderate to severe traumatic brain injury and the development of motor neuron disease were by Turner et al,[26] Peters et al[24] and Seals et al.[25] These studies revealed that a moderate to severe traumatic brain injury is not associated with development of motor neuron disease and that reverse causality best explains the reported association between head injury and amyotrophic lateral sclerosis.

51. The Council noted that the RMA considered that there was sufficient SMSE which pointed to an association. However, the Council considered that due to methodological limitations including, lack of statistical significance, small sample sizes and potential bias due to self-report, as well as poorly defined exposure criteria, poor ascertainment of disease, and the variation seen in the results of different studies, the SMSE evidence did not point to an association between moderate to severe traumatic brain injury and motor neuron disease. The Council considered that the evidence therefore also fell short of supporting an association on the balance of probabilities.

Blows to the Head While Participating in a High Impact Contact Activity

52. The Council considered whether there was evidence for blows to the head while participating in a high impact contact activity causing or worsening motor neuron disease using the available papers.

53. The Council reviewed a number of papers based on sports trauma[2, 5, 15, 18] and found they were not convincing and were generally of poor quality (see Council's comments on these papers at [39]).

54. The Council noted that the RMA considered that there was sufficient SMSE which pointed to an association. However, the Council considered that due to methodological

limitations including, lack of statistical significance, small sample sizes and potential bias due to self-report, as well as poorly defined exposure criteria, poor ascertainment of disease, and the variation seen in the results of different studies, the SMSE evidence did not point to an association between moderate to severe traumatic brain injury and motor neuron disease. The Council considered that the evidence therefore also fell short of supporting an association on the balance of probabilities

Smoking Coupled With Blows to the Head While Participating in a High Impact Contact Activity

51. The Council considered whether there was evidence for smoking coupled with blows to the head while participating in a high impact contact activity causing or worsening motor neuron disease using the available papers.

52. The Council found no SMSE to support an association or biological proven mechanism for smoking coupled with blows to the head while participating in a high impact contact activity, causing or worsening motor neuron disease.

COUNCIL'S ANALYSIS OF THE NEW INFORMATION

53. As mentioned above, in conducting a review, the Council is unable to (and so did not) consider information which was not available to (not before) the RMA at the relevant times. However, having formed the view that there was nothing in the pool of information which pointed to the relevant association, and being mindful of the Applicant's comments, the Council considered whether in its view there was a basis for recommending to the RMA that it (the RMA) undertake a new investigation.

54. The Council has neither the capacity nor the jurisdiction to perform an investigative function, including undertaking a comprehensive literature search. However, by reason of the Councillors' specialist expertise in this kind of injury, disease or death, the Council was aware of some new information (listed at **B2 of Appendix B**) which it considered on a preliminary basis.

55. The Council considered the new information to determine whether, in the Council's view, it warranted the Council making any directions or recommendations to the RMA.

56. In the Council's view any such direction or recommendation should only be made by the Council if it formed the view that the new information comprised sound medical-scientific evidence as defined in section 5AB(2) of the VEA being information which:

- was information epidemiologists would consider appropriate to take into account; and

- in the Council's view, 'touched on' (was relevant to) the contended factor; and could potentially satisfy the reasonable hypothesis and/or balance of probabilities tests (as appropriate; see paragraphs [12] and [13] above for the relevant associations).

57. The Council noted that the new information provided by the Applicant was evidence that related to the association between occupational exposure of para-troopers and head injuries, and did not relate to the association between traumatic brain injury and motor neuron disease.

DECISION

58. The Council made the declarations summarised in paragraph 1 above.

REFERENCES

1. Beard JD, Engel L, Richardson DB, Gammon MD, Baird C, Umbach DM, et al. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology. Environ Int. 2016;91:104-15. (RMA ID: 081009).

2. Belli S, Vanacore N. Proportionate mortality of Italian soccer players: is amyotrophic lateral sclerosis an occupational disease? Eur J Epidemiol. 2005;20(3):237-42. (RMA ID: 038195).

3. Binazzi A, Belli S, Uccelli R, Desiato MT, Talamanca IF, Antonini G, et al. An explanatory case-control study on spinal and bulbar forms of amyotrophic lateral sclerosis in the province of Rome. Amyotroph Lateral Scler. 2009;10(5-6):361-9. (RMA ID: 066651).

4. Chen H, Richard M, Sandler DP, Umbach DM, Kamel F. Head injury and amyotrophic lateral sclerosis. Am J Epidemiol. 2007;166(7):810-6. (RMA ID: 065626).

5. 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):472-6. (RMA ID: 038179).

6. Chiò A, Meineri P, Tribolo A, Schiffer D. Risk factors in motor neuron disease: a case-control study. Neuroepidemiology. 1991;10(4):174-84. (RMA ID: 081340).

7. Deapen DM, Henderson BE. A Case-Control Study of Amyotrophic Lateral Sclerosis. Am J Epidemiol. 1986;123(5):790-9. (RMA ID: 007102).

8. Drouet A, Desjeux G, Balaire C, Thevenin-Garron V. Retrospective study of ALS in French military personnel [article in French]. Rev Neurol (Paris). 2010;166(6-7):621-9. (RMA ID: 081006).

9. Graham AJ, Macdonald AM, Hawkes CH. British motor neuron disease twin study. J Neurol Neurosurg Psychiatry. 1997;62(6):562-9. (RMA ID: 030519).

10. Granieri E, Carreras M, Tola R, Paolino E, Tralli G, Eleopra R, et al. Motor neuron disease in the province of Ferrara, Italy, in 1964-1982. Neurology. 1988;38(10):1604-7. (RMA ID: 007127).

11. Gresham LS, Molgaard CA, Golbeck AL, Smith R. Amyotrophic lateral sclerosis and history of skeletal fracture: A case-control study. Neurology. 1987;37(4):717-9. (RMA ID: 007128).

12. Haley RW. Excess incidence of ALS in young Gulf War veterans. Neurology. 2003;61(6):750-6. (RMA ID: 028860).

13. Kondo K, Tsuhaki T. Case-control studies of motor neuron disease. Association with mechanical injuries. Arch Neurol. 1981;38(4):224-5. (RMA ID: 007138).

14. Kurtzke JF, Beebe GW. Epidemiology of Amyotrophic Lateral Sclerosis: 1. a case-control comparison based on ALS deaths. Neurology. 1980;30(5):453-62. (RMA ID: 007107).

15. Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. Neurology. 2012;79(19):1970-4. (RMA ID: 066793).

16. Provinciali L, Giovagnoli AR. Antecedent events in Amyotrophic lateral sclerosis: Do they influence clinical onset and progression? Neuroepidemiology. 1990;9(5):255-62. (RMA ID: 007124).

17. Pupillo E, Messina P, Logroscino G, Zoccolella S, Chiò A, Calvo A, et al. Trauma and amyotrophic lateral sclerosis: a case-control study from a population-based registry. Eur J Neurol. 2012;19(12):1509-17. (RMA ID: 066227).

18. 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(4):335-40. (RMA ID: 066224).

19. Schmidt S, Kwee LC, Allen KD, Oddone EZ. Association of ALS with head injury, cigarette smoking and APOE genotypes. J Neurol Sci. 2010;291(1-2):22-9. (RMA ID: 058924).

20. Seals RM, Kioumourtzoglou M-A, Gredal O, Hansen J, Weisskopf MG. Amyotrophic lateral sclerosis and the military: a population-based study in the Danish Registries. Epidemiol. 2016;27(2):188-93. (RMA ID: 080149).

21. Seelen M, van Doormaal PT, Visser AE, Huisman MH, Roozekrans MH, de Jong SW, et al. Prior medical conditions and the risk of amyotrophic lateral sclerosis. J Neurol. 2014;261(10):1949-56. (RMA ID: 079714).

22. Weisskopf MG, O'Reilly EJ, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. Prospective study of military service and mortality from ALS. Neurology. 2005;64(1):32-7. (RMA ID: 038177).

23. 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):1554-7. (RMA ID: 015992).

24. Peters TL, Fang F, Weibull CE, Sandler DP, Kamel F, Ye W. Severe head injury and amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(4):267-72. (RMA ID: 067124).

25. Seals RM, Hansen J, Gredal O, Weisskopf MG. Physical trauma and amyotrophic lateral sclerosis: a population-based study using Danish National Registries. Am J Epidemiol. 2016;183(4):294-301. (RMA ID: 080150).

26. Turner MR, Abisgold J, Yeates DG, Talbot K, Goldacre MJ. Head and other physical trauma requiring hospitalisation is not a significant risk factor in the development of ALS. J Neurol Sci. 2010;288(1-2):45-8. (RMA ID: 065631).

27. Wang MD, Little J, Gomes J, Cashman NR, Krewski D. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology. 2016;61:101-31. (RMA ID: 079945).

28. Armon C. Sports and trauma in amyotrophic lateral sclerosis revisited. J Neurol Sci. 2007;262(1-2):45-53. (RMA ID: 066380).

29. Armon C, Nelson LM. Is head trauma a risk factor for amyotrophic lateral sclerosis? An evidence based review. Amyotroph Lateral Scler. 2012;13(4):351-6. (RMA ID: 065625).

30. Beghi E. Are professional soccer players at higher risk for ALS? Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(7-8):501-6. (RMA ID: 081005).

31. Armon C, Albert SM. A blow to the head trauma-ALS hypothesis. Neurology. 2015;84(17):1728-9. (RMA ID: 079715).