Published in final edited form as:

Amyotroph Lateral Scler Frontotemporal Degener. 2017 August ; 18(5-6): 419–425. doi:
10.1080/21678421.2017.1300287.

Association of Fractures with the Incidence of Amyotrophic Lateral Sclerosis

Tracy L. Peters^{1,2}, Caroline E. Weibull¹, Fang Fang¹, Dale P. Sandler², Paul C. Lambert^{1,3},
Weimin Ye¹, and Freya Kamel²

¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

²Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle
Park, North Carolina, USA

³Department of Health Sciences, University of Leicester, Leicester, United Kingdom

Abstract

Objective—Elevated bone turnover observed in ALS patients suggests poor bone health and increased fracture risk. We therefore evaluated the relationship of fracture to subsequent ALS risk.

Methods—We followed 4,529,460 Swedes from 1987 to 2010 and identified ALS and fractures from the Swedish National Patient Register. We examined associations of ALS risk with all fractures, osteoporotic and non-osteoporotic fractures, and traumatic and non-traumatic fractures among individuals aged 30 to 80 years. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). We analyzed the association of ALS with time since fracture using a Poisson regression model.

Results—All fractures (HR: 1.51, 95% CI: 1.39, 1.65) as well as osteoporotic (HR: 1.59, 95% CI: 1.41, 1.79), non-osteoporotic (HR: 1.46, 95% CI: 1.31, 1.63), traumatic (HR: 1.50, 95% CI: 1.37, 1.63), and non-traumatic fractures (HR: 1.80, 95% CI: 1.35, 2.40) were associated with a higher incidence of ALS. Increased ALS incidence was associated with fractures occurring from one (HR: 2.33, 95% CI: 2.04, 2.66) to 18 years (HR: 1.19, 95% CI: 1.01, 1.43) before ALS diagnosis.

Conclusions—Poor bone health may be related to ALS. These findings may offer insight into ALS pathophysiology.

Keywords

Amyotrophic Lateral Sclerosis; Fractures; Cohort Study; Risk Factors

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rare disease, with an annual incidence of 2–3 per 100,000 person-years in the general population (1). Incidence increases with age and is

Corresponding Author: Tracy L. Peters, Ph.D., Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, P.O. Box 281, 171 77 Stockholm, Sweden, tracy.peters@gmail.com, Fax: +46-8-314975, Phone: +46-8-52483943.

DECLARATION OF INTEREST STATEMENT: The authors declare that they have no conflict of interest.

greater among men than women. Up to ten percent of ALS cases have a clear family history, suggesting that both genetic and environmental factors are likely involved in the etiology of ALS (1).

Several studies have specifically investigated fracture (traumatic fracture, any fracture, multiple fractures) as a risk factor for ALS; these studies have varied in design and have reported mixed results (Supplemental Table 1) (2–15). Fractures may be related to bone health, *i.e.* to changes in bone density, structure, or strength resulting from aging, physical inactivity, diet, medical conditions such as hyperparathyroidism or bone disease, or medication use (16, 17). Some fractures – osteoporotic fractures and those not related to trauma – may have a stronger relationship to such changes.

Recently we showed that ALS was related to increased bone turnover (18), extending limited prior reports that ALS is related to features of bone health including bone turnover and bone mineral density as well as bone disease (2, 19–21). These relationships may be a consequence of changes in diet, physical activity level, sun exposure, or other features of disease in ALS patients. Alternatively, changes in bone health might precede the development of ALS. In this regard, it is particularly interesting that familial ALS is associated with polymorphisms in the gene encoding for valosin-containing protein, which plays a role in Paget's disease – a condition involving defective bone remodeling (22). Thus ALS may share genetic or other risk factors with poor bone health, potentially shedding light on its pathophysiology.

We therefore hypothesized that fractures occurring before ALS diagnosis would be associated with an increased risk of ALS. We used data from the Swedish national population and health registers to conduct a prospective cohort study of this relationship. We examined all fractures together as well as those most likely to be related to poor bone health (17). We also investigated whether the association with ALS incidence changed with time since fracture.

MATERIALS AND METHODS

Data sources

We used data from several Swedish national population and health registers. The Swedish Population and Housing Censuses for 1980 and 1990 contain information on sex, birthdate, and citizenship (23). The Cause of Death Register, maintained by The National Board of Health and Welfare since 1952, includes date and causes of death (24). The Swedish Register of Education has information on the highest obtained education level with completion year and is updated annually (25). The Migration Register is updated every few months and records information on emigration and immigration dates of registered residents in Sweden (26).

Information on incident cases of ALS and fractures was retrieved from the Swedish National Patient Register (NPR) which was started in 1964/1965 by the National Board of Health and Welfare. The NPR collects information on all hospitalizations beginning in 1964/1965 and with nationwide coverage after 1987. Starting in 2001, the NPR has also collected

information on hospital-based outpatient specialist visits. Recorded information includes diagnoses and dates of hospital visit, admission and discharge.

Cohort

The personal identification number, a unique individual identifier for Swedish residents, enabled linkage of the registers to create the cohort for this study. All individuals born between 1901 and 1956; included in either the 1980 or the 1990 Census; and alive, living in Sweden and not diagnosed with ALS as of January 1, 1987 were included in the study population, which included 4,529,460 individuals. Follow-up started in 1987, the year that complete nationwide coverage of hospital discharge records began.

The study was approved by the Regional Ethical Vetting Board in Stockholm, Sweden.

Outcome

All first diagnoses of ALS (either as the main or secondary diagnosis at hospital discharge or specialist visit) were identified in the NPR (hospital discharge records from 1987 to 2010 and hospital-based outpatient specialist care from 2001 to 2010). ALS diagnoses were recorded according to the Swedish revisions of the *International Classification of Diseases, Ninth Revision* (335C (335.20 in the English version)) and *Tenth Revision* (G12.2). The quality of hospital discharge diagnoses in the NPR is generally high (24). Using hospital discharge diagnosis as a method to ascertain ALS patients, four studies have found these diagnoses to be valid, and the ICD coding was reported to be accurate in three of the four studies (27, 28).

Exposure

The exposure of primary interest was the first record of any fracture (except head and face) in the NPR (hospital discharge records from 1964 onward or outpatient care from 2001 onward). Fractures can be treated in either the inpatient or outpatient services in Sweden. Only the first record of any fracture was considered because the same fracture may be recorded multiple times in the NPR. Traumatic brain injury may be a risk factor for ALS, so head and face fractures were excluded to avoid combining fractures potentially affecting ALS risk through different mechanisms (29). Fractures were defined according to the *International Classification of Diseases, Seventh Revision* before 1968, *Eighth Revision* during 1968–1986, *Ninth Revision* during 1987–1996, and *Tenth Revision* from 1997 onward.

We sub-classified fractures in two ways. First, osteoporotic fractures were defined as hip, wrist/forearm, rib, or spine fractures and were considered separately from non-osteoporotic fractures. Second, fractures were categorized as traumatic or non-traumatic, using accident codes from the Swedish revisions of the *International Classification of Diseases, Seventh - Tenth*. Accidents included falls, traffic related incidents, open fire, nature & environment, abuse, manslaughter, murder, police abuse and others. Fractures associated with such accidents (traumatic fractures) were separated from those not associated with accidents (non-traumatic fractures).

Potential confounders

Risk factors for fracture included as confounders in this study are age and sex (16, 17), and prevalence of fracture may be greater among people of lower socioeconomic status (30). For ALS, risk factors include age and sex (1). A low level of education, which may be a surrogate for socioeconomic status, has also been identified as a possible risk factor for ALS (31). Thus we considered attained age, sex, and education as potential confounders. Education was categorized into nine years or less of schooling, ten to twelve years of schooling, university, and doctoral studies.

Statistical analyses

The outcome of interest was the first recorded ALS diagnosis during follow-up. Data were analyzed using time-to-event methods. Risk time (expressed in terms of person-years) was accumulated from date of entry (January 1, 1987) until date of first ALS diagnosis, migration out of Sweden, death, turning 81 years old, or December 31, 2010, whichever came first (23 years of follow-up). Incidence rates with 95% confidence intervals (CIs) were calculated as number of events per 100,000 person-years.

We compared incidence of ALS among exposed and unexposed using Cox proportional hazards regression models with attained age as the time scale to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Fracture was treated as a time-varying exposure: individuals with a fracture contributed to unexposed risk time until the date of fracture after which they contributed to exposed risk time. Individuals with fracture diagnosed before entry date began to accumulate exposed risk time at entry date. Both single variable and multivariable models were fitted; the latter were adjusted for sex and education. We conducted two sensitivity analyses, delaying entry into the cohort by two years (January 1, 1989) or ten years (January 1, 1997). Schoenfeld residuals were used to investigate the proportional hazards assumption, using a χ^2 test.

We used Poisson regression to model rates of ALS using time since fracture and attained age as simultaneous time scales. The age range of individuals included in this analysis is 30–80 years old and the longest interval between fracture and end of follow-up was 46 years. Each time scale was split, for precision, into a number of time intervals with one year intervals for attained age and one month intervals for time since fracture. These expanded data were then collapsed, into the same size blocks, according to covariate patterns (sex and education level) and both time scales to give the number of events and total person time within each combination of the covariates and time-intervals. Models were further adjusted for sex and education. These models yielded hazard ratios (HRs) and 95% confidence intervals (CIs). Restricted cubic splines were used to model both attained age (5 knots; placed at the quantile of the variable) and time since fracture (5 knots; placed at the quantile of the variable). Sensitivity analyses were conducted using different numbers of knots for the restricted cubic splines; this procedure changed the association of fracture with ALS only minimally, so only results using 5 knots are presented.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, North Carolina, USA) and Stata v.13 (StataCorp, College Station, TX, USA).

RESULTS

The cohort had similar proportions of men and women, and most individuals had received at most 12 years of schooling (Table 1). ALS risk was lower in women and higher among those with a graduate education (Table 1).

With attained age as the time scale, ALS was positively associated with all fractures (HR: 1.48, 95% CI: 1.36, 1.61), with osteoporotic fractures (HR: 1.53, 95% CI: 1.35, 1.72), with non-osteoporotic fractures (HR: 1.45, 95% CI: 1.30, 1.61), with traumatic fractures (HR: 1.46, 95% CI: 1.34, 1.59), and with non-traumatic fractures (HR: 1.75, 95% CI: 1.31, 2.33) (Table 2). Following additional adjustment for sex and education level, increased risk of ALS remained associated with all categories of fracture (Table 2). For subcategories of fracture (osteoporotic and non-osteoporotic; traumatic and non-traumatic), as well as fracture as a whole, associations with ALS risk were stronger during the first five years after fracture but risk was also elevated in the period more than five years after fracture (except for fractures not related to trauma) (data not shown). Results were similar in additional analysis delaying entry into the cohort by two years (for all fracture, HR: 1.51, 95% CI: 1.38–1.64) or ten years (HR 1.44, 95% CI 1.31, 1.59).

ALS risk varied with time after fracture (Figure 1, Table 3). The association was largest immediately after fracture (1-year estimate: HR: 2.33, 95% CI: 2.04–2.66) and then declined (Figure 1, Table 3). Risk remained significantly elevated until 18 years after fracture (HR: 1.20, 95% CI: 1.01–1.43) (Figure 1, Table 3).

DISCUSSION

In this prospective analysis, we found a positive association between fracture and ALS incidence. The association was present for both osteoporotic and non-osteoporotic and both traumatic and non-traumatic fractures. While falls due to prodromal ALS may explain the association of ALS with fractures occurring shortly before diagnosis, they are unlikely to explain the association with fractures occurring long before diagnosis. Furthermore, similar results were obtained in analyses lagged by two or ten years.

Fourteen case-control studies have considered the association of fracture with ALS (see Supplemental Table 1 for details) (2–15). These studies evaluated either ALS alone or motor neuron disease including both ALS and progressive muscular atrophy. Only six studies had 100 or more cases (3, 10, 12–14, 15), and three (4, 8, 11) had fewer than 60. Sources of controls included the general population; neurological and non-neurological patients in the hospital or medical practice providing cases; and friends and neighbors of cases (Supplemental Table 1). The last choice of controls may lead to overmatching, potentially explaining the lack of an ALS-fracture association in the two studies that used this approach (6, 8). Most studies used self-administered questionnaires or structured interviews as a source of information on fractures (Supplemental Table 1), but a study that compared information obtained through self-report with information from medical records, found good agreement and no indication that cases were more likely than controls to exaggerate the number of fractures they had experienced (10). Three studies relied on medical or

administrative records; two of these found positive associations (3, 13) and one found no association (15). In general, studies evaluated fractures at all sites combined; those that examined fracture by site found no variation in the association with ALS (4, 6, 8, 12). Two studies that considered multiple fractures found results similar to any fracture, either a positive association (4) or no association (10). Three studies that evaluated fracture only in combination with other forms of trauma found no association with ALS (7, 8, 15). To address concerns about reverse causation, two studies evaluated fractures that occurred before ALS symptom onset; both found associations with ALS (2, 10). One study found that cases were younger than controls at the time of their first fracture (11). It is difficult to make generalizations on the basis of studies using such varied approaches, but it is worth noting that of the seven most informative studies – those that had at least 60 cases, were unlikely to involve overmatched controls, and considered fracture separately from trauma – five found positive associations of fracture with ALS (2, 3, 10, 13, 14), while two did not (9, 12).

Our study is unique in its evaluation of fractures potentially related to poor bone health and separate from those related to trauma. Previous studies have suggested that bone health was poor in ALS patients (2, 19–21), and we found that ALS was associated with increased bone turnover assessed with blood biomarkers (18). Osteoporosis may be related to several neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease as well as ALS (32). Both hyperparathyroidism (19, 21, 33) and vitamin D deficiency (19, 21, 34, 35) may be present in ALS patients. While correction of hyperparathyroidism did not alter disease course in five patients (33), supplementation with vitamin D delayed the decline in the ALSFRS-R score in two studies (34, 35) and improved motor function although not lifespan in G93A SOD1 transgenic mice (36). However, although vitamin D affects several mechanisms likely to play a role in ALS (37), evidence that supplementation can affect the course of disease after diagnosis is limited (39). We found little evidence that fractures potentially related to poor bone health, either osteoporotic or nontraumatic fractures, were more likely than others to be associated with ALS.

It seems unlikely that fractures are directly related to ALS. Rather some other factors may contribute to increased risk of both fracture and ALS. One possibility is lead, which may be a risk factor for ALS (18, 39). The majority of the body burden of lead is in bone. Lead can be mobilized from bone during periods of increased bone turnover or demineralization, and bone lead may be a major source of blood lead in individuals with low exogenous exposure (40–42). Interestingly, lead can also promote increased bone turnover and demineralization, leading to a positive feedback cycle: rat and human studies have found that lead exposure is associated with decreased bone strength, decreased bone mineral density, and depression of bone formation (43–45). Thus increased bone turnover and demineralization could result in increased blood lead, which could in turn increase ALS risk as well as further bone turnover and demineralization. Fractures might simply be an indicator of an increase in bone turnover and demineralization.

Like all studies, ours had limitations. Fractures and ALS in Sweden are treated at hospitals, outpatient services and within primary care services. We have no data from the primary care services, and within the NPR ALS, fractures, and accidents may have been misclassified. In particular, we may have missed fractures occurring before 1987, when nationwide coverage

of the NPR became complete; nondifferential misclassification of fractures occurring long before ALS diagnosis may have weakened the apparent association. However, similar results were found in an analysis restricting cases to those diagnosed in 1997 or later, whose past fractures are less likely to have been missed. A further limitation is the lack of clinical data to evaluate whether fractures were related to features of ALS like site of onset or degree of disability. Due to limitations of the register data, we were unable to evaluate multiple fractures, and we lacked information on other potentially confounding factors such as smoking, vitamin D, and body mass index.

This cohort study had several strengths. Our sample was large and population-based, and we used objective data from the Swedish national population and health registers to identify both ALS and fractures. We conducted a prospective analysis and considered first incident cases of both fracture and ALS, allowing us to evaluate the temporal relationship of the two. This strategy also allowed identification of fractures not likely related to prodromal ALS, specifically those occurring five or more years before ALS diagnosis.

In conclusion, we found different types of fractures to be associated with increased incidence of ALS. While the association of ALS with fractures occurring up to five years before diagnosis may be due to reverse causation, the association with those occurring more than five years before diagnosis suggests that bone changes may be related to ALS and may offer insight into its pathophysiological mechanisms. Additional studies exploring the relationship of poor bone health to ALS would be of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by Swedish Research Council (SIMSAM grant no. 80748301 and grant no. 2015-03170), the Swedish Research Council for Health, Working life, and Welfare (grant no. 2011-0172), the Karolinska Institutet, the Swedish Society of Medical Research, the National Institutes of Health/Karolinska Institutet graduate partnership program, the Intramural Research Program of National Institutes of Health, National Institute of Environmental Health Sciences (Z01-ES-049005), and the EU Joint Programme - Neurodegenerative Disease Research (JPND) project (www.jpnd.eu).

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. [PubMed: 24126629]
2. Campbell AM, Williams ER, Barltrop D. Motor neurone disease and exposure to lead. *J Neurol Neurosurg Psychiatr*. 1970; 33:877–85. [PubMed: 5497881]
3. Kurtzke JF, Beebe GW. Epidemiology of amyotrophic lateral sclerosis: 1. A case-control comparison based on ALS deaths. *Neurology*. 1980; 30:453–62. [PubMed: 7189251]
4. Angelini C, Armani M, Bresolin N. Incidence and risk factors of motor neuron disease in the Venice and Padua districts of Italy, 1972–1979. *Neuroepidemiology*. 1983; 2:236–42.
5. Gawel M, Zaiwalla Z, Rose FC. Antecedent events in motor neuron disease. *J Neurol Neurosurg Psychiatr*. 1983; 46:1041–3. [PubMed: 6655478]
6. Gresham LS, Molgaard CA, Golbeck AL, Smith R. Amyotrophic lateral sclerosis and occupational heavy metal exposure: a case-control study. *Neuroepidemiology*. 1986; 5:29–38. [PubMed: 3748267]

7. 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; 38:1604–8. [PubMed: 3419606]
8. Savettieri G, Salemi G, Arcara A, Cassata M, Castiglione MG, Fierro B. A case-control study of amyotrophic lateral sclerosis. *Neuroepidemiology*. 1991; 10:242–5. [PubMed: 1798425]
9. Gunnarsson LG, Bodin L, Soderfeldt B, Axelsson O. A case-control study of motor neurone disease: its relation to heritability, and occupational exposures, particularly to solvents. *Br J Ind Med*. 1992; 49:791–8. [PubMed: 1463680]
10. Chancellor AM, Slattery JM, Fraser H, Warlow CP. Risk factors for motor neuron disease: a case-control study based on patients from the Scottish Motor Neuron Disease Register. *J Neurol Neurosurg Psychiatr*. 1993; 56:1200–6. [PubMed: 8229031]
11. Strickland D, Smith SA, Dolliff G, Goldman L, Roelofs RI. Physical activity, trauma, and ALS: a case-control study. *Acta Neurol Scand*. 1996; 94:45–50. [PubMed: 8874593]
12. Cruz DC, Nelson LM, McGuire V, Longstreth WT Jr. Physical trauma and family history of neurodegenerative diseases in amyotrophic lateral sclerosis: a population-based case-control study. *Neuroepidemiology*. 1999; 18:101–10. [PubMed: 10023133]
13. Kihira T, Kanno S, Miwa H, Okamoto K, Kondo T. The role of exogenous risk factors in amyotrophic lateral sclerosis in Wakayama, Japan. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2007; 8:150–6.
14. Pupillo E, Messina P, Logroscino G, Zoccolella S, Chio A, Calvo A, et al. Trauma and amyotrophic lateral sclerosis: a case-control study from a population-based registry. *Eur J Neurol*. 2012; 19:1509–17. [PubMed: 22537412]
15. 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*. 2015; 183:294–301.
16. van Geel TA, van den Bergh JP, Dinant GJ, Geusens PP. Individualizing fracture risk prediction. *Maturitas*. 2010; 65:143–8. [PubMed: 20053513]
17. Ensrud KE. Epidemiology of fracture risk with advancing age. *J Gerontol A Biol Sci Med Sci*. 2013; 68:1236–42. [PubMed: 23833201]
18. Fang F, Kwee LC, Allen KD, Umbach DM, Ye W, Watson M, et al. Association between blood lead and the risk of amyotrophic lateral sclerosis. *Am J Epidemiol*. 2010; 171:1126–33. [PubMed: 20406759]
19. Mallette LE, Patten B, Cook JD, Engel WK. Calcium metabolism in amyotrophic lateral sclerosis. *Dis Nerv Syst*. 1977; 38:457–61. [PubMed: 862504]
20. Melmed S, Braunstein GD. Endocrine function in amyotrophic lateral sclerosis. A review. *Neurol Clin*. 1987; 5:33–42. [PubMed: 3550415]
21. Sato Y, Honda Y, Asoh T, Kikuyama M, Oizumi K. Hypovitaminosis D and decreased bone mineral density in amyotrophic lateral sclerosis. *Eur Neurol*. 1997; 37:225–9. [PubMed: 9208262]
22. Johnson JO, Mandrioli J, Benatar M, Abramzon Y, Van Deerlin VM, Trojanowski JQ, et al. Exome sequencing reveals VCP mutations as a cause of familial ALS. *Neuron*. 2010; 68:857–64. [PubMed: 21145000]
23. Lagerlund M, Bellocchio R, Karlsson P, Tejler G, Lambe M. Socio-economic factors and breast cancer survival—a population-based cohort study (Sweden). *Cancer Causes Control*. 2005; 16:419–30. [PubMed: 15953984]
24. Ludvigsson JF, Andersson E, Ekblom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011; 11:450. [PubMed: 21658213]
25. Statistics Sweden. The Swedish register of education [Internet]. Sweden: Statistics Sweden; 2004. [updated 2004 December 23; cited 2016 November 17]. Available from: http://www.scb.se/statistik/UF/UF0506/Produktbeskrivning_short_English_UF0506_20040101r.doc
26. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol*. 2016; 31:125–36. [PubMed: 26769609]
27. Kurian KM, Forbes RB, Colville S, Swingler RJ. Cause of death and clinical grading criteria in a cohort of amyotrophic lateral sclerosis cases undergoing autopsy from the Scottish Motor Neurone Disease Register. *J Neurol Neurosurg Psychiatr*. 2009; 80:84–7. [PubMed: 19091712]

28. St Germaine-Smith C, Metcalfe A, Pringsheim T, Roberts JI, Beck CA, Hemmelgarn BR, et al. Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. *Neurology*. 2012; 79:1049–55. [PubMed: 22914826]
29. Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. *Mol Cell Neurosci*. 2015; 55:75–80.
30. Brennan SL, Holloway KL, Williams LJ, Kotowicz MA, Bucki-Smith G, Moloney DJ, et al. The social gradient of fractures at any skeletal site in men and women: data from the Geelong Osteoporosis Study Fracture Grid. *Osteoporos Int*. 2015; 26:1351–9. [PubMed: 25572043]
31. Sutedja NA, Veldink JH, Fischer K, Kromhout H, Wokke JH, Huisman MH, et al. Lifetime occupation, education, smoking, and risk of ALS. *Neurology*. 2007; 69:1508–14. [PubMed: 17923612]
32. Roos PM. Osteoporosis in neurodegeneration. *J Trace Elem Med Biol*. 2014; 28:418–21. [PubMed: 25220531]
33. Jackson CE, Amato AA, Bryan WW, Wolfe GI, Sakhaee K, Barohn RJ. Primary hyperparathyroidism and ALS: is there a relation? *Neurology*. 1998; 50:1795–9. [PubMed: 9633730]
34. Karam C, Barrett MJ, Imperato T, MacGowan DJ, Scelsa S. Vitamin D deficiency and its supplementation in patients with amyotrophic lateral sclerosis. *J Clin Neurosci*. 2013; 20:1550–3. [PubMed: 23815870]
35. Camu W, Tremblier B, Plassot C, Alphandery S, Salsac C, Pageot N, et al. Vitamin D confers protection to motoneurons and is a prognostic factor of amyotrophic lateral sclerosis. *Neurobiol Aging*. 2014; 35:1198–205. [PubMed: 24378089]
36. Gianforcaro A, Hamadeh MJ. Dietary vitamin D3 supplementation at 10x the adequate intake improves functional capacity in the G93A transgenic mouse model of ALS, a pilot study. *CNS Neurosci Ther*. 2012; 18:547–57. [PubMed: 22591278]
37. Long, Kv, Nguyen, LT. Roles of vitamin D in amyotrophic lateral sclerosis: possible genetic and cellular signaling mechanisms. *Mol Brain*. 2013; 6:16. [PubMed: 23570271]
38. ALS Untangled No. 24: Vitamin D. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014; 15:318–20. [PubMed: 24689759]
39. Kamel F, Umbach DM, Hu H, Munsat TL, Shefner JM, Taylor JA, et al. Lead exposure as a risk factor for amyotrophic lateral sclerosis. *Neurodegener Dis*. 2005; 2:195–201. [PubMed: 16909025]
40. Hu H, Payton M, Korrick S, Aro A, Sparrow D, Weiss ST, et al. Determinants of bone and blood lead levels among community-exposed middle-aged to elderly men. The normative aging study. *Am J Epidemiol*. 1996; 144:749–59. [PubMed: 8857824]
41. Nash D, Magder LS, Sherwin R, Rubin RJ, Silbergeld EK. Bone density-related predictors of blood lead level among peri- and postmenopausal women in the United States: The Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol*. 2004; 160:901–11. [PubMed: 15496543]
42. Gulson BL, Mizon KJ, Korsch MJ, Palmer JM, Donnelly JB. Mobilization of lead from human bone tissue during pregnancy and lactation--a summary of long-term research. *Sci Total Environ*. 2003; 303:79–104. [PubMed: 12568766]
43. Escribano A, Revilla M, Hernandez ER, Seco C, Gonzalez-Riola J, Villa LF, et al. Effect of lead on bone development and bone mass: a morphometric, densitometric, and histomorphometric study in growing rats. *Calcif Tissue Int*. 1997; 60:200–3. [PubMed: 9056171]
44. Beier EE, Maher JR, Sheu TJ, Cory-Slechta DA, Berger AJ, Zuscik MJ, et al. Heavy metal lead exposure, osteoporotic-like phenotype in an animal model, and depression of Wnt signaling. *Environ Health Perspect*. 2013; 121:97–104. [PubMed: 23086611]
45. Campbell JR, Rosier RN, Novotny L, Puzas JE. The association between environmental lead exposure and bone density in children. *Environ Health Perspect*. 2004; 112:1200–3. [PubMed: 15289167]

Fig. 1.

Hazard ratios (HR) with 95% confidence limits plotted by time since fracture. The model is adjusted for sex and education level. Underlying time scales are time since fracture and attained age.

Table 1

Characteristics of the Study Population and ALS Cases in Sweden, 1987 – 2010

	ALS Cases n=4,797	Total Population ^a n=4,362,214	Person-time (years)	IR	Incidence Rate per 100,000 Person-years	HR ^a	95% CI
Age at entry, mean (median), years		53 (52)					
Age at exit, mean (median), years		71 (72)					
Sex, No. (%)							
Male ^b	2,736 (57)	2,143,176 (49)	38,002,070	7.20	6.93, 7.47	1.00	
Female	2,061 (43)	2,219,038 (51)	39,472,120	5.22	5.00, 5.45	0.67	0.64, 0.71
Highest level of education, No. (%)							
9 Years of Schooling	2,292 (49)	1,911,454 (47)	32,060,070	7.15	6.86, 7.45	0.86	0.80, 0.91
10–12 Years of Schooling ^b	1,610 (34)	1,402,740 (35)	28,651,540	5.62	5.35, 5.90	1.00	
University Degree	749 (16)	701,900 (17)	15,137,910	4.95	4.61, 5.32	1.01	0.93, 1.10
Doctoral Studies	39 (1)	22,094 (1)	460,490	8.47	6.19, 11.59	1.43	1.04, 1.96
Missing	107	324,026					

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

^aHR and 95% CI estimated from a Cox regression model with attained age as the time-scale.

^bReference

Table 2

Types of Fracture and Risk of ALS within Sweden, 1987 – 2010

	ALS Cases n=4,690	Total Population n=4,038,188	Person-time (years)	Incidence Rate per 100,000 Person-years			
				IR	95% CI	HR ^a	95% CI
All Fractures (minus head and face)							
Unexposed ^c	4,134	4,193,005	71,641,300	5.77	5.60, 5.95	1.00	1.00
Exposed	663	727,563	5,832,890	11.37	10.53, 12.27	1.48	1.36, 1.61
Type of Fracture							
Unexposed ^c	4,134	4,193,005	71,641,300	5.77	5.60, 5.95	1.00	1.00
Osteoporotic fractures	294	343,114	2,193,030	13.41	11.96, 15.03	1.53	1.35, 1.72
Other Fractures	369	384,449	3,639,860	10.14	9.15, 11.23	1.45	1.30, 1.61
Fractures related to trauma							
Unexposed ^c	4,134	4,193,005	71,641,300	5.77	5.60, 5.95	1.00	1.00
Traumatic fractures	616	677,003	5,467,320	11.27	10.41, 12.19	1.46	1.34, 1.59
Nontraumatic fractures	47	50,560	365,570	12.86	9.66, 17.11	1.75	1.31, 2.33

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

^aHR and 95% CI estimated from a Cox regression model with attained age as the time-scale.^bHR and 95% CI estimated from a Cox regression model with attained age as the time-scale and adjustment for sex and education.^cReference.

Table 3

Hazard ratios (HR) and 95% confidence intervals (CI) corresponding to Figure 1

Time Since Fracture (years)	HR (95% CI)
No fracture	1.00
1 year	2.33 (2.04 – 2.66)
2 years	1.76 (1.51 – 2.05)
5 years	1.40 (1.22 – 1.59)
10 years	1.33 (1.14 – 1.54)
18 years	1.19 (1.01 – 1.43)
20 years	1.19 (0.99 – 1.43)
30 years	1.23 (0.96 – 1.57)
46 years	1.52 (0.62 – 3.74)