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**Title:**

Mapping the human exposome – without it, how can we find environmental risk factors for ALS?

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**Running head:** The exposome and ALS

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**Commentary:**

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease. It has been in the public awareness recently because of the Ice Bucket Challenge phenomenon and the multi-award winning film, The Theory of Everything, which tells the story of the renowned physicist Stephen Hawking, focussing on the time around his diagnosis. ALS kills one in every 300 people 1 and does so over a period of a few months to a few years through a slow paralysis that eventually affects the diaphragmatic muscles and therefore prevents breathing.2 Although it was first described nearly 150 years ago, the causes remain largely unknown.3 The heritability of ALS is about 60%,4 which implies 40% of the phenotypic variance is explained by environmental factors – although this does not mean that environmental factors contribute to only 40% of cases, as many cases may occur due to a combination of genetic and environmental factors.5 While great progress is being made in identifying the genetic component of risk, the environmental aspect has been far more challenging, in part because the lack of an apparent disease mechanism makes it difficult to determine which environmental exposures to focus on. Furthermore, although the most promising ideas about the possible causes of other diseases such as cancer and asthma have often come from population comparisons 6 there is limited valid global data on ALS incidence or prevalence outside European populations.7,8

A number of possible occupational or environmental causes have been suggested, but there is little definitive evidence to date.9 In this edition of Epidemiology, two papers try to address this issue by examining the evidence for risk factors that have been previously reported for ALS: military service and exposure to electric shock or electromagnetic fields.

Military service is an attractive subject for epidemiological studies of ALS. The study cohort is relatively clearly defined and documented, and the potential risk factors include several candidates for ALS, including athleticism, high exercise or fitness levels, exposure to toxins or vaccines, and traumatic injury.

Sport and fitness have been considered important in ALS because the motor system is key to sporting success, and the motor pathways are the primary system affected in ALS. Furthermore, it is a frequent anecdotal report of neurologists specialising in ALS that their patients are very fit. A typical presenting complaint is, “I was at the gym when I realized I could no longer do X”. High levels of sporting activity also sit well with the excitotoxic hypothesis of ALS in which overstimulation of motor nerves by glutamate during extreme exercise results in cell death. Evidence apparently supporting the idea that exercise increases risk comes from a study of Italian professional footballers in which a six fold increase in risk of ALS was reported based on estimating the expected number affected using age adjusted incidence.10 Analysis based on lifetime risk however suggests there may be no increase in risk.3 If sport is a risk factor for ALS, the implication is that physical activity, through military training or deployment might be a cause of neurodegeneration, but it is also possible that genetic or developmental factors predisposing someone to athletic ability might be the underlying risk factor, and there are other possible explanations for such associations including a possible role of head trauma.11,12 Deployment increases exposure to toxins from exploded munitions, destroyed buildings, vehicles and landscape. Lead poisoning can cause a motor neuropathy, and other toxins such as pesticides have been proposed to play a role. Physical trauma has been explored as a risk factor, but there is no suggestion in the work on military service that ALS was more frequent in those with physical injuries. Furthermore, studies of military service are notoriously difficult because of the difficulties of finding an appropriate comparison group; in particular, there may be major ‘baseline’ differences between members of the military who are deployed or who are not deployed in a particular conflict, as well as differences between military personnel and the general population.

The study reported here suggests that military service in World War II is a risk factor for ALS. As the authors point out, military service in other wars may also be a risk factor, but if the effect is small, large numbers need to be studied, and any increased risk may not manifest itself until older ages, i.e. several decades after military service has ended. This is true for WWII but not for other more recent conflicts. It may therefore be that military service in general is a risk factor. For example, deployment in the second Gulf War has been considered a strong risk factor for ALS in some studies.13

The finding that military service is associated with ALS risk highlights many of the problems in epidemiological research in a late onset, relatively low prevalence disease. The association could indicate that exercise is a risk factor, or predisposition to high athletic skill, or high developmental levels of testosterone, or something related to military service, or exposure to a factor resulting from deployment. In other words, while the finding is intriguing, it cannot easily be put in context without further information. We need other environmental risk factors, or a robust gene x environment interaction that can guide interpretation of the association.

In contrast to studies of the military, studies of the general workforce have many advantages particularly because of the very low levels of confounding when different groups of workers are compared.14 Exposure to electric shock is an appealing candidate risk factor for ALS because on a very simplistic level, nerves work by electricity, and too much could be thought of as likely to damage them. The problem is that while large electric shocks are known to damage the nervous system, they do so to all modalities, and any motor impairment caused is fixed rather than progressive.15 In contrast, ALS is confined largely to motor neurons, and is progressive, not a static disability. The authors show a non-significant increase in risk of ALS in those whose job left them at risk of electric shock and electromagnetic fields. This might mean that such exposure is a risk factor and the study was underpowered, or that there really is no such association.

Recently, ALS was shown to be a multistep process, like cancer.16 On average, six steps appear to be needed for ALS to develop. While one or two might result from genetic factors, it is likely that many are the consequence of environmental exposures. However, since there is considerable genetic heterogeneity in ALS, there is also likely to be considerable environmental heterogeneity. Identifying the multiple steps in a heterogeneous condition will be particularly challenging.

What both these papers show is the difficulties in establishing or definitively refuting any occupation, exposure or geographical link to ALS. This problem leads directly to two related questions: Should we bother with epidemiological studies of ALS? If so, what could we do to improve the chances of success?

Genetic studies have so far identified about 40 genes for ALS (<http://alsod.iop.kcl.ac.uk>). Even with so many components of the disease pathway, it is not clear why ALS occurs. To have achieved even this modest level of success has taken massive levels of funding, extraordinary technological advances, huge international consortia, new statistical methods, and a system of analysis in which parallels between different discoveries can be found. For epidemiological studies of ALS, the technology needed is available in the form of networked, web-based systems and databases, but it is not possible to assay environmental risk factors in an individual with as much certainty as for a genetic study, and larger numbers and more valid exposure data would therefore be needed to achieve the same statistical power. Mendelian randomization (i.e. using measured variation in genes of known function to examine the causal effect of a modifiable exposure on disease in non-experimental studies) has considerable advantages in theory,17 but its application in practice requires the existence of appropriate genetic polymorphisms, as well as at least some prior knowledge as to what the relevant environmental exposures might be. Epigenetics may offer a way forward, in which methylation and microRNA changes resulting from environmental exposures earlier in life remain imprinted and assayable from blood or tissue samples. A combination of epigenetic and Mendelian randomization approaches, known as ‘two-step epigenetic Mendelian randomization’ may be particularly fruitful.18 The international consortia exist, but funding for organised data collection is not as readily available, in part because questionnaires are regarded as mundane compared with expensive technology. It is also easy to collect case samples, but controls are more challenging. The Wellcome Trust Case Control Consortium galvanised the genetics community by providing universal control data, and now the 1000 Genomes Project, Genomics England, and Genome of the Netherlands are taking this further.19 While there are some equivalent projects with regards to possible environmental causes, they are not on an international level, and do not necessarily have questions compatible with those needed for a particular disease. Furthermore, there is no equivalent of the Human Genome for epidemiology, i.e. there is no ‘human exposome’ to correspond to the ‘human genome’.20 A global map of ALS, as has been done for other diseases such as asthma and cancer, in which a particular environmental factor or variation can be examined to explore its relationship with others and with the corresponding prevalence patterns of ALS would be a powerful tool for epidemiological studies worldwide.

Environmental studies of ALS are essential for a full understanding of the disease process, development of treatment strategies, and the possibility of prevention in susceptible groups. Without a concerted effort and radical action to take things to a new level, it will be difficult to understand and prevent this devastating disease.

**References**

1. Johnston CA, Stanton BR, Turner MR, Gray R, Blunt AH, Butt D, Ampong MA, Shaw CE, Leigh PN, Al-Chalabi A. Amyotrophic lateral sclerosis in an urban setting: a population based study of inner city London. *J Neurol* 2006;**253**(12):1642-3.

2. Creemers H, Grupstra H, Nollet F, van den Berg LH, Beelen A. Prognostic factors for the course of functional status of patients with ALS: a systematic review. *J Neurol* 2015;**262**(6):1407-23.

3. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. *Nat Rev Neurol* 2013;**9**(11):617-28.

4. Al-Chalabi A, Fang F, Hanby MF, Leigh PN, Shaw CE, Ye W, Rijsdijk F. An estimate of amyotrophic lateral sclerosis heritability using twin data. *J Neurol Neurosurg Psychiatry* 2010;**81**(12):1324-6.

5. Vineis P, Pearce NE. Genome-wide association studies may be misinterpreted: genes versus heritability. *Carcinogenesis* 2011;**32**(9):1295-8.

6. Pearce N. Epidemiology as a population science. *Int J Epidemiol* 1999;**28**(5):S1015-8.

7. Marin B, Kacem I, Diagana M, Boulesteix M, Gouider R, Preux PM, Couratier P, Tropals C. Juvenile and adult-onset ALS/MND among Africans: incidence, phenotype, survival: a review. *Amyotroph Lateral Scler* 2012;**13**(3):276-83.

8. Nalini A, Thennarasu K, Gourie-Devi M, Shenoy S, Kulshreshtha D. Clinical characteristics and survival pattern of 1,153 patients with amyotrophic lateral sclerosis: experience over 30 years from India. *J Neurol Sci* 2008;**272**(1-2):60-70.

9. Pearce N, Kromhout H. Neurodegenerative disease: the next occupational disease epidemic? *Occup Environ Med* 2014;**71**(9):594-5.

10. 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**(Pt 3):472-6.

11. Pearce N, Gallo V, McElvenny D. Head trauma in sport and neurodegenerative disease: an issue whose time has come? *Neurobiol Aging* 2015;**36**(3):1383-9.

12. Fournier CN, Gearing M, Upadhyayula SR, Klein M, Glass JD. Head injury does not alter disease progression or neuropathologic outcomes in ALS. *Neurology* 2015;**84**(17):1788-95.

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

14. Pearce N, Checkoway H, Kriebel D. Bias in occupational epidemiology studies. *Occup Environ Med* 2007;**64**(8):562-8.

15. Abhinav K, Al-Chalabi A, Hortobagyi T, Leigh PN. Electrical injury and amyotrophic lateral sclerosis: a systematic review of the literature. *J Neurol Neurosurg Psychiatry* 2007;**78**(5):450-3.

16. Al-Chalabi A, Calvo A, Chio A, Colville S, Ellis CM, Hardiman O, Heverin M, Howard RS, Huisman MH, Keren N, Leigh PN, Mazzini L, Mora G, Orrell RW, Rooney J, Scott KM, Scotton WJ, Seelen M, Shaw CE, Sidle KS, Swingler R, Tsuda M, Veldink JH, Visser AE, van den Berg LH, Pearce N. Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. *Lancet Neurol* 2014;**13**(11):1108-13.

17. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003;**32**(1):1-22.

18. Relton CL, Davey Smith G. Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. *Int J Epidemiol* 2012;**41**(1):161-76.

19. Huang J, Ellinghaus D, Franke A, Howie B, Li Y. 1000 Genomes-based imputation identifies novel and refined associations for the Wellcome Trust Case Control Consortium phase 1 Data. *Eur J Hum Genet* 2012;**20**(7):801-5.

20. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev* 2005;**14**(8):1847-50.