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Neurodegenerative and psychiatric diseases among families with amyotrophic lateral sclerosis

Authors: Elisa Longinetti, MSc, Daniela Mariosa, MSc, Henrik Larsson, PhD, Weimin Ye, MD, PhD, Caroline Ingre, MD, PhD, Catarina Almqvist, MD, PhD, Paul Lichtenstein, PhD, Fredrik Piehl, MD, PhD, Fang Fang, MD, PhD

Elisa Longinetti, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

Daniela Mariosa, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

Henrik Larsson, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, and Department of Medical Sciences, Örebro University

Weimin Ye, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

Caroline Ingre, Department of Clinical Neuroscience, Karolinska Institutet

Catarina Almqvist, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, and Astrid Lindgren Children's Hospital, Lung and Allergy Unit, Karolinska University Hospital

Paul Lichtenstein, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

Fredrik Piehl, Department of Clinical Neuroscience, Karolinska Institutet

Fang Fang, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

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Supplemental data: International Classification of Diseases (ICD) codes used to identify amyotrophic lateral sclerosis (ALS), neurodegenerative diseases, and psychiatric disorders in the Swedish Patient Register, Table e-1; Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their matched ALS-free controls show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases after ALS diagnosis (hazard ratios); follow-up stopped at 69 years, Table e-2; Adjusted associations for age, sex, and county of birth among relatives of patients with amyotrophic lateral sclerosis (ALS) and relatives of their matched ALS-free controls do not show clear temporal pattern in the associations of ALS with neurodegenerative and psychiatric diseases, Table e-3; Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their relatives, compared to ALS-free individuals, show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among ALS patients, of neurodegenerative diseases among siblings of ALS patients, and of psychiatric disorders among children of ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis; separate analysis for males, Table e-4; Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their relatives, compared to ALS-free individuals, show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among ALS patients, and of neurodegenerative diseases among siblings of ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis; separate analysis for females, Table e-5; Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their relatives, compared to ALS-free individuals, show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among ALS patients, and of psychiatric disorders among children of ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis; separate analysis for individuals ≤55 years, Table e-6; Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their relatives, compared to ALS-free individuals, show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among ALS patients,

and of neurodegenerative diseases among siblings of ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis; separate analyses for individuals ≥56 years, Table e-7; Adjusted associations for age, sex, and county of birth among patients with familial amyotrophic lateral sclerosis (ALS) and their matched ALS-free controls show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among familial ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis, Table e-8; Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their matched ALS-free controls show a higher-than-expected occurrence of neurodegenerative diseases among ALS patients, even after excluding frontotemporal dementia from the definition of neurodegenerative diseases, Table e-9.

Corresponding author:

Elisa Longinetti

Department of Medical Epidemiology and Biostatistics

Karolinska Institutet, SE-17177

Stockholm, Sweden

Phone +46(0)8-52482731

Fax: +46 (0)8-31 11 01

elisa.longinetti@ki.se

Elisa Longinetti – elisa.longinetti@ki.se

Daniela Mariosa – daniela.mariosa@ki.se

Henrik Larsson – henrik.larsson@ki.se

Weimin Ye – weimin.ye@ki.se

Caroline Ingre – caroline.ingre@ki.se

Catarina Almqvist – catarina.almqvist@ki.se

Paul Lichtenstein – paul.lichtenstein@ki.se

Fredrik Piehl – fredrik.piehl@ki.se

Fang Fang – fang.fang@ki.se

Statistical Analysis conducted by: Elisa Longinetti, MSc, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

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Author Contributions:

Elisa Longinetti, study concept and design, data analysis and interpretation, first drafting of the manuscript, critical revision of the manuscript for important intellectual content.

Daniela Mariosa, study concept and design, data analysis and interpretation, critical revision of the manuscript for important intellectual content.

Henrik Larsson, critical revision of the manuscript for important intellectual content

Weimin Ye, critical revision of the manuscript for important intellectual content

Caroline Ingre, critical revision of the manuscript for important intellectual content

Catarina Almqvist, critical revision of the manuscript for important intellectual content

Paul Lichtenstein, critical revision of the manuscript for important intellectual content

Fredrik Piehl, study concept and design, data analysis and interpretation, critical revision of the manuscript for important intellectual content

Fang Fang, study concept and design, data analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision

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Abstract

Objective: To estimate risks of neurodegenerative and psychiatric diseases among patients with amyotrophic lateral sclerosis (ALS) and their families.

Methods: We conducted a register-based nested case-control study during 1990-2013 in Sweden to assess whether ALS patients had higher risks of other neurodegenerative and psychiatric diseases before diagnosis. We included 3,648 ALS patients and 36,480 age-, sex-, and county-of-birth matched population controls. We further conducted a follow-up study of the cases and controls to assess the risks of other neurodegenerative and psychiatric diseases after ALS diagnosis. To assess the potential contribution of familial factors, we conducted similar studies for the relatives of ALS patients and their controls.

Results: Individuals with previous neurodegenerative or psychiatric diseases had a 49% increased risk of ALS (odds ratio=1.49, 95% confidence interval=1.35-1.66), compared to individuals without these diseases. After diagnosis, ALS patients had increased risks of other neurodegenerative or psychiatric diseases (hazard ratio=2.90, 95% confidence interval=2.46-3.43), compared to individuals without ALS. The strongest associations were noted for frontotemporal dementia, Parkinson's disease, other dementia, Alzheimer's disease, neurotic disorders, depression, stress-related disorders, and drug abuse/dependence. First-degree relatives of ALS patients had higher risk of neurodegenerative diseases, whereas only children of ALS patients had higher risk of psychiatric disorders, compared to relatives of the controls.

Conclusions: Familial aggregation of ALS and other neurodegenerative diseases implies a shared etiopathogenesis among all neurodegenerative diseases. The increased risk of psychiatric disorders among ALS patients and their children might be attributable to non-motor symptoms of ALS and severe stress response toward the diagnosis.

Introduction

Amyotrophic lateral sclerosis (ALS) overlaps clinically and pathologically with other neurodegenerative diseases [1-5]. Family members of ALS patients have also been reported to have increased risks of dementia and Parkinson's disease (PD) [6, 7], further supporting the hypothesis of a shared etiopathogenesis between ALS and other neurodegenerative diseases [6, 8, 9]. Increased risk of psychiatric disorders has been suggested

among patients with ALS in some but not all studies [10-12] and little is known for the risk of psychiatric disorders among families of ALS patients [6]. We performed therefore a nationwide register-based study in Sweden to estimate the risk of neurodegenerative and psychiatric diseases among patients with ALS and their family members.

Methods

Study base

The Swedish Multi-Generation Register includes information on familial links for all individuals born in Sweden since 1932 [13]. We defined our study population as all individuals included in this register that were born in Sweden during 1932-2013 (N=8,575,515). Using the unique personal identification numbers assigned to all Swedish residents [14], we followed the study population from January 1st 1990 or date of birth, whichever came later, until date of ALS diagnosis, death, emigration out of Sweden, or December 31st 2013, whichever came first, through cross-linkages to the Swedish Patient Register, Causes of Death Register, and Migration Register. The Patient Register collects data on hospital discharge records in Sweden since 1964 and has a nationwide coverage since 1987 [14]. Since 2001 it also collects data on hospital-based outpatient specialist care. Diagnoses from each hospital visit are classified according to the Swedish Revisions of the International Classification of Disease (ICD) codes (ICD-7 before 1969, ICD-8 during 1969-1986, ICD-9 during 1987-1996, and ICD-10 from 1997). We identified all newly diagnosed ALS cases during follow-up through the Patient Register, indicated by a hospital visit concerning ALS, and defined the first hospital visit as ALS diagnosis date. We ascertained date of death from the Causes of Death Register and date of first emigration out of Sweden from the Migration Register. We excluded individuals that had been diagnosed with ALS (N=662), died (N=120,612), or emigrated out of Sweden (N=186,670) before the beginning of follow-up, leaving 8,269,319 (96%) participants in the study base.

Nested case-control study I

We conducted a nested case-control study within the above study base to assess the association of previous neurodegenerative and psychiatric diseases with the subsequent ALS risk. We defined cases as individuals diagnosed with ALS during follow-up (ICD-9 code 335C, ICD-10 code G12.2; N=3,648). For each index case we randomly selected 10 controls from the study base, by incidence density sampling, and individually matched the controls to the cases by year and month of birth, sex, and county of birth (N=36,480). Eligible controls had to be alive, living in Sweden, and ALS-free, at the time of the diagnosis of the index case.

Nested case-control study II

To investigate whether relatives of ALS patients had increased risk of neurodegenerative and psychiatric diseases before the diagnosis of the proband ALS patient, we conducted a second nested case-control study, including relatives of the index ALS patients and their matched controls. We identified parents, full siblings, half-siblings, and children of the index cases and controls from the Multi-Generation Register and used them as cases and controls for the nested case-control study II. We used the index dates of the index cases and controls as the index dates for the respective relatives. We excluded from the analyses relatives that had died or emigrated out of Sweden before the index date.

Follow-up studies

To examine the relative risks of neurodegenerative and psychiatric diseases after ALS diagnosis we prospectively followed the above nested case-control studies from the index date. In these analyses, we included only individuals without any neurodegenerative or psychiatric diseases diagnosed prior to the index dates, leading to 3,169 ALS cases and 33,110 controls in the follow-up study of nested case-control study I, and 13,313 relatives of ALS patients and 130,321 relatives of the index controls in the follow-up study of the nested case-control study II. We followed all individuals from the index date to the date of first diagnosis of neurodegenerative or psychiatric diseases, death, emigration out of Sweden, or December 31st 2013, whichever came first.

Ascertainment of neurodegenerative and psychiatric diseases

Neurodegenerative diseases examined in this study included frontotemporal dementia (FTD), Alzheimer's disease (AD), other or unspecific dementia, and PD, because we had previously reported risk of ALS among relatives of ALS patients [15]. Psychiatric disorders examined in this study included schizophrenia, bipolar disorder, depression, neurotic disorders, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence. We defined a diagnosis of these diseases through a hospital visit concerning the specific disease as recorded in the Patient Register and used the date of first hospital visit as the diagnosis date. Because the Patient Register achieved good coverage on psychiatric diagnoses in 1973 [16], we ascertained the diagnoses of neurodegenerative and psychiatric diseases from 1973 until the index date for the nested case-control studies and from the index date until the end of follow-up for the follow-up studies. A list of the corresponding ICD codes is provided in Table e-1.

Statistical analysis

In the nested-case control studies, we estimated odds ratios (ORs) of ALS (or becoming a relative of an ALS patient) and corresponding 95% confidence intervals (CIs) using conditional logistic regression, as measures of the associations between previous neurodegenerative or psychiatric diseases and the subsequent ALS risk. Because cases and controls were individually matched by year and month of birth, sex, and county of birth in the nested case-control study I, these variables were automatically adjusted for in the analyses. In the nested case-control study II, we adjusted all models for year and month of birth, sex, and county of birth of the relatives as well as of the proband individuals.

In the follow-up studies, we fitted Cox proportional hazard regression to derive hazard ratios (HRs) for the future risk of neurodegenerative and psychiatric diseases, comparing ALS patients to their controls and the relatives of ALS patients to the relatives of the index controls. We used attained age as the underlying time scale and further adjusted all models for sex and county of birth. We tested the assumption of proportional hazards using Schoenfeld residuals.

In addition to the overall analyses, we separately analyzed specific time windows in the nested case-control studies and the follow-up studies (≥6 years, 2-5 years, or 0-1 year before and after the index date). The period ≤1 year before ALS diagnosis might be representative of a time period of symptoms onset and clinical diagnostic workup.

To assess the potential influence of age and sex on the studied associations, we separately analyzed men and women and individuals at age ≤ 55 and at age ≥ 56. Because familial ALS cases might have different association with other neurodegenerative diseases, compared to sporadic ALS cases, we separately analyzed ALS cases with a family history. By cross-linking the nested case-control study I to the Multi-Generation Register, we identified grandparents, parents, uncles/aunts, full and half siblings, children, nephews/nieces, as well as grandchildren of ALS cases and their corresponding controls. We then linked these relatives to the Patient Register to obtain ALS diagnosis among them and defined a family history of ALS as having at least one of these relatives diagnosed with ALS until the end of 2013.

To investigate if misdiagnosis of neurodegenerative diseases might explain some of the associations between other neurodegenerative diseases and ALS, we conducted an additional analysis by restricting the definition of ALS and other neurodegenerative diseases to patients with at least two hospital visits concerning respective diseases. Given the established ALS/FTD overlap [17], we additionally assessed the risk of other neurodegenerative diseases among ALS patients after excluding FTD from the definition of neurodegenerative diseases. Finally, as depression, neurotic disorders, and stress-related disorders might represent collectively the psychological burden of ALS symptoms and diagnosis on ALS patients and their families, we analyzed the risk of having depression, neurotic disorders, or stress-related disorders before and after ALS diagnosis.

We considered statistically significant associations with a two-sided p-value ≤0.05. We performed analyses using Stata software, version 14 (StataCorp. 2015, College Station, TX: StataCorp LP).

Standard Protocol Approvals, Registrations, and Patient Consents

The Regional Ethical Review Board in Stockholm, Sweden, approved this study.

Results

Table 1 shows the sex and age distributions of ALS cases, their controls, and the relatives of both groups. The mean age at diagnosis of ALS patients was 60 years (standard deviation=11.30).

Both before and after the index date, we found higher risks for all neurodegenerative diseases studied and for depression, neurotic disorders, and drug abuse/dependence among ALS patients, compared to controls (Table 2). The associations were strongest for FTD, followed by PD, other or unspecific dementia, and AD. Because the proportional hazards assumption was violated after age 68 in the analyses of any neurodegenerative disease and other or unspecific dementia, we restricted these analyses to attained age <69 years and found largely similar results (Table e-2).

Overall, parents, siblings, and children of ALS patients had higher risk of neurodegenerative diseases, both before and after the index date, compared to relatives of ALS-free individuals, although the associations were only statistically significant for siblings (Table 3). Children of ALS cases had higher risks of psychiatric disorders both before and after the index date, compared to children of the controls.

The associations of FTD, AD, other or unspecific dementia, PD, depression, neurotic disorders, and drug abuse/dependence with the subsequent ALS risk appeared to be strongest during the year before ALS diagnosis, although we also noted positive associations during 2-5 years before diagnosis (Table 4). We

observed further positive associations for schizophrenia and stress-related disorders during the year before ALS diagnosis. We noted similar patterns for the associations of ALS with the subsequent risks of neurodegenerative or psychiatric diseases, with the strongest association during the first year after diagnosis, followed by 2-5 years after diagnosis (Table 4). ALS patients had also an increased risk of stress-related disorders after diagnosis, especially during the first year. A clear temporal pattern was however not identified for the analyses of the relatives (Table e-3).

All results of the main analyses appeared comparable between males and females (Tables e-4-5) and between individuals younger or older than 55 years (Tables e-6-7). We identified a total of 173 ALS patients with a family history of ALS (3.9%); separate analysis of these familial ALS cases generally provided similar results as in the main analyses (Table e-8).

Among the 3,648 cases of ALS in our study, 3,048 had at least two hospital records concerning ALS, and among the 600 cases with only one record, 246 had ALS as a cause of death in the Causes of Death Register. Restricting the definition of ALS and other neurodegenerative diseases to patients with at least two hospital visits concerning respective diseases slightly attenuated the associations between other neurodegenerative diseases and ALS both prior (OR=2.02, 95% CI=1.48-2.77) and after (HR=3.27, 95% CI=2.14-5.00) ALS diagnosis. Excluding FTD from the definition of neurodegenerative diseases attenuated also slightly the associations of ALS with other neurodegenerative diseases in the overall analyses (prior to index date, OR=3.34, 95% CI=2.68-4.16; after index date, HR=3.88, 95% CI=2.87-5.26) and the temporal pattern analyses (Table e-9).

The risk of having depression, neurotic disorders, or stress-related disorders was significantly higher among ALS patients, compared to controls, both before (OR=1.46, 95% CI=1.28-1.66) and after (HR=3.13, 95%

CI=2.50-3.92) ALS diagnosis. The risk increase peaked during the year before (OR=4.87, 95% CI=3.58-6.62) and the year after (HR=5.52, 95% CI=3.93-7.76) ALS diagnosis.

Discussion

Using a nationwide population-based study sample, we found that ALS patients had higher risks of neurodegenerative and psychiatric diseases, both before and after diagnosis. Parents, siblings, and children of ALS patients tended to have increased risk of neurodegenerative diseases, whereas only children of ALS patients had increased risk of psychiatric disorders.

Although previous studies reported increased risks of dementia and PD after ALS diagnosis [3, 4], our study is the first to demonstrate the temporal pattern of the increased risks from years before until years after ALS diagnosis. We further showed that parents, siblings and children of ALS patients tended also to have increased risks of other neurodegenerative diseases, corroborating findings of a recent study in Ireland [6]. Our results lend therefore further support to the hypothesis that shared etiologies or disease mechanisms might underlie different neurodegenerative diseases [6, 8, 9]. Such mechanisms might include shared genetic risk factors [1, 18], leading for example to accumulation of protein aggregates in the brain, a common pathological finding from different neurodegenerative diseases [19]. Non-genetic risk factors such as exposure to agrochemicals and previous head trauma have also been linked to different neurodegenerative diseases [20].

The stronger associations with neurodegenerative diseases noted during the five years before and after ALS diagnosis were not reported previously and might be due to different reasons. Misdiagnosis between ALS and other neurodegenerative diseases could contribute partially to the increased risk of other neurodegenerative diseases among ALS patients. The diagnosis of ALS in the Patient Register appears to have high accuracy because a validation study of 280 patients in Stockholm showed a positive predictive value of 91% for medical records-based ALS diagnosis [21]. Restricting the definition of ALS and other

neurodegenerative diseases to patients with at least two hospital visits concerning respective diseases attenuated slightly, but did not diminish the results, arguing against misdiagnosis as the pure explanation for the observed associations. Furthermore, ALS patients might have been more closely surveyed and more likely to receive a diagnosis of another neurodegenerative disease, compared to ALS-free individuals, leading to a higher-than-expected risk of other neurodegenerative diseases. It is however also possible that some symptoms of other neurodegenerative diseases become under-detected because of the predominant ALS symptoms.

We found an increased risk of psychiatric disorders among ALS patients both before and after diagnosis. The increased risk of depression is in line with previous reports [11, 12]. The increased risks of neurotic disorders and stress-related disorders are not surprising, because depression, neurotic disorders, and stress-related disorders are highly correlated clinically [22].

The stronger associations with psychiatric disorders noted during the five years before and after ALS diagnosis might be due to both non-motor symptoms of ALS and severe stress response toward these symptoms and the final diagnosis. Non-motor symptoms of ALS including cognitive impairment are increasingly recognized [23] and may mimic psychiatric symptoms [24]. The increased risk of depression might partially represent increased prevalence of cognitive impairment among ALS patients. The increased risks of depression, neurotic disorders, and stress-related disorders, peaking during the year before and after ALS diagnosis, might on the other hand collectively suggest a reactive nature of these psychiatric disorders, potentially due to the emotional burden of ALS symptoms and diagnosis.

In line with a previous study that identified an association of schizophrenia with subsequent ALS [11], we noted an increased risk of schizophrenia during the five years before ALS diagnosis although the association

was only statistically significant during the year before diagnosis. A recent GWAS study also suggested a genetic overlap between ALS and schizophrenia [25].

In contrast to previous studies [26-29], we did not find an association between alcohol abuse/dependence and a lower ALS risk. Lack of adjustment for smoking and total energy intake in the present study might partially explain these conflicting results. In accord with the previously suggested association between use of opioids and ALS [30], our study reports a higher risk of drug abuse or dependence (including medicines, cocaine, caffeine, opioids, and cannabis) among ALS patients, both before and after ALS diagnosis. While drug abuse/dependence might be partially secondary to depression and stress-related disorders [31-33], these associations diminished but not disappeared after excluding individuals with concurrent drug abuse/dependence, depression, or stress-related disorders (data not shown).

We observed an increased risk of psychiatric disorders among children, but not siblings or parents, of ALS patients. The vast majority of children of ALS patients that received a psychiatric diagnosis (N=742, 81%) received a diagnosis of depression, neurotic disorders, or stress-related disorders, suggesting that psychological distress was likely the primary reason for such increased risk. This is possibly explained by the fact that children are more involved in caring of ALS patients compared to other relatives [34].

Main strengths of our study are the large sample size and the population-based design. The long-term study period and the complete follow-up, the prospectively collected information, as well as the ability to objectively identify family members and their disease history, represent other main strengths.

We lacked however information on the genetic and clinical characteristics of ALS patients, and were therefore unable to separately analyze different subtypes of ALS. Although the completeness of ALS diagnosis is presumably high in the Swedish Patient Register because all ALS patients are diagnosed by a

specialist, we might have underestimated the prevalence of some neurodegenerative and psychiatric diseases because healthcare provided by general practitioners is not included in the register. The 1% prevalence of FTD among the ALS patients might reflect a lack of FTD detection [35]. Some of the FTD patients might have been misclassified as other dementia, partially accounting for the increased risk of other dementia among ALS patients. Because the vast majority of children of ALS patients were younger than 60 years of age, risk of neurodegenerative diseases at older ages of children needs to be further assessed. Although the clear temporal pattern before and after ALS diagnosis argues against confounding as an important explanation for the noted associations, residual confounding remains a possibility. Finally, whether or not these findings are generalizable to other populations needs to be tested in further studies.

In summary, we found that ALS patients and their first-degree relatives had increased risks of neurodegenerative diseases before and after diagnosis, lending further support to a common etiopathogenesis for different neurodegenerative diseases. The increased risk of psychiatric disorders among ALS patients and their children might be attributable to both the non-motor symptoms of ALS and severe stress response to the progressive symptoms and diagnosis of a fatal disease.

References

1. Andersen PM, Al-Chalabi A. Clinical genetics of amyotrophic lateral sclerosis: what do we really know? Nat Rev Neurol 2011;7:603-615.
2. Cavaleri F. Review of Amyotrophic Lateral Sclerosis, Parkinson's and Alzheimer's diseases helps further define pathology of the novel paradigm for Alzheimer's with heavy metals as primary disease cause. Medical hypotheses 2015;85:779-790.

3. Li X, Sundquist J, Sundquist K. Subsequent risks of Parkinson disease in patients with autoimmune and related disorders: a nationwide epidemiological study from Sweden. Neurodegener Dis 2012;10:277-284.
4. Korner S, Kollewe K, Ilsemann J, et al. Prevalence and prognostic impact of comorbidities in amyotrophic lateral sclerosis. Eur J Neurol 2013;20:647-654.
5. Bradshaw WJ, Rehman S, Pham TT, et al. Structural insights into human angiogenin variants implicated in Parkinson's disease and Amyotrophic Lateral Sclerosis. Scientific reports 2017;7:41996.
6. Byrne S, Heverin M, Elamin M, et al. Aggregation of neurologic and neuropsychiatric disease in amyotrophic lateral sclerosis kindreds: a population-based case-control cohort study of familial and sporadic amyotrophic lateral sclerosis. Annals of neurology 2013;74:699-708.
7. Bryan L, Kaye W, Antao V, Mehta P, Muravov O, Horton DK. Preliminary Results of National Amyotrophic Lateral Sclerosis (ALS) Registry Risk Factor Survey Data. PloS one 2016;11:e0153683.
8. Coppede F, Mancuso M, Siciliano G, Migliore L, Murri L. Genes and the environment in neurodegeneration. Bioscience reports 2006;26:341-367.
9. Fallis BA, Hardiman O. Aggregation of neurodegenerative disease in ALS kindreds. Amyotroph Lateral Scler 2009;10:95-98.
10. Seelen M, van Doormaal PC, Visser A, et al. Prior medical conditions and the risk of amyotrophic lateral sclerosis. J Neurol 2014;261:1949-1956.
11. Turner MR, Goldacre R, Talbot K, Goldacre MJ. Psychiatric disorders prior to amyotrophic lateral sclerosis. Annals of neurology 2016;80:935-938.
12. Roos E, Mariosa D, Ingre C, et al. Depression in amyotrophic lateral sclerosis. Neurology 2016;86:2271-2277.
13. Ekbom A. The Swedish Multi-generation Register. Methods in molecular biology (Clifton, NJ) 2011;675:215-220.
14. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;24:659-667.
15. Fang F, Kamel F, Lichtenstein P, et al. Familial aggregation of amyotrophic lateral sclerosis. Annals of neurology 2009;66:94-99.
16. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC public health 2011;11:450.

17. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. The Lancet Neurology 2007;6:994-1003.
18. Ahmad K, Baig MH, Mushtaq G, Kamal MA, Greig NH, Choi I. Commonalities in biological pathways, genetics, and cellular mechanism between Alzheimer Disease and other neurodegenerative diseases: An in silico-updated overview. Current Alzheimer research 2017.
19. Khanam H, Ali A, Asif M, Shamsuzzaman. Neurodegenerative diseases linked to misfolded proteins and their therapeutic approaches: A review. European journal of medicinal chemistry 2016;124:1121-1141.
20. de Pedro-Cuesta J, Martinez-Martin P, Rabano A, et al. Drivers: A Biologically Contextualized, Cross-Inferential View of the Epidemiology of Neurodegenerative Disorders. Journal of Alzheimer's disease : JAD 2016;51:1003-1022.
21. Mariosa D, Hammar N, Malmström H, et al. Blood biomarkers of carbohydrate, lipid and apolipoprotein metabolism and risk of amyotrophic lateral sclerosis: a more than 20 years follow-up of the Swedish AMORIS cohort. 27th International Symposium on ALS/MND. Dublin, Ireland: Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2016: 25.
22. Elhai JD, de Francisco Carvalho L, Miguel FK, Palmieri PA, Primi R, Christopher Frueh B. Testing whether posttraumatic stress disorder and major depressive disorder are similar or unique constructs. Journal of anxiety disorders 2011;25:404-410.
23. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2009;73:1227-1233.
24. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. The Journal of clinical psychiatry 2011;72:126-133.
25. McLaughlin RL, Schijven D, van Rheenen W, et al. Genetic correlation between amyotrophic lateral sclerosis and schizophrenia. Nature communications 2017;8:14774.
26. Meng E, Yu S, Dou J, et al. Association between alcohol consumption and amyotrophic lateral sclerosis: a meta-analysis of five observational studies. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2016.
27. Huisman MH, Seelen M, van Doormaal PT, et al. Effect of Presymptomatic Body Mass Index and Consumption of Fat and Alcohol on Amyotrophic Lateral Sclerosis. JAMA neurology 2015;72:1155-1162.

28. Ji J, Sundquist J, Sundquist K. Association of alcohol use disorders with amyotrophic lateral sclerosis: a Swedish national cohort study. Eur J Neurol 2016;23:270-275.
29. De Jong SW, Huisman MH, Sutedja NA, et al. Smoking, alcohol consumption, and the risk of amyotrophic lateral sclerosis: a population-based study. American journal of epidemiology 2012:kws015.
30. D'Ovidio F, d'Errico A, Farina E, Calvo A, Costa G, Chio A. Amyotrophic Lateral Sclerosis Incidence and Previous Prescriptions of Drugs for the Nervous System. Neuroepidemiology 2016;47:59-66.
31. Huang B, Dawson DA, Stinson FS, et al. Prevalence, correlates, and comorbidity of nonmedical prescription drug use and drug use disorders in the United States: Results of the National Epidemiologic Survey on Alcohol and Related Conditions. The Journal of clinical psychiatry 2006;67:1062-1073.
32. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama 2003;289:3095-3105.
33. Furnari M, Epstein DH, Phillips KA, et al. Some of the people, some of the time: field evidence for associations and dissociations between stress and drug use. Psychopharmacology 2015;232:3529-3537.
34. Tramonti F, Bongioanni P, Leotta R, Puppi I, Rossi B. Age, gender, kinship and caregiver burden in amyotrophic lateral sclerosis. Psychology, health & medicine 2015;20:41-46.
35. Gislason TB, Ostling S, Borjesson-Hanson A, et al. Effect of diagnostic criteria on prevalence of frontotemporal dementia in the elderly. Alzheimer's & dementia : the journal of the Alzheimer's Association 2015;11:425-433.

Table 1. Characteristics of patients with amyotrophic lateral sclerosis (ALS), their matched ALS-free controls, and the respective relatives of both groups

	N (%)									
	ALS patients	**ALS-free Controls**	**Parents of ALS patients**	**Parents of controls**	**Siblings of ALS patients**	**Siblings of controls**	**Half-siblings of ALS patients**	**Half-siblings of controls**	**Children of ALS patients**	**Children of controls**
Total	3,648	36,480	6,523	65,793	5,593	54,987	662	7,050	6,982	70,964
Sex										
Male	2,185 (59.90)	21,850 (59.90)	3,167 (48.55)	32,130 (48.83)	2,918 (52.17)	28,310 (51.48)	366 (55.29)	3,601 (51.08)	3,561 (51.00)	36,437 (51.35)
Female	1,463 (40.10)	14,630 (40.10)	3,356 (51.45)	33,663 (51.17)	2,675 (47.83)	26,677 (48.52)	296 (44.71)	3,449 (48.92)	3,421 (49.00)	34,527 (48.65)
Age at Index Date										
≤ 60 years	1,575 (43.17)	15,750 (43.17)	197 (3.02)	1,820 (2.77)	3,069 (54.87)	30,173 (54.87)	526 (79.46)	5,563 (78.91)	6,980 (99.97)	70,933 (99.96)
61-65 years	750 (20.56)	7,500 (20.56)	125 (1.92)	1,328 (2.02)	1,105 (19.76)	10,430 (18.97)	69 (10.42)	714 (10.13)	2 (0.03)	31 (0.04)
66-70 years	694 (19.02)	6,940 (19.02)	208 (3.19)	1,970 (2.99)	838 (14.98)	8,200 (14.91)	37 (5.59)	475 (6.74)	0 (0.00)	0 (0.00)
71-75 years	441 (12.09)	4,410 (12.09)	302 (4.63)	3,138 (4.77)	453 (8.10)	4,663 (8.48)	23 (3.47)	229 (3.25)	0 (0.00)	0 (0.00)
≥ 76 years	188 (5.15)	1,880 (5.15)	5,691 (87.25)	57,537 (87.45)	128 (2.29)	1,521 (2.77)	7 (1.06)	69 (0.98)	0 (0.00)	0 (0.00)

Table 2. Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their matched ALS-free controls show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis

	Prior to Index Date			After Index Date		
	ALS Patients N (%)	**ALS-free Controls** N (%)	**OR (95% CI)^**	**ALS Patients** N (%)	**ALS-free Controls** N (%)	**HR (95% CI)^**
Any neurodegenerative or psychiatric disease	**479 (13.13)**	**3,370 (9.24)**	**1.49 (1.35-1.66)**	**218 (6.88)**	**2,138 (6.46)**	**2.90 (2.46-3.43)**
Neurodegenerative diseases*	**119 (3.26)**	**353 (0.97)**	**3.58 (2.89-4.44)**	**77 (2.43)**	**663 (2.00)**	**3.95 (2.92-5.34)**
Frontotemporal dementia	17 (0.47)	9 (0.02)	18.9 (8.4-42.4)	15 (0.47)	14 (0.04)	115.6 (15.1-887.0)
Alzheimer's disease	23 (0.63)	109 (0.30)	2.1 (1.4-3.4)	10 (0.32)	222 (0.67)	1.9 (1.0-3.7)
Other or unspecific dementia	40 (1.10)	130 (0.36)	3.2 (2.2-4.6)	48 (1.51)	317 (0.96)	4.6 (3.1-7.0)
Parkinson's disease	57 (1.56)	152 (0.42)	3.85 (2.83-5.24)	25 (0.79)	209 (0.63)	4.7 (2.8-7.8)
Psychiatric disorders **	**382 (10.47)**	**3,114 (8.54)**	**1.26 (1.12-1.41)**	**150 (4.73)**	**1,595 (4.82)**	**2.52 (2.07-3.07)**
Schizophrenia	22 (0.60)	226 (0.62)	1.0 (0.6-1.5)	1 (0.03)	20 (0.06)	1.7 (0.2-14.1)
Bipolar disorder	23 (0.63)	193 (0.53)	1.2 (0.8-1.8)	3 (0.09)	55 (0.17)	1.4 (0.4-4.8)
Depression	177 (4.85)	1,197 (3.28)	1.51 (1.28-1.77)	60 (1.89)	634 (1.91)	2.78 (2.05-3.79)
Neurotic disorders	136 (3.73)	906 (2.48)	1.53 (1.27-1.84)	58 (1.83)	466 (1.41)	3.07 (2.23-4.24)
Stress-related disorders	54 (1.48)	462 (1.27)	1.17 (0.88-1.56)	23 (0.73)	166 (0.50)	2.9 (1.7-5.0)
Alcohol abuse/dependence	104 (2.85)	1,125 (3.08)	0.92 (0.75-1.13)	14 (0.44)	390 (1.18)	1.0 (0.5-1.7)
Drug abuse/dependence	60 (1.64)	337 (0.92)	1.80 (1.36-2.38)	20 (0.63)	290 (0.88)	2.0 (1.2-3.4)

* Including frontotemporal dementia, Alzheimer's disease, other or unspecific dementia, and Parkinson's disease

** Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence

^ OR: odds ratio; HR: hazard ratio; CI: confidence interval; Adjusted for age, sex, and county of birth

Table 3. Adjusted associations for age, sex, and county of birth among relatives of amyotrophic lateral sclerosis (ALS) patients and their matched ALS-free controls show a higher-than-expected occurrence of neurodegenerative diseases among siblings of ALS patients and of psychiatric disorders among children of ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis

	Prior to Index Date			After Index Date		
	Relatives of ALS Patients N (%)	**Relatives of ALS-free Controls** N (%)	**OR (95% CI)^**	**Relatives of ALS Patients** N (%)	**Relatives of ALS-free Controls** N (%)	**HR (95% CI)^**
Any neurodegenerative or psychiatric disease						
Parents	166 (9.08)	1,871 (9.61)	1.01 (0.82-1.22)	180 (10.82)	2,074 (11.79)	1.06 (0.86-1.30)
Siblings	451 (9.09)	4,417 (8.99)	1.05 (0.94-1.17)	305 (6.76)	2,666 (5.97)	1.25 (1.08-1.45)
Half-siblings	58 (9.83)	739 (11.75)	0.66 (0.42-1.07)	39 (7.33)	410 (7.38)	1.2 (0.6-2.5)
Children	459 (7.03)	4,207 (6.31)	1.11 (1.01-1.23)	418 (6.89)	3,736 (5.98)	1.11 (1.00-1.25)
Neurodegenerative diseases*						
Parents	73 (3.99)	786 (4.04)	1.13 (0.83-1.52)	132 (7.94)	1,456 (8.27)	1.17 (0.91-1.50)
Siblings	48 (0.97)	373 (0.76)	1.41 (1.02-1.96)	93 (2.06)	605 (1.35)	1.76 (1.31-2.36)
Half-siblings	3 (0.51)	14 (0.22)	n/a	3 (0.56)	21 (0.38)	n/a
Children	2 (0.03)	14 (0.02)	1.9 (0.4-8.6)	3 (0.05)	32 (0.05)	1.0 (0.3-3.7)
Psychiatric disorders **						
Parents	109 (5.96)	1,237 (6.35)	0.94 (0.74-1.18)	59 (3.55)	771 (4.38)	0.82 (0.58-1.16)
Siblings	420 (8.47)	4,151 (8.45)	1.04 (0.93-1.16)	225 (4.99)	2,175 (4.87)	1.12 (0.95-1.33)
Half-siblings	55 (9.32)	728 (11.57)	0.69 (0.43-1.12)	36 (6.77)	395 (7.11)	1.2 (0.6-2.5)
Children	457 (7.00)	4,199 (6.30)	1.11 (1.01-1.23)	416 (6.85)	3,713 (5.94)	1.11 (1.00-1.25)

* Including frontotemporal dementia, Alzheimer's disease, other or unspecific dementia, and Parkinson's disease

** Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence

^ OR: odds ratio; HR: hazard ratio; CI: confidence interval; Adjusted for age, sex, and county of birth of the relatives as well as of the proband individuals

Table 4. Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their matched ALS-free controls show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases during the five years before (odds ratios) until the five years after (hazard ratios) ALS diagnosis

	Prior to Index Date; OR (95% CI)^			After Index Date; HR (95% CI)^		
	≥ 6 years	**2-5 years**	**0-1 year**	**0-1 year**	**2-5 years**	**≥ 6 years**
Any neurodegenerative or psychiatric disease	**1.09 (0.95-1.25)**	**1.56 (1.27-1.91)**	**5.48 (4.37-6.87)**	**5.02 (3.91-6.45)**	**2.31 (1.75-3.06)**	**1.30 (0.83-2.05)**
Neurodegenerative diseases*	**1.61 (0.96-2.69)**	**2.50 (1.76-3.55)**	**9.25 (6.54-13.08)**	**10.92 (6.73-17.71)**	**2.47 (1.44-4.24)**	**1.29 (0.58-2.86)**
Frontotemporal dementia	n/a	12.5 (3.4-46.6)	40.0 (11.3-141.8)	n/a	17.8 (1.6-198.2)	n/a
Alzheimer's disease	0.9 (0.2-3.7)	1.3 (0.6-2.8)	4.7 (2.5-9.0)	5.4 (1.8-16.5)	1.5 (0.5-4.3)	0.6 (0.1-4.2)
Other or unspecific dementia	1.3 (0.5-3.8)	1.0 (0.4-2.1)	12.1 (7.0-20.7)	9.4 (4.9-17.9)	3.6 (1.7-7.6)	1.9 (0.7-4.9)
Parkinson's disease	2.1 (1.1-3.9)	3.5 (2.2-5.6)	9.5 (5.2-17.2)	16.9 (6.7-42.5)	3.6 (1.7-7.9)	0.6 (0.1-4.5)
Psychiatric disorders**	**1.05 (0.91-1.21)**	**1.31 (1.04-1.65)**	**3.67 (2.76-4.88)**	**3.89 (2.90-5.24)**	**2.13 (1.54-2.93)**	**1.36 (0.82-2.23)**
Schizophrenia	0.8 (0.5-1.3)	1.4 (0.4-4.8)	5.0 (1.2-20.1)	n/a	10 (0.6-159.9)	n/a
Bipolar disorder	1.1 (0.6-1.9)	1.2 (0.5-3.0)	2.1 (0.6-7.5)	5.8 (1.0-35.0)	n/a	1.3 (0.2-11.1)
Depression	1.1 (0.9-1.3)	1.7 (1.3-2.3)	4.8 (3.3-7.0)	5.6 (3.4-9.2)	2.2 (1.3-3.8)	1.5 (0.7-3.0)
Neurotic disorders	1.3 (1.1-1.7)	1.2 (0.8-1.7)	4.8 (3.0-7.5)	4.8 (2.9-7.9)	2.6 (1.6-4.4)	1.5 (0.7-3.4)
Stress-related disorders	1.1 (0.8-1.6)	0.9 (0.4-1.7)	2.6 (1.3-5.5)	5.5 (2.3-13.4)	2.9 (1.2-6.9)	1.3 (0.4-4.6)
Alcohol abuse/dependence	1.0 (0.8-1.2)	0.8 (0.5-1.3)	0.2 (0.0-1.5)	1.2 (0.4-3.4)	1.0 (0.4-2.3)	0.7 (0.2-2.4)
Drug abuse/dependence	1.9 (1.3-2.7)	1.2 (0.7-2.2)	2.8 (1.5-5.4)	3.1 (1.4-6.6)	1.9 (0.8-4.7)	0.9 (0.2-4.0)

* Including frontotemporal dementia, Alzheimer's disease, other or unspecific dementia, and Parkinson's disease

** Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence

^ OR: odds ratio; HR: hazard ratio; CI: confidence interval; Adjusted for age, sex, and county of birth

Supplementary Table e-1

International Classification of Diseases (ICD) codes used to identify amyotrophic lateral sclerosis (ALS), neurodegenerative diseases, and psychiatric disorders in the Swedish Patient Register

ICD-8	1969-1986		ICD-9	1987-1996		ICD-10	1997-2013
ALS							
348.00	Amyotrophic lateral sclerosis		335.C	Amyotrophic lateral sclerosis		G12.2	Motor neuron disease
Frontotemporal dementia							
290.11	Pick's disease		331.B	Pick's disease		F02.0	Dementia in Pick's disease
						G31.0	Pick's disease
Alzheimer's disease							
290.10	Alzheimer's disease		290.A[a]	Senile dementia		F00	Dementia in Alzheimer's disease
			290.B[a]	Pre-senile dementia		G30	Alzheimer's disease
			331.A	Alzheimer's disease			
Other or unspecific dementia							
290[b]	Senile and pre-senile dementia		290.A	Senile dementia		F01	Vascular dementia
293.0	Psychosis with arteriosclerosis		290.B	Pre-senile dementia		F02[c]	Dementia in other diseases classified elsewhere
293.1	Psychosis with other cerebrovascular condition		290.E	Vascular dementia		F03	Unspecified dementia
			290.W	Other specified senile psychotic conditions		F05.1	Delirium superimposed on dementia
			290.X	Unspecified senile psychotic condition		G31.1	Senile degeneration of brain
			294.B	Dementia in conditions classified elsewhere		G31.8A[d]	Lewy body disease
			331.C	Senile degeneration of brain			
			331.X	Unspecified cerebral degeneration			
Parkinsonian disorders							
342.00	Parkinson's disease		332.A	Parkinson's disease		F02.3[d]	Dementia in Parkinson's disease
342.08	Other defined parkinsonism		333.A	Other degenerative diseases of the		G20	Parkinson's disease

				basal ganglia			
342.09	Unspecified parkinsonism					G21.4	Vascular parkinsonism
						G21.8	Other defined secondary parkinsonism
						G21.9	Unspecified secondary parkinsonism
						G23.1	Progressive supranuclear ophthalmoplegia
						G23.2	Striatonigral degeneration
						G23.9	Unspecified degenerative disease of basal ganglia
						G25.9	Unspecified extrapyramidal and movement disorder
						G31.8A[d]	Lewy body disease
Schizophrenia							
295	Schizophrenia		295	Schizophrenia		F20	Schizophrenia
Bipolar disorder							
296.1	Affective psychosis manic-depressive, manic type		296.A	Unipolar-Manic affective psychosis		F30	Manic episode
296.3	Affective psychosis manic-depressive, circular type		296.C	Bipolar affective psychosis, manic phase		F31	Bipolar disorder
296.8	Affective psychosis manic-depressive, other specified		296.D	Bipolar affective psychosis, melancholic phase			
			296.E	Bipolar affective psychosis, mild form			
			296.W	Other specified affective psychosis			
Depression							
300.4	Depressive neurosis		300.E	Depressive neurosis		F32[e]	Depressive episode
			311	Depression not otherwise specified		F33[f]	Recurrent depressive disorders
						F34	Chronic mood disorder
						F38	Other mood disorders
						F39	Unspecified mood disorder

Neurotic disorders							
300.1	Anxiety disorder		300.A	Anxiety disorder		F40	Phobic disorder
300.2	Phobic disorder		300.B	Hysteria		F41	Other anxiety disorders
300.3	Obsessive compulsive disorder		300.C	Phobic disorder		F42	Obsessive compulsive disorder
300.5	Neurasthenia		300.D	Obsessive compulsive		F44	Dissociative syndrome
300.6	Depersonalization disorder		300.F	Neurasthenia		F45	Somatoform disorder
300.7	Hypochondria		300.G	Depersonalization disorder		F48	Other neurotic disorders
300.8	Other specified neurotic disorder		300.H	Hypochondria			
300.9	Not otherwise specified		300.W	Other specified neurotic disorder			
			300.X	Unspecified			
Stress-related disorders							
307	Transient situational disturbances		308	Acute reaction to stress		F43	Adjustment disorder and reaction to severe stress
			309	Adjustment disorder			
Alcohol abuse/dependence							
303	Alcoholism		303	Alcoholism		F10[g]	Mental and behavioral disorders caused by alcohol
			305.A	Non-dependent alcohol abuse			
Drug abuse/dependence							
304	Drug addiction, abuse of drugs		304	Drug addiction		F11	Mental and behavioral disorders due to use of opioids
			305.X	Abuse of drugs and medicines		F12	Mental and behavioral disorders caused by cannabis
						F13	Mental and behavioral disorders due to use of sedatives and hypnotics
						F14	Mental and behavioral disorders due to use of cocaine
						F15	Mental and behavioral disorders due to use of other stimulants, including caffeine
						F16	Mental and behavioral disorders due to use of hallucinogens

						F17	Mental and behavioral disorders due to use of tobacco
						F18	Mental and behavioral disorders due to use of volatile solvents
						F19	Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances
[a] If found as primary diagnosis							
[b] Except 290.10 (Alzheimer's disease) and 290.11 (Pick's disease)							
[c] Except F02.0 (Dementia in Pick's disease)							
[d] ICD-10 codes considered both dementia and parkinsonian disorder diagnoses							
[e] Except F32.2 (depressive psychosis)							
[f] Except F33.3 (depressive psychosis)							
[g] Except F10.5 (psychotic state)							

Supplementary Table e-2

Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their matched ALS-free controls show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases after ALS diagnosis (hazard ratios); follow-up stopped at 69 years

	After Index Date
	HR (95%CI)*
Any neurodegenerative disease	8.01 (4.97-12.92)
Other or unspecific dementia	13.66 (6.38-29.24)

*HR: hazard ratio; CI: confidence interval; Adjusted for age, sex, and county of birth

Supplementary Table e-3

Adjusted associations for age, sex, and county of birth among relatives of patients with amyotrophic lateral sclerosis (ALS) and relatives of their matched ALS-free controls do not show clear temporal pattern in the associations of ALS with neurodegenerative and psychiatric diseases

	Prior to Index Date; OR (95% CI)^			After Index Date; HR (95% CI)^		
	≥ 6 years	**2-5 years**	**0-1 year**	**0-1 year**	**2-5 years**	**≥ 6 years**
Any neurodegenerative or psychiatric disease						
Parents	0.88 (0.68-1.15)	1.08 (0.79-1.48)	1.3 (0.8-2.2)	0.6 (0.2-1.7)	1.21 (0.81-1.81)	0.97 (0.69-1.35)
Siblings	1.02 (0.90-1.16)	1.01 (0.81-1.25)	1.5 (1.0-2.1)	1.0 (0.5-1.9)	1.25 (0.95-1.65)	1.29 (1.05-1.58)
Half-siblings	0.8 (0.5-1.3)	0.5 (0.2-1.3)	0.2 (0.1-1.8)	n/a	0.2 (0.1-1.5)	2.3 (0.7-8.1)
Children	1.07 (0.93-1.23)	1.25 (1.06-1.47)	0.9 (0.6-1.3)	2.20 (1.32-3.66)	1.07 (0.87-1.32)	0.98 (0.82-1.16)
Neurodegenerative diseases*						
Parents	1.3 (0.7-2.3)	1.0 (0.7-1.5)	1.2 (0.6-2.2)	0.9 (0.2-3.4)	1.27 (0.77-2.10)	0.91 (0.62-1.37)
Siblings	1.6 (0.9-2.8)	1.2 (0.7-1.9)	1.8 (0.9-3.5)	1.1 (0.1-8.3)	1.5 (0.8-2.6)	2.33 (1.57-3.41)
Half-siblings	n/a	n/a	n/a	n/a	n/a	n/a
Children	n/a	3.3 (0.3-33.2)	n/a	n/a	n/a	1.0 (0.2-5.0)
Psychiatric disorders**						
Parents	0.85 (0.64-1.13)	1.1 (0.7-1.6)	1.3 (0.6-2.9)	0.4 (0.1-1.5)	0.9 (0.4-1.7)	0.9 (0.5-1.5)
Siblings	1.01 (0.89-1.16)	1.02 (0.81-1.29)	1.4 (0.9-2.0)	1.1 (0.5-2.2)	1.18 (0.87-1.59)	1.04 (0.82-1.32)
Half-siblings	0.8 (0.5-1.3)	0.5 (0.2-1.5)	0.2 (0.1-1.9)	n/a	0.2 (0.1-1.5)	2.3 (0.7-8.1)
Children	1.07 (0.93-1.23)	1.24 (1.05-1.47)	0.9 (0.6-1.3)	2.19 (1.31-3.65)	1.08 (0.87-1.33)	0.98 (0.83-1.17)

* Including frontotemporal dementia, Alzheimer's disease, other or unspecific dementia, and Parkinson's disease

** Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence

^ OR: odds ratio; HR: hazard ratio; CI: confidence interval; Adjusted for age and county of birth, and for age and county of birth of the proband

Supplementary Table e-4

Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their relatives, compared to ALS-free individuals, show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among ALS patients, of neurodegenerative diseases among siblings of ALS patients, and of psychiatric disorders among children of ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis; separate analysis for males

	Prior to Index Date			After Index Date		
Males	**ALS patients/ Relatives of ALS Patients** N (%)	**ALS-free Controls/ Relatives of ALS-free Controls** N (%)	**OR (95% CI)^**	**ALS patients/ Relatives of ALS Patients** N (%)	**ALS-free Controls/ Relatives of ALS-free Controls** N (%)	**HR (95% CI)^**
Any neurodegenerative or psychiatric disease						
Proband	267 (12.22)	2,041 (9.34)	1.36 (1.18-1.56)	130 (6.78)	1,285 (6.49)	2.77 (2.24-3.42)
Parents	52 (7.09)	554 (7.55)	1.07 (0.75-1.52)	63 (9.25)	691 (10.18)	0.97 (0.63-1.49)
Siblings	226 (8.93)	2.247 (8.98)	1.06 (0.90-1.24)	150 (6.50)	1,363 (5.99)	1.14 (0.90-1.44)
Half-siblings	36 (11.11)	368 (11.53)	0.6 (0.3-1.3)	23 (7.99)	199 (7.04)	1.0 (0.3-3.1)
Children	211 (6.34)	1,932 (5.64)	1.16 (0.99-1.35)	198 (6.36)	1,637 (5.06)	1.28 (1.07-1.54)
Neurodegenerative diseases*						
Proband	62 (2.84)	238 (1.09)	2.74 (2.05-3.67)	51 (2.66)	418 (2.11)	3.46 (2.42-4.94)
Parents	17 (2.32)	208 (2.83)	1.0 (0.5-1.8)	45 (6.61)	481 (7.09)	1.1 (0.6-1.9)
Siblings	24 (0.95)	179 (0.72)	1.5 (0.9-2.5)	53 (2.30)	316 (1.39)	2.18 (1.36-3.49)
Half-siblings	0 (0.00)	7 (0.22)	n/a	2 (0.69)	13 (0.46)	n/a
Children	1 (0.03)	7 (0.02)	1.4 (0.2-12.7)	0 (0.00)	18 (0.06)	n/a
Psychiatric disorders**						
Proband	216 (9.89)	1,859 (8.51)	1.18 (1.02-1.37)	84 (4.38)	945 (4.77)	2.37 (1.84-3.06)
Parents	38 (5.18)	382 (5.20)	1.1 (0.7-1.6)	22 (3.23)	257 (3.79)	0.8 (0.4-1.6)
Siblings	210 (8.29)	2,128 (8.51)	1.04 (0.88-1.22)	109 (4.73)	1,097 (4.82)	1.00 (0.76-1.29)
Half-siblings	36 (11.11)	362 (11.34)	0.6 (0.3-1.3)	21 (7.29)	189 (6.69)	1.0 (0.3-3.1)
Children	210 (6.31)	1,927 (5.62)	1.16 (0.99-1.35)	198 (6.36)	1,625 (5.03)	1.30 (1.08-1.56)

* Including frontotemporal dementia, Alzheimer's disease, other or unspecific dementia, and Parkinson's disease

** Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence

^ OR: odds ratio; HR: hazard ratio; CI: confidence interval; Adjusted for age and county of birth, and for age and county of birth of the proband in the analyses of relatives

Supplementary Table e-5

Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their relatives, compared to ALS-free individuals, show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among ALS patients, and of neurodegenerative diseases among siblings of ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis; separate analysis for females

	Prior to Index Date			After Index Date		
Females	**ALS patients/ Relatives of ALS Patients** N (%)	**ALS-free Controls/ Relatives of ALS-free Controls** N (%)	**OR (95% CI)^**	**ALS patients/ Relatives of ALS Patients** N (%)	**ALS-free Controls/ Relatives of ALS-free Controls** N (%)	**HR (95% CI)^**
Any neurodegenerative or psychiatric disease						
Proband	212 (14.49)	1,329 (9.08)	1.70 (1.46-1.99)	88 (7.03)	853 (6.41)	3.16 (2.40-4.15)
Parents	114 (10.40)	1,317 (10.86)	1.02 (0.80-1.30)	117 (11.91)	1,383 (12.79)	1.05 (0.80-1.39)
Siblings	225 (9.27)	2,170 (9.00)	1.07 (0.91-1.25)	155 (7.04)	1,303 (5.94)	1.29 (1.02-1.62)
Half-siblings	22 (8.27)	371 (11.98)	0.5 (0.2-1.1)	18 (6.72)	217 (7.18)	2.5 (0.7-8.8)
Children	248 (7.75)	2,275 (7.02)	1.06 (0.91-1.22)	220 (7.45)	2,099 (6.96)	1.00 (0.84-1.19)
Neurodegenerative diseases*						
Proband	57 (3.90)	115 (0.79)	5.26 (3.79-7.31)	26 (2.08)	245 (1.84)	5.4 (3.1-9.2)
Parents	56 (5.11)	578 (4.77)	1.18 (0.82-1.70)	87 (8.86)	975 (9.02)	1.18 (0.84-1.66)
Siblings	24 (0.99)	194 (0.81)	1.5 (0.9-2.4)	40 (1.82)	289 (1.32)	1.6 (1.0-2.6)
Half-siblings	3 (1.13)	7 (0.23)	n/a	1 (0.37)	9 (0.30)	n/a
Children	1 (0.03)	7 (0.02)	3.1 (0.3-35.3)	3 (0.10)	14 (0.05)	6.0 (0.9-41.2)
Psychiatric disorders**						
Proband	166 (11.35)	1,255 (8.58)	1.37 (1.15-1.62)	66 (5.28)	650 (4.89)	2.76 (2.03-3.76)
Parents	71 (6.48)	855 (7.05)	0.94 (0.70-1.26)	37 (3.77)	514 (4.75)	0.8 (0.5-1.3)
Siblings	210 (8.65)	2,023 (8.39)	1.06 (0.90-1.25)	116 (5.27)	1,078 (4.92)	1.17 (0.90-1.52)
Half-siblings	19 (7.14)	366 (11.81)	0.6 (0.3-1.2)	17 (6.34)	211 (6.98)	2.5 (0.7-8.8)
Children	247 (7.71)	2,272 (7.01)	1.05 (0.91-1.22)	218 (7.38)	2,088 (6.93)	0.99 (0.83-1.18)

* Including frontotemporal dementia, Alzheimer's disease, other or unspecific dementia, and Parkinson's disease

** Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence

^ OR: odds ratio; HR: hazard ratio; CI: confidence interval; Adjusted for age and county of birth, and for age and county of birth of the proband in the analyses of relatives

Supplementary Table e-6

Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their relatives, compared to ALS-free individuals, show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among ALS patients, and of psychiatric disorders among children of ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis; separate analysis for individuals ≤55 years

	Prior to Index Date			After Index Date		
≤ 55 years at Index date	**ALS patients/ Relatives of ALS Patients** N (%)	**ALS-free Controls/ Relatives of ALS-free Controls** N (%)	**OR (95% CI)^**	**ALS patients/ Relatives of ALS Patients** N (%)	**ALS-free Controls/ Relatives of ALS-free Controlss** N (%)	**HR (95% CI)^**
Any neurodegenerative or psychiatric disease						
Proband	96 (9.93)	726 (7.51)	1.36 (1.09-1.71)	67 (7.69)	636 (7.11)	2.45 (1.82-3.30)
Parents	8 (7.34)	73 (7.14)	0.9 (0.4-2.3)	7 (6.93)	80 (8.42)	0.5 (0.2-1.6)
Siblings	141 (7.44)	1,426 (7.52)	0.95 (0.77-1.16)	139 (7.92)	1,252 (7.14)	1.18 (0.95-1.46)
Half-siblings	37 (9.44)	485 (11.47)	0.5 (0.3-1.0)	30 (8.45)	334 (8.92)	1.0 (0.4-2.1)
Children	455 (7.02)	4,137 (6.25)	1.12 (1.01-1.25)	418 (6.94)	3,730 (6.01)	1.11 (0.99-1.25)
Neurodegenerative diseases*						
Proband	19 (1.96)	7 (0.07)	27.1 (11.4-64.6)	15 (1.72)	48 (0.54)	6.7 (2.8-15.9)
Parents	0 (0.00)	0 (0.00)	n/a	1 (0.99)	6 (0.63)	3.3 (0.2-45.1)
Siblings	2 (0.11)	19 (0.10)	0.9 (0.2-5.1)	16 (0.91)	108 (0.62)	1.8 (0.9-3.5)
Half-siblings	0 (0.00)	4 (0.09)	n/a	1 (0.28)	9 (0.24)	n/a
Children	1 (0.02)	12 (0.02)	1.1 (0.1-9.3)	3 (0.05)	32 (0.05)	1.0 (0.3-3.5)
Psychiatric disorders**						
Proband	81 (8.38)	722 (7.47)	1.13 (0.89-1.44)	55 (6.31)	600 (6.71)	2.25 (1.64-3.08)
Parents	8 (7.34)	73 (7.14)	0.9 (0.4-2.3)	6 (5.94)	78 (8.21)	0.4 (0.1-1.3)
Siblings	139 (7.34)	1,413 (7.45)	0.94 (0.76-1.15)	128 (7.30)	1,175 (6.70)	1.12 (0.90-1.40)
Half-siblings	37 (9.44)	483 (11.42)	0.5 (0.3-1.0)	29 (8.17)	329 (8.79)	1.0 (0.4-2.1)
Children	454 (7.00)	4,130 (6.24)	1.12 (1.01-1.24)	416 (6.90)	3,707 (5.97)	1.11 (0.99-1.25)

* Including frontotemporal dementia, Alzheimer's disease, other or unspecific dementia, and Parkinson's disease

** Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence

^ OR: odds ratio; HR: hazard ratio; CI: confidence interval; Adjusted for age and county of birth, and for age and county of birth of the proband in the analyses of relatives

Supplementary Table e-7

Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their relatives, compared to ALS-free individuals, show a higher than expected occurrence of neurodegenerative and psychiatric diseases among ALS patients, and of neurodegenerative diseases among siblings of ALS patients, both before (odds ratios) and after (hazard ratios) ALS diagnosis; separate analyses for individuals ≥56 years

	Prior to Index Date			After Index Date		
≥ 56 years at Index date	**ALS patients/ Relatives of ALS Patients** N (%)	**ALS-free Controls/ Relatives of ALS-free Controls** N (%)	**OR (95% CI)^**	**ALS patients/ Relatives of ALS Patients** N (%)	**ALS-free Controls/ Relatives of ALS-free Controls** N (%)	**HR (95% CI)^**
Any neurodegenerative or psychiatric disease						
Proband	383 (14.29)	2,644 (9.86)	1.53 (1.36-1.72)	151 (6.57)	1,502 (6.22)	3.15 (2.57-3.86)
Parents	158 (9.19)	1,798 (9.75)	1.01 (0.82-1.23)	173 (11.08)	1,994 (11.98)	1.10 (0.88-1.3)
Siblings	310 (10.11)	2,991 (9.92)	1.06 (0.93-1.21)	166 (6.03)	1,414 (5.21)	1.36 (1.10-1.68)
Half-siblings	21 (10.61)	254 (12.32)	0.5 (0.2-1.7)	9 (5.08)	76 (4.21)	n/a
Children	4 (8.70)	70 (13.73)	1.0 (0.3-3.9)	0 (0.00)	6 (1.36)	n/a
Neurodegenerative diseases*						
Proband	100 (3.73)	346 (1.29)	3.05 (2.42-3.83)	62 (2.70)	615 (2.54)	3.71 (2.68-5.13)
Parents	73 (4.24)	786 (4.26)	1.08 (0.80-1.46)	131 (8.39)	1,450 (8.71)	1.17 (0.91-1.50)
Siblings	46 (1.50)	354 (1.17)	1.6 (1.1-2.3)	77 (2.79)	497 (1.83)	1.81 (1.29-2.53)
Half-siblings	3 (1.52)	10 (0.49)	n/a	2 (1.13)	12 (0.66)	n/a
Children	1 (2.17)	2 (0.39)	n/a	0 (0.00)	0 (0.00)	n/a
Psychiatric disorders**						
Proband	301 (11.23)	2,392 (8.92)	1.29 (1.14-1.47)	95 (4.13)	995 (4.12)	2.71 (2.10-3.48)
Parents	101 (5.87)	1,164 (6.31)	0.95 (0.75-1.21)	53 (3.39)	693 (4.16)	0.89 (0.62-1.28)
Siblings	281 (9.17)	2,738 (9.08)	1.05 (0.91-1.21)	97 (3.52)	1,000 (3.68)	1.16 (0.89-1.50)
Half-siblings	18 (9.09)	245 (11.89)	0.5 (0.2-1.7)	7 (3.95)	66 (3.65)	n/a
Children	3 (6.52)	69 (13.53)	0.8 (0.2-3.5)	0 (0.00)	6 (1.36)	n/a

* Including frontotemporal dementia, Alzheimer's disease, other or unspecific dementia, and Parkinson's disease

** Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence

^ OR: odds ratio; HR: hazard ratio; CI: confidence interval; Adjusted for age and county of birth, and for age and county of birth of the proband in the analyses of relatives

Supplementary Table e-8

Adjusted associations for age, sex, and county of birth among patients with familial amyotrophic lateral sclerosis (ALS) and their matched ALS-free controls show a higher-than-expected occurrence of neurodegenerative and psychiatric diseases among familial ALS patients, both before (odds ratios) and after(hazard ratios) ALS diagnosis

	Prior to Index Date			After Index Date		
	ALS Patients N (%)	**ALS-free Individuals** N (%)	**OR (95% CI)^**	**ALS Patients** N (%)	**ALS-free Individuals** N (%)	**HR (95% CI)^**
Any neurodegenerative or psychiatric disease	21 (12.14)	153 (8.84)	1.4 (0.9-2.4)	10 (6.58)	113 (7.17)	3.1 (1.3-7.3)
Neurodegenerative diseases*	5 (2.89)	9 (0.52)	5.9 (1.9-18.0)	2 (1.32)	29 (1.84)	2.2 (0.2-20.1)
Psychiatric disorders**	17 (9.83)	147 (8.50)	1.2 (0.7-2.0)	8 (5.26)	92 (5.83)	3.1 (1.2-7.9)

* Including frontotemporal dementia, Alzheimer's disease, other dementia, and Parkinson's disease

** Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence

Supplementary Table e-9

Adjusted associations for age, sex, and county of birth among patients with amyotrophic lateral sclerosis (ALS) and their matched ALS-free controls show a higher-than-expected occurrence of neurodegenerative diseases among ALS patients, even after excluding frontotemporal dementia from the definition of neurodegenerative diseases

	Prior to Index Date; OR (95% CI)^			After Index Date; HR (95% CI)^		
	≥ 6 years	**2-5 years**	**0-1 year**	**0-1 year**	**2-5 years**	**≥ 6 years**
Neurodegenerative diseases*	1.60 (0.96-2.69)	2.18 (1.51-3.15)	8.80 (6.20-12.50)	10.04 (6.14-16.44)	2.76 (1.64-5.63)	1.29 (0.58-2.86)

* Including Alzheimer's disease, other dementia, and Parkinson's disease

^ Adjusted for age, sex, and county of birth