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Risk factors for amyotrophic lateral sclerosis: A regional United States case-control study

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Abstract

Most amyotrophic lateral sclerosis (ALS) cases are considered sporadic, without a known genetic basis, and environmental exposures are thought to play a causal role. To learn more about sporadic ALS etiology, we recruited n = 188 ALS patients from northern New England and Ohio and matched controls 2:1 from the general population of the same regions. Questionnaires evaluated the association between a variety of lifestyle, behavioral (ie, hobbies and activities), and occupational factors and the risk of ALS, including the duration of time between exposure and ALS onset, and exposure frequency. Head trauma was associated with increased ALS risk (adjusted odds ratio [OR] 1.60 95% confidence interval [CI] 1.04-2.45), with significantly greater effects for injuries occurring 10 or more years prior to symptom onset

ABBREVIATIONS: ALS, amyotrophic lateral sclerosis; CDC, Centers for Disease Control and Prevention; 95% CI, 95% confidence interval; IRB, institutional review board; PLS, primary lateral sclerosis; PMS, primary muscular atrophy; OR, odds ratio; Pb, lead; sALS, sporadic amyotrophic lateral sclerosis; SMR, standardized morbidity ratio.

(*P* = .037). ALS risk was increased for those reporting severe electrical burns (adjusted OR 2.86, 95% CI 1.37-6.03), with odds ratios highest for burns after age 30 (OR 3.14), and for burns 10 or more years prior to symptom onset (OR 3.09). Hobbies involving lead were the most strongly associated with ALS risk (adjusted OR 2.92, 95% CI 1.45-5.91). Exposures to lead 20 or more years prior to diagnosis had larger effect sizes compared to those occurring more recently. Holding a job in mechanics, painting, or construction was associated with ALS. The identification of these specific environmental factors associated with ALS highlight the need for future prospective and laboratory studies to assess causality, biological mechanisms, and find prevention or treatment opportunities.

KEYWORDS

amyotrophic lateral sclerosis, electrocution, head injury, lead, occupation, risk factors

1 | INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a debilitating lethal disease characterized by progressive loss of motor neurons.[1] The majority of cases are considered sporadic, and several environmental associations have been reported.[2] In sporadic ALS (sALS), patients may have a genetic predisposition to develop the disease that interacts with environmental influences to produce motor neuronal degeneration and manifestation of ALS over time.[3,4]

A systematic review of observational studies found evidence supporting the following risk factors: exposure to the toxic metals lead (Pb) and mercury, pesticides, and solvents, electric shock, head trauma, and occupation (reviewed in Wang et al[5]). Another meta-analysis of 16 different exposures found lead to be the only factor with "convincing evidence".[6] Head injury was one of the associations supported by "suggestive evidence"; however, the authors raised the concern that this observation could be due to reverse causation.[6] In this scenario, patients experiencing early unrecognized ALS symptoms of weakness could fall and be injured. While these falls are statistically associated with the disease, they could not be considered a potential antecedent or causal factor. Additional work evaluating the time lag between these exposures and ALS diagnosis is needed to clarify this relationship.

We performed a case-control study of ALS patients from northern New England and Ohio, using age- and gender-matched random controls from the general population of these regions. Questionnaires evaluated the association between the timing of a variety of lifestyle, behavioral (ie, hobbies and activities) and occupational factors as risk factors for ALS.

2 | METHODS

ALS patients were enrolled through medical centers and clinics in New Hampshire, Vermont, and Ohio (Supplement 1). Participants were required to be at least 21 y of age and residents of New Hampshire, Vermont, Maine, or Ohio at the time of enrollment (2016-2020). The eligible ALS patients were newly diagnosed cases with either definite or probable ALS according to the Awaji-modified El Escorial criteria.[7] Eligible diagnoses included progressive bulbar palsy, but not primary muscular atrophy (PMA) or primary lateral sclerosis (PLS).

The population-control participants, selected from among the same catchment counties as the cases, were identified as residents of New Hampshire, Vermont, or Ohio using the U.S. Postal Service Delivery Sequence file licensed to Marketing Systems Group (Horsham, PA). The sampling algorithm was designed based on the expected demographic distribution of the ALS cases, with oversampling of 50-75 y-olds and males. Questionnaires were mailed out to the sampled individuals, followed by a postcard reminder. Questionnaire response rates were 56% for ALS patients and 10% for the population controls. We had eligible participant questionnaire data on n = 188 ALS cases and n = 508 population controls. We used the R-package "MatchIt" to perform propensity score matching with a 2:1 ratio to select a subset of n = 376 population control questionnaires as a comparison group with a similar distribution of age and gender to that of the cases.[8] This procedure selects two controls with the nearest age and same gender as each case. Participants who returned a completed questionnaire received a $20 reimbursement.

We evaluated lifestyle and environmental risk factors using a questionnaire (Supplement 2). Subjects were asked to report if they participated in a variety of activities at least twice a month for a year or longer, as well as questions about employment and hobbies. Coding of occupational titles was performed manually to assign job titles to an industry. Based on our prior work, we assessed the ALS risk associated with occupations that are likely to involve industrial chemical exposure. Specifically job titles involved in construction, manufacturing, mechanics, or painting were used as a surrogate for possible exposure.[9]

Participants consented to join the study. All study procedures were approved by the Committee for Protection of Human Subjects at Dartmouth College and the local committees at each contributing institution. The Centers for Disease Control and Prevention (CDC) provided technical assistance and CDC Institutional Review Board (IRB) approval was not warranted.

TABLE 1 Characteristics of questionnaire participants in Ohio and northern New England

		Controls N = 376 (%)	ALS patients[a] N = 188 (%)	Univariate *P*-value
Gender	Female	142 (37.8)	78 (41.5)	.45
	Male	234 (62.2)	110 (58.5)	
Age (y)	<50	33 (8.8)	15 (8.0)	.98
	50-65	174 (46.3)	86 (45.7)	
	65-75	129 (34.3)	66 (35.1)	
	75+	40 (10.6)	21 (11.2)	
Family history	No	368 (97.9)	170 (90.4)	<.001
	Yes	8 (2.1)	18 (9.6)	
Race white	No	27 (7.2)	16 (8.5)	.70
	Yes	349 (92.8)	172 (91.5)	
Smoked >100 cigarettes	Ever	195 (51.9)	98 (54.1)	.68
	Never	181 (48.1)	83 (45.9)	
Strenuous athletic activities	No	212 (57.0)	105 (58.0)	.89
	Yes	160 (43.0)	76 (42.0)	
Education	<=High school	127 (34.2)	65 (36.7)	.90
	College	113 (30.5)	48 (27.1)	
	Other	21 (5.7)	12 (6.8)	
	Graduate school	64 (17.3)	32 (18.1)	
	Technical degree	46 (12.4)	20 (11.3)	

[a]Confirmed cases (El Escorial). Includes OH, NH, VT, ME. Age > 25, controls age-matched.

TABLE 2 Head injuries associated with ALS risk in Ohio and northern New England

		Controls N = 376 (%)	ALS patients N = 188 (%)	Univariate *P*-value	Multivariable[a] OR	95% CI	
"Head trauma or concussion that caused you to black out or lose consciousness"	No	298 (80.3)	131 (71.2)	.021	1.0 (ref)		
	Yes	73 (19.7)	53 (28.8)		1.60	1.04	2.45
Head injury frequency	None	311 (82.9)	140 (74.5)	.057	1.0 (ref)		
	One	45 (12.0)	35 (18.6)		1.66	1.00	2.75
	Multiple	19 (5.1)	13 (6.9)		1.51	0.68	3.22
Last injury occurred:							
<=10 y of index year	No	360 (95.7)	178 (94.7)	.72	1.0 (ref)		
	Yes	16 (4.3)	10 (5.3)		1.21	0.50	2.78
10+ y prior to index year	No	320 (85.1)	146 (77.7)	.037	1.0 (ref)		
	Yes	56 (14.9)	42 (22.3)		1.64	1.02	2.61
20+ y prior to index year	No	327 (87.0)	153 (81.4)	.10	1.0 (ref)		
	Yes	49 (13.0)	35 (18.6)		1.56	0.94	2.55
30+ y prior to index year	No	334 (88.8)	158 (84.0)	.14	1.0 (ref)		
	Yes	42 (11.2)	30 (16.0)		1.61	0.95	2.72
40+ y prior to index year	No	351 (93.4)	167 (88.8)	.092	1.0 (ref)		
	Yes	25 (6.6)	21 (11.2)		1.92	1.02	3.58
Age at last injury:							
Age < =30 y	No	317 (84.3)	153 (81.4)	.45	1.0 (ref)		
	Yes	59 (15.7)	35 (18.6)		1.28	0.78	2.06
Age 30+ y	No	353 (93.9)	166 (88.3)	.032	1.0 (ref)		
	Yes	23 (6.1)	22 (11.7)		1.80	0.94	3.43

[a]Adjusted for age, gender, smoking, family history.

TABLE 3 Electrical burns associated with ALS risk in Ohio and northern New England

		Controls N = 376 (%)	ALS patients N = 188 (%)	Univariate *P*-value	Multivariable[a]		
					OR	95% CI	
Severe electrical burn/electrocuted	No	357 (96.0)	166 (90.2)	.012	1.0 (ref)		
	Yes	15 (4.0)	18 (9.8)		2.86	1.37	6.03
Electrocution frequency	None	362 (96.3)	174 (92.6)	.16	1.0 (ref)		
	One	11 (2.9)	11 (5.9)		2.20	0.90	5.37
	Multiple	3 (0.8)	3 (1.6)		2.51	0.46	13.79
Last burn occurred:							
<=10 y of index year	No	374 (99.5)	187 (99.5)	1	1.0 (ref)		
	Yes	2 (0.5)	1 (0.5)		1.22	0.06	13.02
10+ y prior to index year	No	363 (96.5)	171 (91.0)	.010	1.0 (ref)		
	Yes	13 (3.5)	17 (9.0)		3.09	1.44	6.77
20+ y prior to index year	No	363 (96.5)	173 (92.0)	.034	1.0 (ref)		
	Yes	13 (3.5)	15 (8.0)		2.66	1.21	5.94
30+ y prior to index year	No	364 (96.8)	174 (92.6)	.04	1.0 (ref)		
	Yes	12 (3.2)	14 (7.4)		2.81	1.24	6.42
40+ y prior to index year	No	370 (98.4)	182 (96.8)	.35	1.0 (ref)		
	Yes	6 (1.6)	6 (3.2)		2.46	0.74	8.13
Age at last burn:							
Age < =30	No	366 (97.3)	178 (94.7)	.17	1.0 (ref)		
	Yes	10 (2.7)	10 (5.3)		2.32	0.91	5.88
Age 30+	No	370 (98.4)	179 (95.2)	.052	1.0 (ref)		
	Yes	6 (1.6)	9 (4.8)		3.41	1.17	10.57

[a]Adjusted for age, gender, smoking, family history.

2.1 | Statistical analysis

We started by testing for univariate associations between the response variable, ALS case-control status of participants, and categorical predictor variables by utilizing the chi-squared test of independence and Fisher's exact test. These analyses were used to select exposures or lifestyle factors for the subsequent multivariable analysis described below.

Multivariable modeling used case-control status as the outcome in an unconditional logistic regression analysis with adjustment for the potential confounders age, gender, family history, and smoking status. The index year was defined as the year of diagnosis for ALS patients, or an equivalent year for controls. We assessed latency by calculating the time between the year of last exposure and the index year, grouped in decades (years prior to index year <=10, 10+, 20+, 30+, 40+). We assessed the frequency of injury as none, one, or multiple. These analyses were all performed using R: A Language and Environment for Statistical Computing, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

ALS patients (n = 188) and their 2:1 matched controls were similar for age, gender, race, and smoking (Table 1). Approximately half of the ALS patients were in the age range of 50-65 y. Almost all of the controls and ~90% of the ALS patients had no family history of ALS. The proportion participating in strenuous athletic activities was similar among cases and controls. The level of education was also similar among the two groups, with approximately one-third having finished their schooling with no more than a high school degree, and one-fifth having attended graduate school. The demographics of age and race for those who answered the questionnaire were similar to the identified cases who did not submit a questionnaire (Supplement 3). The questionnaire respondents included a slightly higher proportion of males, were more likely to have had genetic testing, and to be taking riluzole. The median time from symptom onset to the questionnaire was 1.5 y.

Our questionnaire asked about head trauma or concussion that caused a "blackout" or loss of consciousness. More ALS patients reported ever having such an injury, compared to controls, adjusted for age, gender, smoking, and family history (Table 2). ALS risks were similarly increased in participants reporting single or multiple injuries. Injuries occurring less than 10 y prior to symptom onset were not significantly related to ALS. Earlier injuries significantly increased risk if the last injury was 10 or more years prior to diagnosis, and the risk was even higher if the last injury was 40 or more years prior, slope = 0.014). The risk was increased for head injuries that occurred both before age 30 and after age 30, but was stronger for the latter.

TABLE 4 Lead exposure via hobbies associated with ALS risk in Ohio and northern New England

		Controls N = 376 (%)	ALS patients N = 188 (%)	Univariate *P*-value	Multivariable[a] OR	95% CI	
Compilation of cast Pb bullets, used Pb weights, glass with Pb joints	No	359 (95.5)	169 (89.9)	.018	1.0 (ref)		
	Yes	17 (4.5)	19 (10.1)		2.92	1.45	5.91
Glass with Pb joints	No	373 (99.2)	184 (97.9)	.35	1.0 (ref)		
	Yes	3 (0.8)	4 (2.1)		3.03	0.66	15.64
Cast Pb bullets	No	372 (98.9)	180 (95.7)	.03	1.0 (ref)		
	Yes	4 (1.1)	8 (4.3)		4.97	1.52	19.05
Cast or used Pb sinkers	No	365 (97.1)	179 (95.2)	.38	1.0 (ref)		
	Yes	11 (2.9)	9 (4.8)		2.05	0.80	5.14
Stopped using Pb:							
<=10 y of index year	No	366 (97.3)	178 (94.7)	.171	1.0 (ref)		
	Yes	10 (2.7)	10 (5.3)		2.48	0.98	6.26
10+ y prior to index year	No	369 (98.1)	180 (95.7)	.165	1.0 (ref)		
	Yes	7 (1.9)	8 (4.3)		2.76	0.97	8.03
20+ y prior to index year	No	373 (99.2)	180 (95.7)	.013	1.0 (ref)		
	Yes	3 (0.8)	8 (4.3)		6.54	1.85	30.29
30+ y prior to index year	No	373 (99.2)	181 (96.3)	.032	1.0 (ref)		
	Yes	3 (0.8)	7 (3.7)		5.79	1.57	27.34
40+ y prior to index year	No	375 (99.7)	185 (98.4)	.214	1.0 (ref)		
	Yes	1 (0.3)	3 (1.6)		6.70	0.84	136.94

[a]Adjusted for age, gender, smoking, family history.

TABLE 5 Jobs associated with ALS risk in Ohio and northern New England

Ever held a job in:		Controls N = 376 (%)	ALS patients N = 188 (%)	Univariate *P*-value	Multivariable[a] OR	95% CI	
Mechanics	No	349 (92.8)	165 (87.8)	.067	1.0 (ref)		
	Yes	27 (7.2)	23 (12.2)		2.05	1.10	3.79
Painting	No	366 (97.3)	177 (94.1)	.099	1.0 (ref)		
	Yes	10 (2.7)	11 (5.9)		2.37	0.96	5.92
Manufacturing	No	330 (87.8)	162 (86.2)	.69	1.0 (ref)		
	Yes	46 (12.2)	26 (13.8)		1.16	0.66	1.99
Construction	No	348 (92.6)	165 (87.8)	.087	1.0 (ref)		
	Yes	28 (7.4)	23 (12.2)		2.17	1.16	4.02

[a]Adjusted for age, gender, smoking, family history.

More than twice as many ALS cases than controls reported ever having had severe electrical burns or having been electrocuted (Table 3). Risks did not significantly differ for single vs multiple burns ($P = .16$). The risk of ALS was not elevated for events occurring within 10 y of symptom onset but was >three-fold higher for burns 10 or more years prior to diagnosis and remained more than two-fold for burns occurring 20, 30, and 40 y prior. This risk was more elevated among those suffering burns after age 30 (~ three-fold), vs before age 30 (~ two-fold).

Among all the various hobbies, those involving lead were the most strongly associated with ALS risk, with a approximately three-fold increased risk adjusted for age, gender, family history, smoking status (Table 4). These activities included casting lead bullets, making stained glass with lead joints, and casting or using lead fishing sinkers. Latency analysis showed that the larger effect sizes were associated with exposures many year prior to diagnosis, rather than those occurring more recently (going from approximately two-fold for exposures ≤10 y prior, up to approximately six-fold for exposures 20+ y prior, slope = 0.11) (Table 4).

Each participant in the study reported up to five past occupations, and increased risk of ALS was associated with ever holding a job in mechanics, painting, or construction, compared to all other job

categories pooled together (Table 5). Compared to controls, more ALS patients had been mechanics, painters, or construction workers (adjusted for age, gender, family history, and smoking status). However, manufacturing jobs were not significantly associated with increased odds of ALS.

After stratifying the results by gender, we saw similar trends in the risk of ALS for head injury and lead exposure (adjusted ORs: head injury 1.49 for males, 1.86 for females; lead exposure 3.06 for males, 2.30 for females). Several risk factors were rare among females (with 3 or fewer ALS cases), but in an analysis restricted to males, the risks remained similar to those reported overall (adjusted ORs for males: electrocution 2.70; job as a mechanic 2.41, a painter 3.28, in manufacturing OR 1.32, and in construction 1.85).

Within ALS patients, we assessed whether risk factors modified the age at diagnosis (Supplement 4). Family history of ALS was associated with diagnosis at a mean age of ~60 y, vs age ~ 65 y for those without (P = .049), while the other factors did not show substantial differences.

Post-hoc calculations show that our study had 62% power to detect an OR of 1.60 for head trauma, 84% power for an OR of 2.86 for electric shock, 88% power for an OR of 2.92 for lead exposure, 69% power for an OR of 2.05 for mechanics, 52% power for an OR of 2.37 for painting, and 77% power for an OR of 2.17 for construction.

4 | DISCUSSION

Results of our case-control study of ALS risk in northern New England and Ohio support the environmental factors reported in studies in other geographic regions. We provide new temporal insights into the relationship between ALS and head injury, electric burns, and lead exposure.

Our data show that the association between head trauma and ALS risk increased for injuries more than 10 y prior to disease onset, and was larger with injuries occurring after age 30. A 1987 report showed a history of physical injuries to the head, neck, shoulder, or arm in a majority (58% of n = 78) of ALS patients.[10] Longitudinal studies following n = 821 brain-injured patients, and 438 American football players compared to 140 controls attending high-school 1946-1956, were suggestive of increased ALS risk, but did not achieve statistical significance.[11,12] Reports of high rates of ALS among Italian soccer players brought international attention to this hypothesis,[13] prompting the 2006 meta-analysis that found increased risk of ALS associated with prior head injuries (OR 1.7, 95% CI 1.3-2.2), but not with physical injuries to other body parts.[14] Chio et al. reanalyzed this cohort in 2009 and confirmed a higher rate of ALS in Italian professional soccer players (standardized morbidity ratio [SMR] 6.45, 95% CI 2.78-12.70, P < .00001), but not in professional basketball players or road cyclists, who in general do not suffer frequent head injuries.[15] Among the soccer players, midfielders (who head the ball back from goal kicks) have the highest risk of all positions.[15]

Analyses of medical records in the United Kingdom and in Sweden both found an overall increased risk of ALS with severe head injury, but only within a year after the injury, raising controversy about the causal link and speculation about reverse causation.[16,17] The lack of an association within 10 y of symptoms, and the consistency of the positive odds ratios that we observed for injuries occurring out to 40 or more years prior to diagnosis argues against reverse causation as an explanation for our finding. The medical records analyses quoted in these United Kingdom and Swedish studies could not evaluate the risk of more mild injuries and blackouts that rarely lead to physician care, but which are included in questionnaire-based studies such as ours, which also included frequency of injuries. Supporting the difference between acute and chronic repeated injuries, a single focal brain injury did not induce ALS-like signs in a transgenic SOD1 rat model[18]; however, repeated mild bilateral traumatic brain injury accelerated ALS-like signs onset in this model.[19] Likewise, *Drosophila* ALS models demonstrated that chronic traumatic brain injury induces stress granule formation and neurodegeneration.[20] A study of the records of 3650 incident Danish ALS cases found an association between head trauma prior to age 55 (OR 1.22, 95% CI 1.08-1.37), but not at older ages (OR = 0.97).[21] Likewise, a study of 575 European ALS patients and 1150 controls found a three-fold increased risk of ALS with two or more head injuries, and a two-fold increased risk in 35-54 y-olds.[22] Similarly, a Chinese case-control study found a 3.4-fold increased risk associated with head trauma.[23]

A 1991 study of n = 17 cases and other case-reports documented ALS developing following electrical accidents.[24,25] In one case, a 42 y-old shocked on the left hand from a 110 V circuit developed left arm progressive weakness and atrophy within 3 mo. The symptoms then spread, leading to death after 3 y, with classical ALS neuropathology in the corticospinal tracts.[26] While the mechanism is unknown, electrocution causes neuronal damage, ischemia, and neuronal death, and might also impair vasculature, leading to delayed spinal cord injury.[26]

Our data show that self-reported electrical injury, defined as a severe electrical burn or electrocution, may act as a potential risk factor for ALS. The findings were statistically significant for burns occurring 10 or more years prior to disease onset. Effect sizes were larger after age 30, vs before. A case-control study of 110 ALS cases vs 240 controls linked electrical injury to a 6.2-fold increased ALS risk.[27] A recent pooled European case-control study using job-exposure matrices also found increased risk associated with potential for electric shock exposure (OR 1.23, 95% CI 1.05-1.43),[28] supporting our findings.

We found that participating in hobbies involving lead exposure, including casting lead bullets, making stained glass with lead joints, and casting or using lead sinkers, was associated with a nearly three-fold increase in ALS risk. Lead exposure has been consistently documented as an ALS risk factor.[5] Animal studies demonstrate the transport of Pb^{++} ions across the blood-brain barrier.[29] The mechanisms linking lead to ALS are not fully understood, but lead induces free radical formation that causes peroxidative damage to cell walls, resulting in neuronal cell death.[30] A recent study found that both lead and methyl mercury can disrupt TDP-43 in cultured neurons, forming nuclear granules and accumulation of insoluble TDP-43 in the cortex of exposed mice.[31] Also, blood lead levels in ALS patients have been reported to be significantly higher than controls.[32-34]

Our historical data on the interval from exposure to diagnosis of ALS demonstrate a greater risk of ALS with earlier lead exposures that stopped 20 to 40+ y prior to diagnosis, compared to exposures stopping

more recently (<20 y ago). Consistent with this is a Danish report that occupational lead exposure 10-y prior to diagnosis increased ALS risk (OR 1.33, 95% CI 1.03-1.72).[35] Bone lead levels have been reported to be higher in ALS patients.[36,37] The long intervals between exposure and diagnosis could be related to re-cycling of stored bone lead later in life.[38] Lead is predominantly stored in bone, replacing calcium. When the bone is remodeled, lead is released into the bloodstream, thus serving as a long-term endogenous exposure source many years or decades after the original inhalation or ingestion events.[39] A large Swedish record-based study linked fractures outside the head/face region to an increased risk of ALS, which remained elevated up to 18 y after the fracture (n = 4690 cases, HR 1.20, 95% CI 1.01-1.43).[40] The authors of this Swedish study speculated that lead exposure could promote an "increase of bone turnover and demineralization leading to a positive feedback cycle" that involved decreased bone strength (fractures) and increased blood lead.[40] Because of these unique pharmacokinetics, lead exposure may have a longer-term impact on ALS risk than other contaminants. Geospatial analysis by Sabel et al. detected a cluster of ALS cases based on mapping residential location the time of birth, supporting the idea that early life exposures may play a role in ALS.[41]

We specifically analyzed occupations identified in our prior study assessing the relationship between workplace exposures and the risk of ALS in northern New England.[9] In the current study with a more recent and larger northern New England / Ohio ALS cohort, ever holding a job in mechanics, painting, and construction were each associated with a 2-fold increased risk of ALS. Other studies have reported a higher risk of ALS for construction workers, both in New England 1993-1996 (OR = 2.9, 95% CI 1.2-7.2), and in Denmark 1982-2013 (OR 1.21, 95% CI 1.05-1.39).[42,43] In a Pennsylvania study of 66 cases and matched controls, occupational exposure to metals was associated with a 3.65-fold increased risk (95% CI 1.15-11.60).[44] While the "manufacturing" category did not show a statistically significant association with ALS in our current analysis, this is likely due to the lack of specificity of the jobs that we aggregated in this group. Prospective assessment of a large cohort of 1 million subjects detected an increased risk of ALS mortality for female "machine assemblers" (OR 2.81, 95% CI 1.05-7.53, P = .04).[45] Likewise, a nested case-control study in the Swedish National Patient Register found an increased association of "precision tool manufacturing" with ALS diagnoses 1991-2010 (OR 1.68, 95% CI 1.11-2.52).[46]

Limitations of our study include small numbers of cases for the analysis of subgroups of certain exposure and latency factors, and lower questionnaire response rates. The demographics of those who answered the questionnaire were similar to those of the non-respondents. The associations we observed are unlikely to be due to recall bias, as the cases were not significantly more likely than controls to respond affirmatively to the general question: "Did your job(s) or hobbies involve exposure to potentially harmful chemicals?" (P = .18). If cases had recalled more exposures than controls, we would have expected to see an association with this question. Nevertheless, ALS patients may be more likely to recall life events (eg, head injury) due to thinking about what may have caused their illness.

Overall, our results support previous reports of head injury, electric shock, lead exposure, and certain occupations as ALS risk-factors. Our findings of the long interval between exposures and the diagnosis of ALS are particularly important. Some exposures 20 or more years prior to diagnosis had the largest effects on ALS risk. Beyond the well-documented effects of lead on cognitive impairment in children, the potential long-term risks of age-related ALS linked to adult lead exposure needs more emphasis. From a public health standpoint, the increases in ALS risk reported here and in the literature are important to address and prompt a need for encouraging public use of mitigation strategies, such as switching to lead substitutes, promoting helmet use, and installing ground fault circuit interrupters, which are important for overall health, and may also reduce the possibility of later development of ALS.

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DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of ATSDR, CDC, and/or the HHS.

FINANCIAL DISCLOSURE

The authors report no disclosures.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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