Potential Environmental Factors in Amyotrophic Lateral Sclerosis

Björn Oskarsson, MD[a],*, D. Kevin Horton, DrPH, MSPH, CPH[b],
Hiroshi Mitsumoto, MD, DSc[c]

KEY POINTS

- Proven risk factors for ALS are genetic variants, male gender, and advanced age.
- The only environmental factor that is generally accepted to be associated with ALS is smoking.
- Some evidence supports US military service, lead exposure, physical activity, β-N-methylamino-L-alanine (BMAA), head trauma, electromagnetic fields, agricultural chemicals, and heavy metals as possible factors.
- ALS/Parkinson-dementia complex of Guam and the western Pacific is a distinct clinicopathologic entity; its cause may be different from ALS.
- Oxidative stress is a plausible mechanism through which many environmental risk factors may affect ALS.

INTRODUCTION

The causes of amyotrophic lateral sclerosis (ALS) are unknown for most patients. ALS is a clinically defined syndrome where upper and lower motor neurons degenerate, but

---

neurologic.theclinics.com

it is not clear that the pathogenesis is identical across individual cases. It has been suggested that, for all cases, multiple events need to occur or multiple factors need to be present for the disease to manifest. Presumably these would include genetic susceptibility factors and the environmental or random factors that influence them. As of yet there are not any specific environmental factors that are proven to cause ALS, apart from smoking, but this article discusses several factors that have been examined, and their possible mechanisms. We summarize these in the table (Table 1) and rate of the strength of the association using the grading system proposed by Armon. Many proposed factors are not covered because there are more than 1000 epidemiologic ALS studies published. Controversy exists in regards to each of these factors ranging from limited data to conflicting evidence.

GENE-ENVIRONMENT INTERACTION

No gene conferring susceptibility to a certain environmental exposure has been established in ALS, but the search continues.[1] Several candidate ALS risk genes have emerged from association studies, but these results have not been replicable in other populations outside of where they were identified. Theoretically this could

Table 1
Proposed Risk factors for ALS

Proposed Risk Factor	Level of Increased Risk	Strength[62] and Type of Evidence	Proposed Mechanisms	References
Male gender	OR, 1.5	Level A	Early testosterone exposure	4
Smoking	OR, 1.1	Level A	Oxidative stress Lead Other toxins	63
US military service	OR, 0.22 to SMR, 1.92	Level B	Multiple	29
Lead	OR, 1.81	Level B	Neurotoxicity	42
Pesticides	OR Men, 1.88 Women, 1.31	Level B	Neurotoxic	51
Physical activity (or predilection thereof)	Unknown	Level U	Physical fitness, early testosterone exposure	43,44
Head trauma	Unknown	Level U	Direct neuronal injury	64
Electromagnetic radiation	Unknown	Level U	Electromagnetic field	37
Low body mass index	Unknown	Level U	Higher metabolism	45
Statin treatment	Unknown	Level U	Altered lipid metabolism	47
BMAA	Unknown	Level U	Neurotoxicity	17,18

Abbreviations: BMAA, β-N-methylamino-L-alanine; OR, odds ratio; SMR, standardized morbidity/mortality ratio.

Level A rating: This is an established risk factor, Level B rating: This is a probable risk factor ('more likely than not'), Level C rating: This is a possible risk factor (does not attain a 'more likely than not' status). Better-designed studies may be warranted with regard to this risk factor, Level U rating: It is unknown whether this is a risk factor.

be caused by differing environmental exposures. For a condition to be influenced by an environmental factor there must be susceptibility, and there is evidence that susceptibility can vary among individuals in conditions related to exposure to a toxic risk factor. Examples from the neuromuscular field include where certain gene variations confer increased susceptibility: statins (SLCO1B1), azathioprine (TPMT), and vincristine (PMP 22). Varied susceptibility makes the relationship between exposure and disease more complex. A long delay between exposure and clinical disease also complicates ascertainment of risk factors. The onset of clinical ALS has generally been thought of as the disease onset, but a long preclinical phase of neuronal dysfunction may precede frank cell death. Other more common neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, have a preclinical disease phase and this is certainly also possible in ALS. Epigenetic modifications caused by environmental factors may be the mediators of such delayed mechanisms.[2]

Most of the monogenetic types of familial ALS (fALS) do not lead to ALS in utero or in childhood years, but rather these diseases manifest later in adult life. Yet, on average fALS presents at an earlier age than sporadic ALS (sALS). Mathematical modeling using multistep disease occurrence borrowed from the cancer field suggests that, to develop ALS, six events need to occur in an individual.[3] The presence of a fALS gene is one such event. This type of modeling data implies that environmental factors also play a role in the cause of ALS, not just sALS. As the understanding of genetics and environmental medicine improves, gene-environment interactions will become clearer.

Age is a known strong risk factor for ALS. The incidence of ALS increases markedly with older age. There does, however, seem to be a slight reduction of incidence after the eighth or ninth decade, a finding that contrasts with many other neurodegenerative diseases. This could support the idea that only a portion of the human population is susceptible to ALS. By the time the ninth decade is reached, most people at risk of developing ALS have developed the disease, and this could explain the diminishing incidence. Otherwise the accrual of risk factors for ALS to manifest would be expected to increase, resulting in an ever increasing incidence for fALS and sALS.

PROPOSED ENVIRONMENTAL FACTORS
Gender

The strongest risk factor for ALS outside of fALS is male gender. Male gender is consistently detected as a factor associated with a 1.5 times increased risk of developing ALS compared with female gender.[4] Human males and females differ genetically, physiologically socially, and in their activities and environmental exposures. It is likely that multiple factors contribute to the observed gender difference in ALS incidence. A direct genetic connection seems likely, but the only X-linked fALS identified to date is a very rare defect in Ubiquilin 2; otherwise there is no proven direct gender-genetic connection. After menopause the incidence of ALS becomes nearly equal between the genders in many series.

The increased male risk could be mediated by the sex hormone testosterone, one of the major determinants of male sex characteristics. Testosterone begins to affect an individual in utero and fetal testosterone has been suggested as a risk factor for ALS, with anthropomorphic measures supporting this connection. The relative length of the second and fourth finger is influenced by the level of fetal testosterone,[5] and patients with ALS have relative finger length difference that are statistically greater than the mean population.[6] Later in life men are also more likely to be exposed to many

environmental risk factors, including physical activity, head trauma, military service, heavy metal exposure, high field electromagnetic exposure, and other professions that have been suggested as risk factors.

Geographic Region

Environmental exposures and disparate genetic heritage can be expected to vary by region in the world and a varying incidence of ALS across different regions would therefore seem likely. The best current nationwide epidemiologic data are from different industrial nations, mostly from Western Europe or countries with majority European emigrant populations. At the large national scale these first-world countries show no large differences. In European studies the estimated incidence is around 1.47 per 100,000, with most studies ranging from 1.0 to 3.0 per 100,000.[7] Prevalence in Western Europe was estimated at 4.06 per 100,000.[7] North American studies have estimated incidences around 1.75.[7] The US National ALS Registry has provided US prevalence estimates of 3.9 per 100,000 for 2010 to 2011.[4] Thus the differences between Western Europe and the United States are small. Japanese estimates have consistently been slightly higher with the latest incidence and prevalence being 2.2 and 9.9, respectively.[8] Japanese prevalence numbers could be higher because of a relatively higher use of mechanical ventilation as treatment, thereby prolonging survival of patients.

In less developed countries the estimated prevalence of ALS is generally lower and this is most likely because of less complete case ascertainment and diagnoses. Alternatively there are important environmental risk factors that are increased with highly developed countries, but in general exposures to known environmental toxins are higher in developing nations.[9] Lower and higher rates have been suggested for sub-Saharan Africa, but no good quality data exist.[10]

Clusters

Regional geographic variability in ALS incidence has been shown many times. Generally these variations are small (relative risk, 0.5–2) but statistically significant. Different analysis strategies of the same data may also provide different conclusions, as demonstrated in the rigorous national Irish 1995 to 2013 cohort.[11] In this well-regarded study two types of analysis were done. Bayesian risk mapping identified several clusters of increased incidence, but with even more sophisticated formal cluster analysis (conducted by the same group of investigators) the clusters disappeared, but similar areas of relatively low incidence were identified again. It is worth keeping in mind that an uneven distribution could be the result of random variation, particularly when small numbers of cases are considered.

Most published studies looking to identify clusters have done so. Examples include Italian,[12] English,[13] French,[14] and Japanese[15] cluster studies. Differing explanations have been proposed, such as two Finnish clusters attributed to genetics or perinatal factors,[16] and both northeastern United States[17] and French[18] clusters proposed to be caused by proximity to water where cyanobacterial blooms occur, possibly mediated by β-N-methylamino-L-alanine (BMAA). Such connections are at this time speculative and require further study for verification.[19]

Amyotrophic Lateral Sclerosis/Parkinson-Dementia Complex

The most well established geographic cluster of an ALS-like disease has been on the island of Guam. This cluster, with an incidence of 140 per 100,000 population, is not only limited geographically, but also temporally. On Guam there was a marked increase in incidence of ALS among the Chamorro people that decreased from the early

1950s to the 1980s, with much fewer cases reported since that time.[20] This Guamanian ALS is distinct from sALS and fALS. It clinically associates with Parkinson disease and dementia and is labeled ALS/Parkinson-dementia complex (ALS/PDC).

Neuropathologically ALS/PDC is a tauopathy and this may suggest a quite different pathologic process from ALS; however, both share ubiquitin and TDP43 pathology.[21] Some Chamorros without ALS/PDC also demonstrate tau pathology. This could suggest either a premanifestation state or that the tauopathy is not purely a consequence of the ALS/PDC. Clinically the presentation can be typical for ALS, Parkinson, or a dementia, but often overlapping features exist. The mechanism behind ALS/PDC remains unproved and the disappearance of the disease from Guam makes it harder to study. Some Filipino immigrants to Guam who adopted the native lifestyle also developed the disease, suggesting an acquired nature. Natives who emigrated at an early age later developed the disease, possibly indicating that early life exposure could affect later manifestation. Extensive genetic studies have also failed to yield any genetic associations.

The current leading hypothesis behind ALS/PDC is neurotoxicity from BMAA. This amino acid is produced by blue-green algae and it is a neurotoxin that can cause motor neuron disease in animal models.[22] BMAA is present in high levels in the cycad plants native to Guam and further bioaccumulated by fruit bats, which were a popular food for the decades preceding the ALS/PDC outbreak. BMAA has been proposed to be an environmental risk factor not just for ALS/PDC, but for ALS, Parkinson disease, Alzheimer disease, and other neurodegenerative diseases. This remains controversial and only limited evidence supports this idea. Blue-green algae and BMAA are nearly ubiquitous so if this connection could be established it might have wide ranging implications. On Japan's Kii peninsula ALS/PDC also occurred,[23] and a third focus for ALS/PDC exists in western Papua.[24] Both clusters seem to be disappearing, but still have higher than expected rates for ALS. Cycads grow and are used as medicines and food in both regions.

Smoking

Tobacco smoking has been posited to increase the risk for ALS in several studies.[25] Pooled analysis[26] and meta-analysis supports this notion, at least in women.[27] A minority of studies suggest a reduced risk.[28] It is not known whether the association between ALS and smoking is caused by nicotine, oxidative stress, or one of the many other known toxic substances in tobacco smoke.

Occupational Risks

Many occupations share common exposures and arguably many of the occupations proposed to predispose to ALS are physically active ones with high risk for trauma. No causal factors have been identified.

US military service has been suggested as being a risk factor for ALS in several studies examining the topic.[29] The risk has been estimated with an odds ratio of 0.22,[30] to a standardized morbidity/mortality ratio of 1.92.[31] No singular factor has been discernable; no link to combat, service branch, or place of deployment has been consistently identified. Other exposures that are common in military service are strenuous physical exertion, poor sleep, trauma, psychological stress, and lead exposure (some of which are discussed later).

Furthermore, there does not seem to be a general association between ALS and military service. French,[32] Italian,[33] and British[34] data do not suggest a positive association between ALS and their respective militaries. The Institute of Medicine determined that the evidence is limited but suggestive, and recommends further

studies.[35] US medical providers should be aware that there are special veteran's benefits for all US veterans with ALS.

High linesmen and electricians and other professions with exposure to high-strength electromagnetic fields have been suggested as having an increased risk of ALS. Odds ratios as high as 6.7 have been proposed,[36] but the association is not consistent. Residential exposure to electromagnetic fields does not seem to infer a risk of developing ALS.[37]

Other occupations that have been proposed to have an increased risk of ALS include welders,[36] agricultural workers,[38] and soccer players.[39] The methodology used for the many studies trying to discern occupational risk for developing ALS are varied, which complicates attempts to conduct systematic reviews. However, in one systematic review military service was considered to be a likely factor, and health care workers (including veterinarians), hairdressers, and power plant and electrical workers were candidate professions with a possibility for increased risk.[40] The US National ALS Registry is currently collecting data related to occupation and it is hoped this will lead to a better understanding of occupational risk within the United States.

Lead

Many metals, including lead, are neurotoxic and can cause neuropathies with strong motor nerve involvement. Several studies have found a connection between lead and ALS, whereas others have found no relationship.[41] A recent meta-analysis does support the connection,[42] but flaws in the original retrospective case control studies, particularly in regard to ascertainment of exposure, makes the conclusion arguable. The connection between lead and ALS is unproven and unclear. Many of the lead studies have also seen prolonged survival in patients with ALS who have higher lead levels. This could mean that lead is a risk factor for developing ALS and a protective factor that slows ALS disease progression. Selenium, mercury, and other metals are less well studied and no firm connections with ALS are established.

Physical Exercise

Physical exercise and activity has been positively correlated with ALS incidence in many studies, but not all.[43] The American moniker for ALS - "Lou Gehrig's disease" – after the baseball player who succumbed to the disease - exemplifies and/or contributes to this idea. A dose relationship between physical exercise and ALS has not been shown and it has been suggested that the increased risk is not due to actual physical activity itself, but instead it is due to unknown congenital factors predisposing individuals to physical activity and fitness.[44] It has been proposed that it is this "athletic phenotype" that conveys the increased risk of ALS.[45] There are several plausible explanations for how exercise directly could cause ALS including increased oxidative stress and potentiation of environmental toxins.[45,46]

Trauma

A relationship between head trauma and ALS has not been definitively proved, but several studies have examined head trauma as a risk factor for ALS.[47,48] Head trauma can cause a neurodegenerative disease called chronic traumatic encephalopathy (CTE). A misclassification of some patients with CTE as having ALS has been proposed as a possible explanation for the apparent increase of ALS cases in patients with prior head trauma. CTE shares tau and TDP43 pathologic features with ALS/PDC, and is more clearly differentiated from sALS.

Limb or other injury is frequently described preceding the first manifestation of disease by patients with ALS. A positive linear relationship between ALS severity and

number of trauma events has been observed,[49] but other studies were unable to find a relationship between trauma and ALS. Weakness from ALS commonly result in traumatic falls, when they occur prior to the ALS diagnosis patients may interpret the trauma as the cause of the ALS.

Agricultural Chemicals

Many pesticides are known to be neurotoxic and such substances as organophosphates have a direct effect on the lower motor neuron synapse.[50] Farm workers[51,52] and athletes working on grass covered playing fields[52] may have increase incidences of ALS. Several studies have found an association between ALS and chemicals including pesticides and herbicides, but a meta-analysis does not confirm this relationship.[51]

Other

An association between cancers and ALS has been considered,[53] but such a connection has not been found in methodologically rigorous studies.[47,54]

Statin medications have been suggested both to increase the risk[55] of ALS and decrease it.[47] At this time the evidence favors a protective or null effect.[56] Other protective environmental factors that have been suggested include vitamins E[57] and D, but strong evidence is lacking.[58]

COMBINED OXIDATIVE STRESS THEORY

Any factor that favors a pro-oxidative state could contribute to oxidative stress, and there are many indicators that oxidative stress is one of the central pathways in motor neuron disease.[59,60] Oxidative stress could potentially be the common aspect of many studied environmental risk factors in ALS, including lead (and other heavy metals), organophosphate pesticides, trauma, physical activity, and smoking. Studies evaluating a potential factor individually, along with biomarkers measuring a summation of oxidative factors, could help better define their contribution to ALS risk.[61]

CASE VIGNETTE

A 45-year-old US Navy veteran presents to the ALS clinic after a referral from his Veterans Affairs neurologist for suspected ALS. He started developing slurring of his speech 9 months earlier and this has gradually progressed. He also noted choking on liquids in the last 2 months. He is no longer working as an electrician and he is less interested in pursuing his action shooting hobby and is no longer recharging his casings. He notes no cognitive change but his wife thinks that he is a bit more withdrawn and more easily frustrated. Despite this he is generally quite positive and considers himself blessed with a very good life up until this point. His past medical history includes two concussions and hyperlipidemia. He has been taking a statin medication for the last 4 years. The only neurologic disease that he knows of in his family is dementia. His mother is 75 years old and has dementia; she lives in a nursing home. She had been "acting strangely" even before her "memory got bad" and she still easily recognizes her family members. Her father also had dementia with onset in his 70s.

His general examination reveals a well-nourished man in no distress; he communicates using a writing board. His mental status examination is grossly intact with a normal Folstein mini-mental status examination, but a bedside frontal lobe instrument reveals mild impairment. His cranial nerves are notable for mild facial weakness and a tongue with atrophy and fasciculation. On motor examination he has increased tone and mild atrophy of his cervical paraspinal muscles. He has moderate weakness for neck extension and mild weakness in his shoulders. His tendon reflexes are brisk and his sensory examination normal.

> Records of his electromyogram at the Veterans Affairs show acute and chronic denervation changes in the tongue, cervical and thoracic paraspinal muscles, and muscles of both arms. He had a brain MRI that has been read as normal, but on review you appreciate a slight hyperintensity of the corticospinal tracts. His blood work has been unremarkable except for a mildly elevated serum lead level.
>
> You conclude that he has clinically probable ALS and one issue that you discuss is genetic testing. After education the patient is interested in getting C9ORF72 gene sequencing, which shows an abnormal repeat expansion of 800 times. Thus it is likely that his ALS relates to the C9ORF72 repeat expansion, and he has a family history consistent with this dominantly inherited gene. Additional environmental factors could also be playing a role, which is suggested by his phenotype being different than the dementia that affected his other relatives, and by his relatively younger age of ALS onset. In his case ALS risk factors could include male gender/testosterone exposure, US military service, head trauma, and low-level lead exposure.

SUMMARY

The current state of research in environmental risk factors of ALS has provided many intriguing possible associations. Yet only one-smoking is at this time firmly established. The methodologic difficulties with studying a rare disease that occurs late in life, which could be related to exposures many decades ago, make relationships dauntingly difficult to prove. Despite continued improvement in methodology, significant challenges remain. The diagnostic criteria for ALS are complicated and there are continued efforts to improve them. As they are, the criteria do not yet capture all people with ALS, which further complicates epidemiologic studies. It is hoped that larger datasets with better characterization of different clinical features and laboratory markers will provide more robust estimates of risk factors in ALS in the years to come. A better understanding of environmental risk factors could help reduce exposures and it is hoped markedly reduce ALS incidence over time. Epidemiologic research is critical to advance this field, but the relative rarity of ALS and the current notion that exposures may affect the risk of ALS only decades later make such projects complex with many challenges. One US project of great potential is the National ALS Registry. It is a congressionally-mandated prospective population-based registry encompassing the entire US population. In addition to quantifying the incidence, prevalence, and demographics of ALS in the US, another main goal of the Registry is to examine the risk factors for the disease through online risk factor modules. There are currently 17 different risk factor modules that persons with ALS can complete including, but not limited to, cigarette smoking, alcohol consumption, military service history, occupational history, and a family history of ALS. Since the Registry's launch in October 2010, over 45,000 online risk factor modules have been completed. To our knowledge, this is the largest and most geographically diverse collection of risk factor data available about adults with ALS. Findings from these surveys may provide important insights into the pathology of ALS.

REFERENCES

1. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. Nat Rev Neurol 2013;9:617–28.
2. Eisen A, Kiernan M, Mitsumoto H, et al. Amyotrophic lateral sclerosis: a long preclinical period? J Neurol Neurosurg Psychiatry 2014;85:1232–8.
3. Al-Chalabi A, Calvo A, Chio A, et al. Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. Lancet Neurol 2014;13: 1108–13.

4. Mehta P, Antao V, Kaye W, et al. Prevalence of amyotrophic lateral sclerosis—United States, 2010-2011. MMWR Surveill Summ 2014;63(Suppl 7):1–14.
5. Manning JT, Bundred PE. The ratio of 2nd to 4th digit length: a new predictor of disease predisposition? Med Hypotheses 2000;54:855–7.
6. Vivekananda U, Manjalay ZR, Ganesalingam J, et al. Low index-to-ring finger length ratio in sporadic ALS supports prenatally defined motor neuronal vulnerability. J Neurol Neurosurg Psychiatry 2011;82:635–7.
7. Chio A, Logroscino G, Traynor BJ, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology 2013;41:118–30.
8. Doi Y, Atsuta N, Sobue G, et al. Prevalence and incidence of amyotrophic lateral sclerosis in Japan. J Epidemiol 2014;24:494–9.
9. Smith KR, Corvalan CF, Kjellstrom T. How much global ill health is attributable to environmental factors? Epidemiology 1999;10:573–84.
10. Lekoubou A, Echouffo-Tcheugui JB, Kengne AP. Epidemiology of neurodegenerative diseases in sub-Saharan Africa: a systematic review. BMC Public Health 2014;14:653.
11. Rooney J, Vajda A, Heverin M, et al. Spatial cluster analysis of population amyotrophic lateral sclerosis risk in Ireland. Neurology 2015;84(15):1537–44.
12. Uccelli R, Binazzi A, Altavista P, et al. Geographic distribution of amyotrophic lateral sclerosis through motor neuron disease mortality data. Eur J Epidemiol 2007;22:781–90.
13. Scott KM, Abhinav K, Stanton BR, et al. Geographical clustering of amyotrophic lateral sclerosis in South-East England: a population study. Neuroepidemiology 2009;32:81–8.
14. Boumediene F, Druet-Cabanac M, Marin B, et al. Contribution of geolocalisation to neuroepidemiological studies: incidence of ALS and environmental factors in Limousin, France. J Neurol Sci 2011;309:115–22.
15. Doi Y, Yokoyama T, Tango T, et al. Temporal trends and geographic clusters of mortality from amyotrophic lateral sclerosis in Japan, 1995-2004. J Neurol Sci 2010;298:78–84.
16. Sabel CE, Boyle PJ, Loytonen M, et al. Spatial clustering of amyotrophic lateral sclerosis in Finland at place of birth and place of death. Am J Epidemiol 2003;157:898–905.
17. Caller TA, Chipman JW, Field NC, et al. Spatial analysis of amyotrophic lateral sclerosis in Northern New England, USA, 1997-2009. Muscle Nerve 2013;48:235–41.
18. Masseret E, Banack S, Boumediene F, et al. Dietary BMAA exposure in an amyotrophic lateral sclerosis cluster from southern France. PLoS One 2013;8:e83406.
19. Delzor A, Couratier P, Boumediene F, et al. Searching for a link between the L-BMAA neurotoxin and amyotrophic lateral sclerosis: a study protocol of the French BMAALS programme. BMJ Open 2014;4:e005528.
20. Galasko D, Salmon DP, Craig UK, et al. Clinical features and changing patterns of neurodegenerative disorders on Guam, 1997-2000. Neurology 2002;58:90–7.
21. Geser F, Winton MJ, Kwong LK, et al. Pathological TDP-43 in parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam. Acta Neuropathol 2008;115:133–45.
22. Yin HZ, Yu S, Hsu CI, et al. Intrathecal infusion of BMAA induces selective motor neuron damage and astrogliosis in the ventral horn of the spinal cord. Exp Neurol 2014;261:1–9.

23. Mimuro M, Kokubo Y, Kuzuhara S. Similar topographical distribution of neurofibrillary tangles in amyotrophic lateral sclerosis and parkinsonism-dementia complex in people living in the Kii peninsula of Japan suggests a single tauopathy. Acta Neuropathol 2007;113:653–8.

24. Okumiya K, Wada T, Fujisawa M, et al. Amyotrophic lateral sclerosis and parkinsonism in Papua, Indonesia: 2001-2012 survey results. BMJ Open 2014;4: e004353.

25. de Jong SW, Huisman MH, Sutedja NA, et al. Smoking, alcohol consumption, and the risk of amyotrophic lateral sclerosis: a population-based study. Am J Epidemiol 2012;176:233–9.

26. 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; 68:207–13.

27. Alonso A, Logroscino G, Hernan MA. Smoking and the risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2010;81:1249–52.

28. Fang F, Bellocco R, Hernan MA, et al. Smoking, snuff dipping and the risk of amyotrophic lateral sclerosis: a prospective cohort study. Neuroepidemiology 2006;27:217–21.

29. Beard JD, Kamel F. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology and survival. Epidemiol Rev 2015;37:55–70.

30. Qureshi MM, Hayden D, Urbinelli L, et al. Analysis of factors that modify susceptibility and rate of progression in amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler 2006;7:173–82.

31. Horner RD, Kamins KG, Feussner JR, et al. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. Neurology 2003;61:742–9.

32. Drouet A, Desjeux G, Balaire C, et al. Retrospective study of ALS in French military personnel. Rev Neurol (Paris) 2010;166:621–9 [in French].

33. Binazzi A, Belli S, Uccelli R, et al. An exploratory case-control study on spinal and bulbar forms of amyotrophic lateral sclerosis in the province of Rome. Amyotroph Lateral Scler 2009;10:361–9.

34. Gale CR, Braidwood EA, Winter PD, et al. Mortality from Parkinson's disease and other causes in men who were prisoners of war in the Far East. Lancet 1999;354: 2116–8.

35. Medicine Io. Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature. Washington, DC: The National Academies Press; 2006.

36. Gunnarsson LG, Bodin L, Söderfeldt B, et al. A case-control study of motor neurone disease: its relation to heritability, and occupational exposures, particularly to solvents. Br J Ind Med 1992;49:791–8.

37. Seelen M, Vermeulen RC, van Dillen LS, et al. Residential exposure to extremely low frequency electromagnetic fields and the risk of ALS. Neurology 2014;83: 1767–9.

38. Rosati G, Pinna L, Granieri E, et al. Studies on epidemiological, clinical, and etiological aspects of ALS disease in Sardinia, Southern Italy. Acta Neurol Scand 1977;55:231–44.

39. Belli S, Vanacore N. Proportionate mortality of Italian soccer players: is amyotrophic lateral sclerosis an occupational disease? Eur J Epidemiol 2005;20: 237–42.

40. Sutedja NA, Fischer K, Veldink JH, et al. What we truly know about occupation as a risk factor for ALS: a critical and systematic review. Amyotroph Lateral Scler 2009;10:295–301.

41. Callaghan B, Feldman D, Gruis K, et al. The association of exposure to lead, mercury, and selenium and the development of amyotrophic lateral sclerosis and the epigenetic implications. Neurodegener Dis 2011;8:1–8.

42. Wang MD, Gomes J, Cashman NR, et al. A meta-analysis of observational studies of the association between chronic occupational exposure to lead and amyotrophic lateral sclerosis. J Occup Environ Med 2014;56:1235–42.

43. Hamidou B, Couratier P, Besancon C, et al. Epidemiological evidence that physical activity is not a risk factor for ALS. Eur J Epidemiol 2014;29:459–75.

44. Huisman MH, Seelen M, de Jong SW, et al. Lifetime physical activity and the risk of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2013;84:976–81.

45. Mattsson P, Lonnstedt I, Nygren I, et al. Physical fitness, but not muscle strength, is a risk factor for death in amyotrophic lateral sclerosis at an early age. J Neurol Neurosurg Psychiatry 2012;83:390–4.

46. Longstreth WT, Nelson LM, Koepsell TD, et al. Hypotheses to explain the association between vigorous physical activity and amyotrophic lateral sclerosis. Med Hypotheses 1991;34:144–8.

47. Seelen M, van Doormaal PT, Visser AE, et al. Prior medical conditions and the risk of amyotrophic lateral sclerosis. J Neurol 2014;261:1949–56.

48. McKee AC, Gavett BE, Stern RA, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. J Neuropathol Exp Neurol 2010;69:918–29.

49. 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;19:1509–17.

50. Singh G, Khurana D. Neurology of acute organophosphate poisoning. Neurol India 2009;57:119–25.

51. Malek AM, Barchowsky A, Bowser R, et al. 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;117:112–9.

52. Chio A, Calvo A, Dossena M, et al. ALS in Italian professional soccer players: the risk is still present and could be soccer-specific. Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases 2009;10:205–9.

53. Corcia P, Gordon PH, Camdessanche JP. Is there a paraneoplastic ALS? Amyotrophic lateral sclerosis & frontotemporal degeneration 2015;16:252–7.

54. Fang F, Al-Chalabi A, Ronnevi LO, et al. Amyotrophic lateral sclerosis and cancer: a register-based study in Sweden. Amyotroph Lateral Scler Frontotemporal Degener 2013;14:362–8.

55. Edwards IR, Star K, Kiuru A. Statins, neuromuscular degenerative disease and an amyotrophic lateral sclerosis-like syndrome: an analysis of individual case safety reports from vigibase. Drug Saf 2007;30:515–25.

56. Zheng Z, Sheng L, Shang H. Statins and amyotrophic lateral sclerosis: a systematic review and meta-analysis. Amyotroph Lateral Scler Frontotemporal Degener 2013;14:241–5.

57. Ascherio A, Weisskopf MG, O'Reilly EJ, et al. Vitamin E intake and risk of amyotrophic lateral sclerosis. Ann Neurol 2005;57:104–10.

58. Camu W, Tremblier B, Plassot C, et al. Vitamin D confers protection to motoneurons and is a prognostic factor of amyotrophic lateral sclerosis. Neurobiol Aging 2014;35:1198–205.

59. Simpson EP, Yen AA, Appel SH. Oxidative stress: a common denominator in the pathogenesis of amyotrophic lateral sclerosis. Curr Opin Rheumatol 2003;15:730–6.

60. D'Amico E, Factor-Litvak P, Santella RM, et al. Clinical perspective on oxidative stress in sporadic amyotrophic lateral sclerosis. Free Radic Biol Med 2013;65: 509–27.
61. Mitsumoto H, Factor-Litvak P, Andrews H, et al. ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS): study methodology, recruitment, and baseline demographic and disease characteristics. Amyotroph Lateral Scler Frontotemporal Degener 2014;15:192–203.
62. Armon C. An evidence-based medicine approach to the evaluation of the role of exogenous risk factors in sporadic amyotrophic lateral sclerosis. Neuroepidemiology 2003;22:217–28.
63. Armon C. Smoking may be considered an established risk factor for sporadic ALS. Neurology 2009;73:1693–8.
64. Armon C, Nelson LM. Is head trauma a risk factor for amyotrophic lateral sclerosis? An evidence based review. Amyotroph Lateral Scler 2012;13:351–6.