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Neurodegenerative and psychiatric diseases among families with amyotrophic lateral sclerosis

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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 patients with ALS had higher risks of other neurodegenerative and psychiatric diseases before diagnosis. We included 3,648 patients with ALS 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 patients with ALS 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, patients with ALS 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 disease, other dementia, Alzheimer disease, neurotic disorders, depression, stress-related disorders, and drug abuse/dependence. First-degree relatives of patients with ALS had higher risk of neurodegenerative diseases, whereas only children of patients with ALS 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 patients with ALS and their children might be attributable to nonmotor symptoms of ALS and severe stress response toward the diagnosis. *Neurology*® 2017;89:1–8

GLOSSARY

AD = Alzheimer disease; **ALS** = amyotrophic lateral sclerosis; **CI** = confidence interval; **FTD** = frontotemporal dementia; **HR** = hazard ratio; **ICD** = International Classification of Disease; **OR** = odds ratio; **PD** = Parkinson disease.

Amyotrophic lateral sclerosis (ALS) overlaps clinically and pathologically with other neurodegenerative diseases.[1–5] Family members of patients with ALS have also been reported to have increased risks of dementia and Parkinson 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 patients with ALS.[6] We performed a nationwide register-based study in Sweden to estimate the risk of neurodegenerative and psychiatric diseases among patients with ALS and their family members.

Supplemental data at Neurology.org

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 who were born in Sweden during

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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 1, 1990, or date of birth, whichever came later, until date of ALS diagnosis, death, emigration out of Sweden, or December 31, 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 who 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 patients with ALS 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 patients with ALS 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 who 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 patients with ALS 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 31, 2013, whichever came first.

Ascertainment of neurodegenerative and psychiatric diseases. Neurodegenerative diseases examined in this study included frontotemporal dementia (FTD), Alzheimer disease (AD), other or unspecific dementia, and PD, because we had previously reported risk of ALS among relatives of patients with ALS.[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 at Neurology.org.

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 patients with ALS to their controls and the relatives of patients with ALS 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 crosslinking the nested case-control study I to the Multi-Generation Register, we identified grandparents, parents, uncles/aunts, full and half siblings, children, nephews/nieces, and grandchildren of patients with ALS 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 2 hospital visits concerning respective diseases. Given the established ALS/FTD overlap,[17] we additionally assessed the risk of other neurodegenerative diseases among patients with ALS after excluding FTD from the definition of neurodegenerative diseases. Finally, as depression, neurotic disorders, and stress-related disorders might represent

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

	Patients with ALS	ALS-free controls	Parents of patients with ALS	Parents of controls	Siblings of patients with ALS	Siblings of controls	Half-siblings of patients with ALS	Half-siblings of controls	Children of patients with ALS	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, y										
≤60	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	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	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	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	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)

Values are n (%).

collectively the psychological burden of ALS symptoms and diagnosis on patients with ALS 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 2-sided p value ≤0.05. We performed analyses using Stata software, version 14 (StataCorp, College Station, TX).

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 patients with ALS, their controls, and the relatives of both groups. The mean age at diagnosis of patients with ALS was 60 years (SD 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 patients with ALS, 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 patients with ALS 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 patients with ALS 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). Patients with ALS had an increased risk of stress-related disorders after diagnosis, especially during the first year. A clear temporal pattern was 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 and e-5) and between individuals younger or older than 55 years (tables e-6 and e-7). We identified a total of 173 patients with ALS with a family history of ALS

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 patients with ALS, both before (odds ratios [ORs]) and after (hazard ratios [HRs]) ALS diagnosis

	Prior to index date			After index date		
	Patients with ALS, n (%)	ALS-free controls, n (%)	OR (95% CI)[a]	Patients with ALS, n (%)	ALS-free controls, n (%)	HR (95% CI)[a]
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[b]	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 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 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[c]	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)

Abbreviation: CI = confidence interval.
[a] Adjusted for age, sex, and county of birth.
[b] Including frontotemporal dementia, Alzheimer disease, other or unspecific dementia, and Parkinson disease.
[c] Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence.

(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 patients with ALS in our study, 3,048 had at least 2 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 2 hospital visits concerning respective diseases slightly attenuated the associations between other neurodegenerative diseases and ALS both prior to (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 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 patients with ALS, 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 patients with ALS had higher risks of neurodegenerative and psychiatric diseases, both before and after diagnosis. Parents, siblings, and children of patients with ALS tended to have increased risk of neurodegenerative diseases, whereas only children of patients with ALS 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 patients with ALS tended also to have increased risks of other neurodegenerative diseases, corroborating findings of a recent study in Ireland.[6] Our results lend 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 pathologic finding from different neurodegenerative diseases.[19] Nongenetic 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 5 years before and after

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

	Prior to index date			After index date		
	Relatives of patients with ALS, n (%)	Relatives of ALS-free controls, n (%)	OR (95% CI)[a]	Relatives of patients with ALS, n (%)	Relatives of ALS-free controls, n (%)	HR (95% CI)[a]
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[b]						
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[c]						
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)

Abbreviation: CI = confidence interval.
[a] Adjusted for age, sex, and county of birth of the relatives as well as of the proband individuals.
[b] Including frontotemporal dementia, Alzheimer disease, other or unspecific dementia, and Parkinson disease.
[c] Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence.

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 patients with ALS. 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 2 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, patients with ALS 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 also possible that some symptoms of other neurodegenerative diseases become underdetected because of the predominant ALS symptoms.

We found an increased risk of psychiatric disorders among patients with ALS 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 5 years before and after ALS diagnosis might be due to both nonmotor symptoms of ALS and severe stress response toward these symptoms and the final diagnosis. Nonmotor 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 patients with ALS. 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

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 5 years before (odds ratios [ORs]) until the 5 years after (hazard ratios [HRs]) ALS diagnosis

	Prior to index date, y, OR (95% CI)[a]			After index date, y, HR (95% CI)[a]		
	≥6	2–5	0–1	0–1	2–5	≥6
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[b]	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 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 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[c]	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)

Abbreviation: CI = confidence interval.
[a] Adjusted for age, sex, and county of birth.
[b] Including frontotemporal dementia, Alzheimer disease, other or unspecific dementia, and Parkinson disease.
[c] Including schizophrenia, bipolar disorder, depression, neurotic disorder, stress-related disorders, alcohol abuse/dependence, and drug abuse/dependence.

the 5 years before ALS diagnosis, although the association was only statistically significant during the year before diagnosis. A recent genome-wide association 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 patients with ALS, 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 did not disappear 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 patients with ALS. The vast majority of children of patients with ALS who 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 for patients with ALS 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 information on the genetic and clinical characteristics of patients with ALS, 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 patients with ALS are diagnosed by a specialist, we might have underestimated the prevalence of some neurodegenerative and psychiatric diseases because health care provided by general practitioners is not included in the register. The 1% prevalence of FTD among the patients with ALS might reflect a lack of FTD detection.[35] Some of the patients with FTD might have been misclassified as other dementia, partially accounting for the increased risk of other dementia among patients with ALS. Because the vast majority of children of patients with ALS were younger than 60 years, 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.

We found that patients with ALS 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 patients with ALS and their children might be attributable to both the nonmotor symptoms of ALS and severe stress response to the progressive symptoms and diagnosis of a fatal disease.

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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DISCLOSURE

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