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RESEARCH ARTICLE

Mortality among family members of patients with amyotrophic lateral sclerosis – a Swedish register-based study

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Abstract

Objective: To test two hypotheses: (1) partners of ALS patients have higher mortality due to outcomes related to psychological distress, and (2) parents and siblings of ALS patients have higher mortality due to diseases that co-occur with ALS.

Methods: We performed a nationwide, register-based cohort study in Sweden. We included ALS-free partners, biological parents and full siblings ($N = 11{,}704$) of ALS patients, as well as ALS-free partners, biological parents and full siblings ($N = 14{,}460{,}150$) of ALS-free individuals, and followed them during 1961–2013. Hazard ratios (HRs) and 95% confidence intervals (CIs) of overall and cause-specific mortality were derived from Cox regression.

Results: Partners of ALS patients, compared to partners of ALS-free individuals, displayed higher mortality due to external causes (HR 2.14; 95% CI 1.35–3.41), including suicide (HR 2.44; 95% CI 1.09–5.44) and accidents (HR 2.09; 95% CI 1.12–3.90), after diagnosis of the ALS patients. Parents of ALS patients had a slightly higher overall mortality (HR 1.03; 95% CI 1.00–1.07), compared with parents of ALS-free individuals. This was driven by mortality due to dementias and cardiovascular, respiratory, and skin diseases. Parents of ALS patients had, however, lower mortality than parents of ALS-free individuals due to neoplasms. Siblings of ALS patients had higher mortality due to dementias, and digestive and skin diseases.

Conclusions: Increased mortality due to suicide and accidents among partners of ALS patients is likely attributable to severe psychological distress following the ALS diagnosis. Increased mortality due to dementias among parents and full siblings of ALS patients suggests shared mechanisms between neurodegenerative diseases.

Keywords: *Amyotrophic lateral sclerosis, family members, mortality, psychological distress, register-based study*

Introduction

It is known that caregivers of ALS patients experience raised levels of psychological distress and depression (1). Caregivers of ALS patients are also likely exposed to the loss of the ALS patient due to death from ALS. Individuals with bereavement have been shown to have higher risk of developing future diseases, including cardiovascular disease (2–5) and psychiatric disorders (6–8). The mortality of primary caregivers of ALS patients has, to our knowledge, not been studied.

Both ALS patients and their biological relatives have increased risk for psychiatric and neurodegenerative diseases than the general population (9–12), suggesting shared disease mechanisms between ALS and other neurological diseases. Compared to the general population, ALS patients have also been suggested to have lower risk of cardiometabolic diseases (12–14) including diabetes (15,16), similar risk of cancer (17,18), and higher risk of autoimmune diseases (19). Whether these

Supplemental data for this article can be accessed here.

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result patterns also apply to biological relatives of ALS patients remains largely unknown.

Using a nationwide historical cohort based on the Swedish population and health registers, we investigated if family members of ALS patients had altered mortality compared with family members of ALS-free individuals. We aimed to address two hypotheses. First, partners of ALS patients have higher mortality due to outcomes related to psychological distress, after receiving the ALS diagnosis. Second, biological relatives of ALS patients have higher mortality due to diseases that are known to cooccur with ALS.

Materials and methods

Nationwide ascertainment of ALS patients and ALS-free individuals

The Swedish Multi-Generation Register connects each individual born in Sweden since 1932 and alive from 1961 onward, to their biological parents (20). We selected all individuals included in this register who were born in Sweden during 1932–1993 ($N = 6{,}434{,}635$), and followed them from 1 January 1961 or date of birth, whichever came later, until date of ALS diagnosis, emigration out of Sweden, death, or end of follow-up (31 December 2013), whichever came first, by cross-linkages to the Swedish Patient Register, Causes of Death Register, and Total Population Register via the unique personal identification numbers assigned to all Swedish residents (21).

We identified ALS diagnoses from the Swedish Patient Register, which collects data on hospital discharge records in Sweden since 1964 and became nationwide in 1987 (22). This register has since 2001 included also records from hospital-based outpatient specialist care. To increase the specificity of our ALS definition, we defined an individual as diagnosed with ALS if they had at least two hospital visits concerning ALS, according to the Swedish Revisions of the International Classification of Disease (ICD) codes (Supplementary Table 1). During follow-up, a total of 3,092 individuals were diagnosed with ALS in the cohort according to this definition, while the other 6,431,543 individuals were ALS-free.

Identification of partners, parents and siblings of ALS patients and ALS-free individuals

Using the familial links recorded in the Multi-Generation Register, we identified the partners as well as the biological parents and full siblings of the ALS patients and ALS-free individuals. We defined partners as persons that shared at least one biological or adoptive child. If a person had common children with multiple individuals, we defined the partner as the individual with whom the person shared the youngest child. We included parents, siblings, and partners born up to 1993, whether they were born in Sweden or elsewhere. In total we identified 2,604 partners of ALS patients and 4,088,662 partners of ALS-free individuals. We identified 4,658 parents and 4,593 siblings of the ALS patients, and 5,468,603 parents and 4,954,427 siblings of the ALS-free individuals.

Follow-up study of the relatives to ascertain mortality

We followed the partners, parents and siblings from 1 January 1961 or date of birth, whichever came later, until emigration out of Sweden, death, or end of follow-up (31 December 2013), whichever came first, by cross-linkages to the Causes of Death Register (23) and Total Population Register. We first excluded 21 partners and 36,651 parents that had conflicting information on date of death, and 221 partners, 3,304 parents, and 6,908 siblings that died or emigrated out of Sweden before 1 January 1961. Because we wanted to study mortality among relatives that were free of ALS, we also excluded 3,080 partners, 8,124 parents, and 2,384 siblings that were diagnosed with ALS before or during follow-up or had ALS as a cause of death during follow-up. The persons excluded were from both groups, i.e. partners, parents and siblings of ALS patients as well as partners, parents and siblings of ALS-free individuals. As a result, we included in the final analysis 2,650 partners, 4,512 parents, and 4,542 siblings of ALS patients, and 4,085,294 partners, 5,420,670 parents, and 4,954,186 siblings of ALS-free individuals.

We identified the underlying cause of death for the partners, parents and siblings of ALS patients and ALS-free individuals from the Causes of Death Register, which collects information on causes of death since 1952 (24). We classified the underlying causes of death according to the ICD codes (Supplementary Table 1). Because we excluded relatives with ALS, ALS was not included in the category diseases of the nervous system. Further, because cognitive impairment is increasingly recognized in the ALS disease spectrum, dementias were studied as a separate category.

Statistical analyses

We fitted Cox regression to derive hazard ratios (HRs) and their 95% confidence intervals (CIs) of overall and cause-specific mortality, comparing partners, parents, and siblings of ALS patients to partners, parents, and siblings of ALS-free individuals. Because we hypothesized that the altered mortality among partners of ALS patients was attributable to psychological distress in relation to

the diagnosis of the proband ALS patients, we only compared the mortality of the partners of ALS patients during the time after ALS diagnosis. We used the mortality during the entire follow-up of the partners of ALS-free individuals and the mortality of partners of ALS patients before the ALS diagnosis, as the reference. In a sensitivity analysis, we also compared the mortality rate during the follow-up before ALS diagnosis for the partners of ALS patients to the mortality rate during the entire follow-up of the partners of the ALS-free individuals. Because we hypothesized that the altered mortality among parents and siblings of ALS patients was mainly attributable to shared disease mechanisms between ALS and other diseases, we compared the mortality during the entire follow-up of the parents and siblings of ALS patients, to the mortality during the entire follow-up of the parents and siblings of ALS-free individuals.

In all models we used attained age as the underlying time scale and further adjusted for sex, socioeconomic status (SES), and country of birth of the partners, parents, and siblings, as well as age and sex of the index person (ALS patient or ALS-free individual). Sex and country of birth were obtained from the Multi-Generation Register. We defined SES according to employment information recorded in the Longitudinal Integration Database for Health Insurances and Labor Market Studies (23), and classified as blue-collar, white-collar, farmers, self-employed/other, unemployed or unknown. To assess whether the results differed by sex, in the secondary analyses, we studied male and female partners, fathers and mothers, and brothers and sisters separately. We tested the assumption of proportional hazards using Schoenfeld residuals and found little evidence to support violation of such assumption.

In all analyses we considered associations with two-sided $p < 0.05$ statistically significant. We performed the analyses in Stata software, version 16 (StataCorp, College Station, TX, USA).

Standard protocol approvals, registrations, and patient consents

This study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr 2017/1729-31/1). Individual informed consents were not possible to obtain due to the large sample size and the fact that all study participants with the outcome are deceased. Therefore, consent was waived by the Regional Ethical Review Board.

Results

Table 1 describes the distributions of sex, SES, and country of birth among the partners, parents,

Table 1. Characteristics of the partners, parents and siblings of persons with and without ALS.

	Partners of				Parents of				Siblings of			
	ALS-free individuals ($N = 4,085,294$)		ALS patients ($N = 2,650$)		ALS-free individuals ($N = 5,420,670$)		ALS patients ($N = 4,512$)		ALS-free individuals ($N = 4,954,186$)		ALS patients ($N = 4,542$)	
Characteristics	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Sex												
Men	2,103,629	51.49	1,083	40.87	2,629,210	48.50	2,062	45.71	2,537,794	51.24	2,346	51.65
Women	1,981,665	48.51	1,567	59.13	2,791,460	51.50	2,449	54.29	2,411,419	48.76	2,196	48.35
Socio-economic status												
Blue-collar	1,920,055	47.00	1,362	51.40	2,024,148	37.34	879	19.49	2,371,072	47.95	2,418	53.24
White-collar	1,036,353	25.37	567	21.40	915,068	16.88	372	8.25	1,131,145	22.87	870	19.15
Farmers	97,030	2.38	69	2.60	132,015	2.44	100	2.22	104,460	2.11	160	3.52
Self-employed/Other	778,108	19.05	417	15.74	1,337,771	24.68	1,966	43.58	878,348	17.76	706	15.54
Unemployed	244,136	5.98	233	8.79	956,002	17.64	1164	25.80	388,748	7.86	379	8.34
Unknown	9,612	0.24	2	0.08	55,666	1.03	30	0.67	71,413	1.44	9	0.20
Country of birth												
Sweden	3,798,856	92.99	2,516	94.94	4,877,500	89.98	4,319	95.74	4,864,979	98.38	4,530	99.74
Denmark, Finland, Iceland or Norway	103,389	2.53	76	2.87	256,294	4.73	103	2.28	35,598	0.72	8	0.18
Other	181,784	4.45	56	2.11	259,858	4.79	60	1.33	42,760	0.86	3	0.07
Unknown	1,265	0.03	2	0.08	27,018	0.50	29	0.64	1,849	0.04	1	0.02

Table 2. Mortality among partners of ALS patients after ALS diagnosis in the proband patient, compared with partners of ALS-free individuals, a nationwide cohort study of Sweden, 1961–2013.

	Partners		Male partners		Female partners	
Cause of death	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)
All-cause mortality	357,313	0.98 (0.85–1.12)	255,199	1.03 (0.86–1.23)	102,114	0.91 (0.72–1.14)
Cause-specific mortality						
Infectious and parasitic diseases	4,014	1.41 (0.53–3.77)	2,870	2.40 (0.90–6.44)*	1,144	NA
Neoplasms	141,689	0.84 (0.67–1.06)	86,940	0.94 (0.69–1.28)	54,749	0.75 (0.53–1.06)
Diseases of the blood	708	NA	484	NA	224	NA
Endocrine, nutritional and metabolic disease	7,940	0.83 (0.31–2.22)	5,942	1.29 (0.48–3.44)	1,998	NA
Psychiatric disorders, excluding dementias	4,657	0.82 (0.12–5.83)	3,816	1.31 (0.18–9.32)	841	NA
Diseases of the nervous system, excluding ALS and dementias	5,521	0.84 (0.27–2.60)	3,569	0.51 (0.07–3.63)	1,952	1.25 (0.31–5.01)
Dementias	6,203	1.17 (0.58–2.37)	4,605	0.98 (0.37–2.63)	1,598	1.49 (0.54–4.12)
Diseases of the circulatory system	107,856	0.95 (0.74–1.22)	88,771	0.93 (0.69–1.25)	19,085	1.02 (0.65–1.59)
Diseases of the respiratory system	15,588	1.16 (0.69–1.97)	10,735	1.15 (0.57–2.31)	4,853	1.18 (0.53–2.64)
Diseases of the digestive system	13,315	0.62 (0.23–1.66)	9,763	0.56 (0.14–2.24)	3,552	0.69 (0.17–2.78)
Disease of the skin and subcutaneous tissue	224	NA	165	NA	59	NA
Diseases of the musculoskeletal system	1,413	2.07 (0.52–8.31)	727	2.82 (0.40–20.09)	686	1.65 (0.23–11.74)
Diseases of the genitourinary system	2,251	NA	1,743	NA	508	NA
Unclassified	4,366	1.81 (0.75–4.36)	3,186	1.91 (0.61–5.96)	1,180	1.67 (0.42–6.74)
External causes	38,611	**2.14 (1.35–3.41)*****	29,616	**2.10 (1.16–3.80)****	8,995	**2.21 (1.05–4.65)****
- Suicide	15,721	**2.44 (1.09–5.44)****	11,773	**2.70 (1.01–7.23)****	3,948	2.02 (0.50–8.09)
- Accidents	17,134	**2.09 (1.12–3.90)****	13,810	**2.24 (1.06–4.72)****	3,324	1.82 (0.59–5.67)
- External all other	5756	1.74 (0.43–6.98)	4,033	NA	1,723	3.81 (0.95–15.33)*

HR: hazard ratio; CI: confidence interval; estimates were adjusted for attained age, sex, socio-economic status, and country of birth of the partners as well as age and sex of the index person. NA: not available due to zero deaths among partners of ALS patients. ***$p < 0.001$; **$p < 0.05$; *$p < 0.1$. Bold font indicates associations with two-sided $p < 0.05$.

and siblings of ALS patients and ALS-free individuals.

The mean follow-up time for partners was 54.2 years (standard deviation [SD]: 15.4). After ALS diagnosis, partners of ALS patients had a comparable overall mortality (HR 0.98; 95% CI 0.85–1.12) but a higher mortality due to external causes (HR 2.14; 95% CI 1.35–3.41), both suicide (HR 2.44; 95% CI 1.09–5.44) and accidents (HR 2.09; 95% CI 1.12–3.90), compared with partners of ALS-free individuals (Table 2). Before ALS diagnosis, partners of ALS patients had, however, similar mortality rate as partners of ALS-free individuals, both overall (HR 1.02; 95% CI 0.90–1.14) and for external causes (HR 1.16; 95% CI 0.83–1.62), including suicide (HR 1.30; 95% CI 0.80–2.12) and accidents (HR 1.12; 95% CI 0.67–1.90).

The mean follow-up time for parents was 68.1 years (SD: 15.3). Parents of ALS patients had slightly higher overall mortality than parents of ALS-free individuals (HR 1.03; 95% CI 1.00–1.07) (Table 3). There was a higher mortality due to dementias (HR 1.35; 95% CI 1.17–1.56) as well as diseases of the circulatory system (HR 1.06; 95% CI 1.02-1.11), the respiratory system (HR 1.14; 95% CI 1.01–1.29), and the skin and subcutaneous tissue (HR 2.29; 95% CI 1.26–4.18). They had, however, lower mortality than parents of ALS-free individuals due to neoplasms (HR 0.90; 95% CI 0.83–0.97).

The mean follow-up time for siblings was 47.2 years (SD: 17.5). Siblings of ALS patients had similar overall mortality than siblings of ALS-free individuals (HR 1.06; 95% CI 0.98–1.15) (Table 4). There was however a higher mortality due to dementias (HR 2.30; 95% CI 1.44–3.67), and diseases of the digestive system (HR 1.74; 95% CI 1.27–2.38) and the skin and subcutaneous tissue (HR 4.37; 95% CI 1.05–18.18). Brothers of ALS

Table 3. Mortality among parents of ALS patients, compared with parents of ALS-free individuals, a nationwide cohort study of Sweden, 1961–2013.

	Parents		Fathers		Mothers	
Cause of death	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)
All-cause mortality	2,199,548	**1.03 (1.00–1.07)****	1,169,906	1.00 (0.95–1.05)	1,029,642	**1.07 (1.02–1.12)*****
Cause-specific mortality						
Infectious and parasitic diseases	24,468	1.02 (0.74–1.41)	11,689	1.28 (0.82–1.99)	12,779	0.84 (0.53–1.33)
Neoplasms	574,303	**0.90 (0.83–0.97)*****	300,354	**0.88 (0.79–0.97)****	273,949	0.92 (0.83–1.02)
Diseases of the blood	5,451	0.79 (0.38–1.67)	2,467	1.44 (0.60–3.49)	2,984	0.37 (0.09–1.50)
Endocrine, nutritional and metabolic disease	45,230	0.94 (0.74–1.19)	21,602	0.65 (0.41–1.01)*	23,628	1.14 (0.86–1.51)
Psychiatric disorders, excluding dementias	12,318	1.29 (0.79–2.12)	8,504	1.10 (0.55–2.22)	3,814	1.56 (0.78–3.13)
Diseases of the nervous system, excluding ALS and dementias	21,690	1.32 (0.95–1.82)*	11,169	1.20 (0.73–1.96)	10,521	1.42 (0.93–2.18)
Dementias	81,177	**1.35 (1.17–1.56)*****	26,842	**1.35 (1.03–1.78)****	54,335	**1.35 (1.14–1.61)*****
Diseases of the circulatory system	983,554	**1.06 (1.02–1.11)*****	536,465	1.05 (0.98–1.12)	447,089	**1.08 (1.01–1.15)****
Diseases of the respiratory system	132,851	**1.14 (1.01–1.29)****	70,890	0.98 (0.81–1.17)	61,961	**1.32 (1.13–1.55)*****
Diseases of the digestive system	68,101	0.90 (0.74–1.10)	36,188	0.75 (0.55–1.04)*	31,913	1.04 (0.80–1.35)
Disease of the skin and subcutaneous tissue	2,519	**2.29 (1.26–4.18)*****	930	**3.42 (1.41–8.31)*****	1,589	1.79 (0.79–4.03)
Diseases of the musculoskeletal system	10,569	1.23 (0.81–1.88)	3,346	0.78 (0.29–2.08)	7,223	1.42 (0.89–2.25)
Diseases of the genitourinary system	26,753	1.03 (0.78–1.35)	14,654	1.00 (0.68–1.47)	12,099	1.06 (0.71–1.57)
Unclassified	32,821	**1.30 (1.03–1.63)****	12,353	**1.61 (1.09–2.37)****	20,468	1.16 (0.87–1.56)
External causes	107,082	0.98 (0.81–1.17)	68,461	1.03 (0.82–1.31)	38,621	0.90 (0.68–1.19)
- Suicide	32,160	0.77 (0.50–1.18)	22,061	0.85 (0.51–1.42)	10,099	0.61 (0.28–1.37)
- Accidents	61,095	1.03 (0.83–1.28)	37,904	1.06 (0.79–1.42)	23,191	1.00 (0.73–1.37)
- External all other	13,827	1.06 (0.62–1.83)	8,496	1.34 (0.69–2.58)	5,331	0.72 (0.27–1.93)

HR: hazard ratio; CI: confidence interval; estimates were adjusted for attained age, sex, socio-economic status, and country of birth of the parents as well as age and sex of the index person. NA: not available due to zero deaths among parents of ALS patients. ***$p < 0.001$; ** $p < 0.05$; *$p < 0.1$. Bold font indicates associations with two-sided $p < 0.05$.

patients had a higher overall mortality (HR 1.11; 95% CI 1.00–1.22) and a higher mortality due to suicide (HR 1.50; 95% CI 1.01–2.25).

Supplementary Tables 2–4 display the numbers of deaths among relatives of ALS patients and ALS-free individuals, overall and according to causes of death, during follow-up.

Discussion

Using a nationwide cohort of >50 years of follow-up in Sweden, we found that after ALS diagnosis, partners of ALS patients had a higher mortality due to external causes, especially suicide and accidents, compared with partners of individuals free of ALS. Biological parents and full siblings of ALS patients had a higher mortality due to dementias, compared with parents and siblings of ALS-free individuals. To our knowledge this is the first study to explore causes of mortality among the partners and biological relatives of ALS patients. These findings provide evidence for the need of support to primary caregivers (namely partners) of ALS patients with the aim to achieve best management of ALS care, as well as additional insights to shared mechanisms between ALS and other neurological diseases.

Partners

Although partners of ALS patients had a similar overall mortality compared with partners of ALS-free individuals before the ALS diagnosis, they had a higher mortality due to external causes, including suicide and accidents, after the ALS diagnosis. The increased mortality due to external causes after ALS diagnosis supports our hypothesis that caregivers of ALS patients have an increased mortality due to health outcomes related to severe psychological distress.

Caregivers of patients with chronic and disabling diseases have impaired psychological well-being (25–29), including suicidal ideation (29,30). However, there is a growing body of evidence to

Table 4. Mortality among full siblings of ALS patients, compared with full siblings of ALS-free individuals, a nationwide cohort study of Sweden, 1961–2013.

	Siblings		Brothers		Sisters	
Cause of death	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)
All-cause mortality	300,016	1.06 (0.98–1.15)	184,999	**1.11 (1.00–1.22)****	115,017	1.00 (0.87–1.14)
Cause-specific mortality						
Infectious and parasitic diseases	3,747	1.16 (0.58–2.32)	2,270	1.47 (0.66–3.28)	1,477	0.70 (0.17–2.84)
Neoplasms	103,535	0.94 (0.82–1.08)	52,011	1.02 (0.85–1.22)	51,524	0.86 (0.70–1.05)
Diseases of the blood	669	NA	380	NA	289	NA
Endocrine, nutritional and metabolic disease	7,397	1.38 (0.89–2.14)	4,865	1.54 (0.92–2.55)*	2,532	1.06 (0.44–2.54)
Psychiatric disorders, excluding dementias	4,872	1.15 (0.62–2.14)	3,916	1.00 (0.48–2.10)	956	1.77 (0.57–5.51)
Diseases of the nervous system, excluding ALS and dementias	6,843	1.37 (0.83–2.28)	3,935	1.14 (0.54–2.39)	2,908	1.68 (0.83–3.37)
Dementias	2,872	**2.30 (1.44–3.67)*****	1,430	**2.64 (1.45–4.82)*****	1,442	1.91 (0.91–4.03)*
Diseases of the circulatory system	64,912	0.97 (0.82–1.14)	46,363	0.90 (0.74–1.10)	18,549	1.13 (0.85–1.50)
Diseases of the respiratory system	11,683	1.29 (0.92–1.82)	6,342	1.35 (0.86–2.13)	5,341	1.21 (0.72–2.05)
Diseases of the digestive system	10,559	**1.74 (1.27–2.38)*****	6,973	**1.96 (1.36–2.82)*****	3,586	1.31 (0.70–2.45)
Disease of the skin and subcutaneous tissue	181	**4.37 (1.05–18.18)****	106	**8.28 (1.98–34.73)*****	75	NA
Diseases of the musculoskeletal system	1,263	1.12 (0.36–3.49)	469	1.96 (0.49–7.90)	794	0.60 (0.08–4.30)
Diseases of the genitourinary system	1,475	0.63 (0.16–2.54)	858	1.01 (0.25–4.05)	617	NA
Unclassified	5,524	1.29 (0.69–2.40)	3,574	0.95 (0.39–2.28)	1,950	2.02 (0.84–4.88)
External causes	47,581	1.14 (0.89–1.46)	35,287	1.25 (0.95–1.64)	12,294	0.85 (0.48–1.49)
- Suicide	17,536	1.39 (0.97–1.99)*	12,756	**1.50 (1.01–2.25)****	4,780	1.06 (0.47–2.36)
- Accidents	23,391	1.07 (0.73–1.56)	17,812	1.19 (0.79–1.80)	5,579	0.67 (0.25–1.78)
- External all other	6,654	0.73 (0.33–1.64)	4,719	0.70 (0.26–1.87)	1,935	0.81 (0.20–3.23)

HR: hazard ratio; CI: confidence interval; estimates were adjusted for attained age, sex, socio-economic status, and country of birth of the siblings as well as age and sex of the index person. NA: not available due to zero deaths among siblings of ALS patients. ***$p < 0.001$; ** $p < 0.05$; *$p < 0.1$. Bold font indicates associations with two-sided $p < 0.05$.

suggest that overall mortality might be lower among caregivers compared with the general population (25,26,31–33). For instance, mortality due to external causes was shown to be lower among caregivers (31), but only among the ones with "good mental health" (34). Yet, studies focusing on the level of caregiver burden have shown an increased overall mortality among caregivers with higher perceived burden (35,36). Caregivers of patients with ALS are known to experience severe burden both physically and mentally (1), which could possibly explain our results of an increased mortality due to suicide among partners of ALS patients. This is also in line with a Danish study which found increased mortality due to external causes, including suicide, among spouses of patients with Parkinson's disease (37).

The increased mortality due to accidents among partners of ALS patients could possibly also be caused by impaired psychological wellbeing after ALS diagnosis. For instance, depressive symptoms are known to increase the risk of accidental falls (38–40). Depressive symptoms and treatment of depression (e.g. antidepressants) might also contribute to the risk of traffic accidents. For instance, studies have shown driving impairment and increased risk of car accidents among patients with depression who were on treatment of antidepressants (41–43). Because our study is, to our knowledge, the first to assess mortality among partners to ALS patients, these findings need to be verified in future studies of independent populations.

Finally, although not statistically significant, there was some evidence for a higher mortality due to dementias and diseases of the musculoskeletal system among female partners whereas a higher mortality due to infectious or parasitic diseases, psychiatric disorders, and diseases of the musculoskeletal system among the male partners of ALS

patients. These results must be interpreted with caution however, considering the possibility of chance finding.

Parents

Parents of ALS patients had a slightly higher overall mortality, compared with parents of ALS-free individuals. To our best knowledge, there has been one previous study on overall mortality among parents of ALS patients, which failed to find a difference in overall mortality between parents of ALS patients and parents of ALS-free controls (44). The previous study included however only 487 ALS patients and used self-reported information, making recall bias and random error potential concerns.

The increased mortality in cardiovascular diseases among parents, primarily mothers, has not been reported before. Visser et al. found a lower mortality due to cardiovascular diseases among parents of 487 ALS patients compared with parents of controls (44). Huisman et al. found a lower risk of myocardial infarction among parents, siblings, grandparents, aunts, and uncles of 635 ALS patients when compared with relatives of controls (45). Byrne et al. found no difference in mortality due to cardiac disease or stroke, when comparing first- and second-degree relatives of 172 ALS patients to relatives of controls (46). The conflicting findings between the present study and these previous studies might be due to different study design (cohort study versus case-control study), nature of data collection (prospective data collection through registers versus retrospective data collection through self-report), sample size (3,092 ALS cases in the present study versus 487, 635 and 172 ALS cases respectively in the previous studies), definition of cardiovascular outcomes (mortality versus clinical diagnosis), and perhaps also the representativeness of the ALS sample (entire population of ALS patients in the present study). Using a large register-based study in Denmark, Trabjerg et al. did not find an increased risk of clinical diagnosis of cardiovascular disease among first-degree relatives of ALS patients (47). This study did, however, not study death due to cardiovascular disease and also used a narrower definition of cardiovascular disease than the present study.

Mortality due to other reasons is less studied in parents of ALS patients. A higher mortality due to dementias was expected (9,10,12). The underlying reason for a higher mortality due to respiratory diseases among the parents of ALS patients (primarily mothers) remains unknown. Underdiagnosis of ALS among parents might be one possible explanation as respiratory failure is a common cause of death among patients with ALS. The finding on reduced mortality due to neoplasms among parents of ALS patients is intriguing. No difference in cancer mortality has previously been found between parents of ALS patients and parents of controls (44,46). A meta-analysis failed to detect an association between ALS and cancer, relying on two studies of 4,836 participants (18). Neither did our previous study find an association between cancer and ALS (17). In contrast to these, Gibson et al (2016) found a lower risk of cancer among ALS patients (48). Finally, the increased mortality due to diseases in skin or subcutaneous tissue seen in parents and siblings (mainly male relatives), has never been reported and needs to be verified. One study did find an increased prevalence of bullous pemphigoid in a cohort of 168 ALS patients (49). Turner et al. did, however, not find an elevated risk of ALS among persons with pemphigoid (19).

Siblings

There was no difference in overall mortality between siblings of ALS patients and siblings of ALS-free individuals. When studying brothers and sisters separately, we found the brothers of ALS patients to have a slightly higher overall mortality compared with brothers of ALS-free individuals.

Siblings of ALS patients had a higher mortality due to dementias, corroborating the findings of concurrence between ALS and other neurodegenerative diseases (9,10,12). Brothers appeared to be main contributors to the increased mortality due to dementias. Further studies are needed to verify this possible sex difference, which was not noted among parents.

Siblings, primarily brothers, of ALS patients also had a higher mortality due to diseases of the digestive system, which includes alcoholic liver disease. Two studies reported a higher prevalence of alcoholism among first- and second-degree relatives of ALS patients (11,46). A study by Yu et al. found elevated alcohol consumption to be causally associated with ALS using Mendelian randomization (50). Ji et al., however, found an inverse association between alcohol use disorders and incidence of ALS (51). Two other studies found however no difference in alcohol intake between ALS patients and controls (52,53).

A higher risk of suicide was also noted among brothers, but not sisters, of ALS patients, compared with brothers of ALS-free individuals. The underlying reason for this risk increase is unknown but might be partially attributable to the shared genetic background between ALS and psychiatric disorders (e.g. schizophrenia) (54) and likely also the higher prevalence of dementias and alcohol misuse among brothers of ALS patients. The latter hypothesis is based on the increased mortality due to dementias and digestive diseases as discussed above, and needs to be verified in future studies.

We found some different results between parents and siblings. This might be explained by a greater number of deaths among parents due to their older age and longer follow-up, in addition to perhaps also socioeconomic differences between the generations.

Strengths and limitations

The main strength of our study is the nationwide population-based design, the complete follow-up, the large sample size, and the prospectively and independently collected information on ALS diagnosis, familial links, and causes of death. A few limitations need to be discussed. For instance, we lacked information on clinical characteristics of ALS, and could not study if the result pattern would differ for ALS patients of different subgroups (e.g. genetic causes). The prevalence of C9orf72 expansion repeats in ALS in Scandinavian countries is reported higher than in other European countries (55–57). C9orf72 expansion repeats offer a link between ALS, frontotemporal dementia, and other neurological diseases and psychiatric disorders (54,58). Although the ALS diagnosis of the Swedish Patient Register has a positive predictive value of >90% according to a validation study from Stockholm (59), some misclassification of ALS diagnosis might still occur. To increase the accuracy, we identified ALS patients via at least two hospital records. Because we identified ALS patients from the Swedish Patient Register with records on hospital discharge diagnoses since 1964 and outpatient specialist care since 2001, ALS patients that were merely cared for in outpatient specialist care and never in an inpatient setting before 2001 would not have been captured in our data. The proportion of such patients is however believably low. For instance, in our data, among all patients diagnosed with ALS during 2001–2010, 11.9% had only records from outpatient hospital care. In addition, although the Causes of Death Register is shown to have high accuracy, misclassification exists to some extent still, especially among elderly people (60). Another limitation is the definition of partners. As we did not possess information on who the ALS patient was living with at the time of diagnosis, we defined partners as the ones sharing the youngest child (biological or adoptive) with the patient. Since the birth of the youngest child, some couples might have separated or were never cohabitating. As a result, some partners we identified might not be the primary caregivers of ALS patients. Also, we did not capture partners that did not have a child in common. These issues are however not likely to be differential between the exposed (partners of ALS patients) and unexposed (partners of ALS-free individuals) groups and would most likely have led to an underestimate of the real association. Further, due to their relatively young age, we did not study mortality among children of ALS patients. Future studies are needed to understand the non-fatal health outcomes of these children. Finally, because of the relatively big number of tests performed in the study, some of the findings might have been due to chance.

Conclusion

After ALS diagnosis, partners of ALS patients showed a higher mortality due to external causes (e.g. suicide and accidents), potentially attributable to severe psychological distress experienced after the ALS diagnosis. Parents and full siblings of ALS patients showed a higher mortality due to dementias, providing further evidence for the shared mechanisms between ALS and other neurodegenerative diseases.

Disclosure statement

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Data availability statement

The data are not publicly available due to privacy or ethical restrictions.

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