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Population-based study of amyotrophic lateral sclerosis and occupational lead exposure in Denmark

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Abstract

Objectives—Previous research has indicated links between lead (Pb) exposure and increased risk of neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS). in this study, we evaluated the association between occupational Pb exposures and ALS.

Methods—ALS cases were ascertained through the Danish National Patient Registry from 1982 to 2013 and age and sex-matched to 100 controls. Using complete employment history since 1964 from the Danish Pension Fund, cumulative Pb exposure was estimated for each subject via a Danish job exposure matrix. Associations were evaluated using conditional logistic regression analyses and stratified by sex.

Results—For men with >50% probability of exposure, there was an increase in odds of ALS for exposures in the 60th percentile or higher during any time 5 years prior to diagnosis (aOR: 1.35; 95% Ci 1.04 to 1.76) and 10 years prior to diagnosis (aOR: 1.33; 95% Ci 1.03 to 1.72). No significant associations were observed in women, and there were no linear trends seen for Pb exposures for either sex.

Conclusions—Our study indicates an association between consistently higher occupational Pb exposures and ALS. These findings support those of previously reported associations between ALS and specific occupations that commonly experience Pb exposure.

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Contributors MGW and JH designed the study and directed its implementation. JH and OG gathered data. ASD performed data analysis and drafted the article. MGW, JH and AJS revised the manuscript.

Competing interests None declared.

Patient consent for publication Not required.

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease with an average survival time of 3–5 years postdiagnosis.[1] Reports from Denmark indicate an annual incidence of 1–2 new ALS cases per 100 000 people.[2] Although approximately 10% of ALS cases are attributed to genetic inheritance,[3] the aetiology of sporadic ALS is not generally understood. However, many hypothesise that ALS may be the result of pre-existing genetic risk and environmental triggers.[14]

Lead (Pb) is one environmental exposure that is a well-known neurotoxicant with previous evidence of cognitive impairment and decline.[56] Pb typically interacts with tissues through transport pathways for calcium and iron and has been shown to enter brain cells primarily through calcium pathways.[7] Similarly, the neurotoxicity of Pb is primarily through the disruption of calcium-dependent processes in the brain, altering the release of neurotransmitters, causing oxidative damage and cell death.[89] Additionally, Pb can circumvent the blood-brain barrier and allow further oxidative damage to neural tissue.[89] Through these disruption pathways and increased susceptibility to environmental insults, Pb could play a part in substantially increasing the risk of neurological disorders such as ALS, with epidemiological evidence in other neurodegenerative diseases and cognitive function supporting this association.[51011] Some meta-analyses have suggested that exposure to Pb and other heavy metals may be a risk factor for ALS.[12] Additionally, increased risk of ALS has been observed in certain occupations with high exposure to Pb, including construction workers,[1314] military servicemen[1516] and mechanics.[1718]

Although a few studies tried to assess Pb exposure level in relation to ALS, each used categorical classifications of exposure in relatively small samples.[1920] No previous study has used a job exposure matrix (JEM) to estimate cumulative Pb exposure from all jobs held. In this population-based study, we utilise a JEM for an investigation of the relationship between Pb exposure and ALS in Denmark using data from nationwide Danish registries.

MATERIALS AND METHODS

Case ascertainment

We identified ALS cases via an extended Danish version of the *International Classification of Diseases and Related Health Problems, Eighth Revision* (ICD-8) codes from 1977 to 1994 and *International Classification of Diseases and Related Health Problems,Tenth Revision* (ICD-10) codes from 1994 to 2013 acquired from patient records included in the Danish National Patient Registry.[2122] Patients with a primary discharge diagnosis of ‘amyotrophic lateral sclerosis’ (ICD-8 code 348.0) or ‘motor neuron disease’ (ICD-10 code G12.2) were designated as ALS cases. In prior work, we found this case ascertainment to have high concordance with medical record review (93%).[23] The date of the first recorded ALS diagnosis was defined as the ‘index date’. For each case, records for 100 birth year-matched and sex-matched controls alive at the time of the index date were randomly selected using the Danish Central Person Registry,[24] which keeps track of vital and emigration status, and assigned the same index date. To exclude potential prevalent cases, we limited our analysis

to subjects with a first recorded diagnosis on 1 January 1982 or later, 5 years after the initiation of the Danish National Patient Registry in 1977.[2122]

Exposure assessment

Unique Central Person numbers, assigned to all residents in Denmark since 1968, allowed for the linkage of demographic and diagnosis data to employment history data from the Danish Pension Fund.[25] Employment records from the Danish Pension Fund are based on eight-digit employer tax ID numbers and five-digit industry codes derived from an extended version of International Standard Industrial Classification codes by Statistics Denmark.[25] Companies in Denmark are classified into main branches based on the company's primary activities by Statistics Denmark and are categorised into 579 different entities.[25] Membership of the Pension Fund is compulsory for all employees working at least 9 hours per week, and records are kept even if a person has emigrated or died. To diminish potential exposure misclassification due to work held prior to the start of the Danish Pension Fund in 1964,[26] we excluded subjects who were older than 25 years of age in 1964 (born before 1939), which leaves 1639 cases under study.[24]

Cumulative occupational Pb exposure was estimated using a JEM constructed by the Nordic Occupational Cancer Study for Denmark.[27] Development of Nordic, and specifically Danish JEMs, have been previously described.[2728] In summary, a team of exposure experts from the five Nordic countries (Finland, Norway, Sweden, Denmark and Iceland) used the template of previously developed Finnish JEMs with information on exposure, occupations and exposure periods covering over 300 occupation categories.[27] Annual mean levels of exposure for the original Finnish JEMs are based on biomonitoring data and environmental measurements to assess chemical exposures.[28] Annual mean levels of exposure for the original JEMs are based on biomonitoring data and environmental measurements to assess chemical exposures. For Pb, 61 023 blood Pb levels and area (eg, air and dust) measurements were collected in different occupational categories.[28] These measurements were used to create an estimated blood concentration (μmol/L) in the different occupations. This Danish JEM was modified from the Finnish JEM for relevance to Danish occupations based on industrial measurements of Pb and probability of exposure for each job in Denmark, with a priori time-specific measurement periods of 1945–1959, 1960–1974, 1975–1984 and after 1984. Probability of exposure was based on the Work Environment and Health in Denmark Survey, with the highest probability of Pb exposure belonging to those working as electronics and telecommunications workmen, telephone installation crew, linemen and cable jointers, electrical and electronic equipment assemblers, typographers and plumbers. Other exposed occupations in this JEM included machine and engine mechanics, sheet metal workers, welders, construction workers, glass and ceramic decorators and policemen.

We calculated individual exposure by multiplying the concentration and probability of exposure for each job,[27] then multiplying this by the duration of employment determined by employment history acquired from the Pension Fund data. We refer to this metric as 'cumulative estimated exposure,' which was calculated as the sum of each job exposure for each participant, including matched controls, up to the index date. In our secondary analysis,

we limited exposure calculations to occupations with 50% probability of exposure or more and those jobs with <50% probability of exposure were considered unexposed. For this metric, we then calculated exposure by multiplying the expected exposure by duration of employment in each occupation and did not consider the specific probability of exposure above the 50% threshold. We also explored 5-year and 10-year exposure lag periods before the index date (ie, excluding exposures that occurred within those time periods) to omit exposures that could have occurred during any time of undiagnosed ALS, examine possible variations in associations due to timing and mitigate potential healthy worker bias.

Statistical analysis

ALS cases and controls were classified as ever or never exposed to Pb. Using conditional logistic regression, we obtained ORs and 95% CIs. Cumulative estimated exposure or level was categorised with cut-points at the 30th and 60th percentiles to have three categories representing low, medium and high exposures with no exposure as the reference. Cut-points were based on the distributions among exposed controls for the 10-year lagged exposures and kept the same for the different lagged analyses for comparability. We included these categories as the primary predictive variable in our conditional logistic regression models. In multivariable analysis, we adjusted for residential location and socioeconomic status (SES) categories at the index date. SES was based on five ordered categories determined from tax-recorded occupation title as follows: (1) academics and corporate managers, (2) people with high-salary positions, (3) low-salary positions, (4) skilled workers and (5) unskilled workers. For subjects who were married at the time of the index date, SES was based on the highest SES of the participant or spouse. We removed participants with less than 5 years of total work experience from the analysis in order to avoid healthy worker hire bias. Tests for trend were based on logistic regression analysis with Pb measures in continuous format and scaled per 100 μmol/L. Because employment status and expected job tasks vary greatly between men and women in this population, all analyses were stratified a prior by sex and conducted using SAS V9.4.[29] This secondary data analysis was exempt from full review by the Harvard T.H. Chan School of Public Health Institutional Review Board.

RESULTS

A total of 1639 ALS cases and 151 974 controls met our inclusion criteria (see online supplementary figure). As shown in table 1, although only 52% of those never occupationally exposed to Pb were men, a notable 75% of those ever Pb-exposed were men (not displayed). When demographic factors for exposed subjects were stratified by those ever working in industries with ≥50% probability of exposure, the proportion of men with a higher probability of exposure was slightly lower at 68%. Most subjects (>64%) were married at the time of the index date. Additionally, a greater portion of subjects who were Pb exposed were categorised as ‘skilled workers’ (37%) compared with those who were not Pb exposed (27%).

Results of our analysis of cumulative estimated exposure among men are shown in table 2. Although odds of ALS in men were consistently slightly higher for cumulative estimated exposures greater than the 60th percentile in all lag periods, none of these results were

statistically significant. However, when examining expected exposure measures jobs with ≥50% probability of Pb exposure among men, exposures greater than the 60th percentile resulted in significantly higher adjusted ORs (aORs) (table 3) for extended lag periods of 5 years prior (aOR: 1.35; 95% CI 1.04 to 1.76) and 10 years prior to the index date (aOR: 1.33; 95% CI 1.03 to 1.72). There was not a consistent pattern in lower exposure categories and the overall trend was not significant for any of these analyses.

Among women, the aORs were slightly elevated in the highest exposure categories, but these were not statistically significant (table 4), and there was no consistent pattern in lower cumulative estimated exposure categories. Analyses of Pb expected exposure among women showed no consistent pattern (table 5). Although the aOR for ALS was higher for measures greater than the 60th percentile for analyses with no lag (aOR: 1.04; 95% CI 0.73 to 1.48), this was not significant (table 5).

DISCUSSION

In our nested, matched nationwide case-control study of ALS in Denmark from 1982 to 2013, we found an association between expected occupational Pb exposure and odds of ALS among men holding jobs with a high (≥50%) probability of Pb exposure. It is important to note that when exposure was limited to occupations with at least 50% probability of exposure, only approximately 15% of study subjects were Pb exposed. The increased odds were limited to those exposed at the highest level, and results were slightly stronger when occupational exposures were limited to jobs held 5 and 10 years prior to the ALS index date. Although one study previously suggested an association between cumulative estimated exposure among women,[5] we did not see any significant associations among women, which could potentially be explained by sex differences in job tasks, and thereby exposure within the same job, which is not taken into account by our JEM. We examined potential associations in women using cut-points based on levels estimated in men and still saw no statistically significant results, suggesting that associations seen in men are not strictly due to industry exposure levels but may be due to job differences, although differences in underlying biological responses to Pb exposure cannot be ruled out. Notably, we had fewer exposed female cases than male cases, as well as fewer women with at least 5 years of work experience, which could also have contributed to the observed differences in associations.

Pb is known to have adverse neurodegenerative effects.[30] Additionally, as Pb can accumulate over years and be stored in bone, it can later be metabolised and mobilise to other tissues, including the brain, where it can easily cross the blood-brain barrier into neural tissues.[31] Therefore, several studies have investigated associations between ALS and Pb exposure using various biomarkers, including cerebrospinal fluid,[32] blood[3334] and bone.[34] Although some Pb biomarker studies have indicated significantly elevated associations with risk of ALS,[33] other studies reported elevated, but not significant, associations.[32] However, with the exception of bone Pb, a major problem in using biomarkers as a measure for Pb exposure is that they may not capture historical exposures and thus would not serve as a relevant indicator of neurotoxicity experienced for several years prior to ALS diagnosis. Considering studies showing increased risk of ALS in people working certain occupations with consistent Pb exposure, estimates of Pb exposure via occupation history is potentially a better exposure

measurement than biomarkers with short half-lives for Pb. It is important to note that earlier studies of occupation exposures were based on retrospectively collected occupation data in small samples.[1935] Importantly, however, these studies examined specific jobs individually, each of which may have involved many exposures. Our study is the first to estimate Pb exposure across all jobs by using an objective JEM with prospectively and objectively collected population-based employment history. The use of a JEM to estimate participants' cumulative exposures to Pb allows for better estimations of total exposure specifically to Pb across all jobs held and consideration of aspects of timing of exposures relative to disease onset.

Despite the unparalleled data source used for this study, we acknowledge that there are some limitations. As we did not have information on smoking status of subjects, which has been suggested as a potential risk factor for ALS,[3637] we could not adjust for smoking as a potential confounder in our multivariable analyses. However, by adjusting for SES in our analyses, which has been correlated with smoking habits in Denmark,[38] we likely indirectly adjusted for smoking status. Additionally, there is evidence that positive associations of ALS and smoking seen in other studies may be more prominent among women than in men.[3940] Thus, the positive results seen only in men in our study may not be fully consistent with smoking as a residual confounder.

There is unavoidable measurement error relative to actual personal exposures with use of a JEM to estimate Pb exposures. Using the product of probability and level of exposure to calculate cumulative exposure indices may introduce exposure misclassification, particularly in occupations with low probability of exposure.[41] Therefore, attenuation bias would likely be observed for the results of associations between Pb exposure and ALS.[42] However, in the process of modifying the Finnish JEM to construct the Danish JEM, priority for classification was given to occupations with high exposures,[28] which potentially reduces this bias. Additionally, it has been suggested that focusing analyses on occupations with a greater probability of exposure should reduce the risk of misclassification,[41] and this is what we have done in reporting exposures based on occupations with >50% probability in tables 3 and 5. Although exposure estimates from 1945 to 1959 were meagre due to lack of available data,[27] measurement data were available after this point, and only occupations held after 1964, the year the Danish Pension Fund was established, were included in our analysis. Due to the employment history registry beginning on 1 April 1964, some exposure misclassification may have been introduced for subjects employed prior to that date, as we were unable to determine exposures for any jobs held before that time point. However, we attempted to minimise this misclassification by restricting the analysis to those who were 25 years or younger at the start of the Pension Fund. Finally, the validation of the specific JEM used for this study is limited and indirect, although its construction was based on biosample testing of Pb levels among thousands of workers in difference occupations. Some evidence of the validity is provided by studies with the original Finnish JEM, as well as those similarly adapted for Norway and Sweden that replicated established associations (or lack of) with cancer risk.[4344] Additionally, all JEMs for the Nordic Occupational Cancer Study are edited as necessary if new information becomes available to improve on estimates and are re-evaluated by numerous experts on a consistent basis.[28] However, we also acknowledge that the priority given to high-exposure occupations,[28] and subsequent

omission of occupations with lower exposures (<5% probability), could reduce the sensitivity of this JEM.

This was, to our knowledge, the first study to estimate cumulative occupational Pb exposure in relation to ALS. Our results suggest that, at least for men, those exposed at the highest levels are at higher risk of ALS for those with a greater probability of exposure. Although Pb exposures in the general population have been significantly mitigated over the past few decades, there are populations that still experience high Pb exposures, in particular certain occupations such as construction work. Additionally, as some population exposures to Pb through residential proximity to industrial facilities, hobbies such as hunting and fishing, home renovation activities and smoking are still prevalent, further action may need to be taken to expand on mechanisms for reducing Pb exposure from other sources. Lastly, understanding the biological mechanisms by which Pb may increase risk of ALS could help further understand ALS pathophysiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

What is already known about this subject?

- Previous research has indicated links between environmental lead (Pb) exposure and increased risk of neurodegenerative disorders.
- Prior studies of Pb and amyotrophic lateral sclerosis (ALS) have used retrospectively collected occupation history in small study samples, or occupations at a certain time point.

What are the new findings?

- Men occupationally exposed to Pb at the highest levels in industries with at least 50% probability of Pb exposure have a greater risk of ALS.
- Using prospectively collected surveillance data, we observed a consistent positive association across different windows of exposure in men.

How might this impact on policy or clinical practice in the foreseeable future?

- Although Pb exposures in the general population have been significantly mitigated over the past few decades, more guidelines should be put in place to further protect populations that still experience high Pb exposures, in particular certain occupations such as construction work.
- Further regulatory action may need to be taken to reduce Pb exposures from industrial facilities, home renovation activities and roadwork.

Table 1

Demographic characteristics at the index date by lead exposure

	Lead unexposed (n=93 773)		Lead exposed <50% probability (n=39 877)		Lead exposed ≥50% probability (n=20 203)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Sex						
Male	48 304	51.57	31 498	79.16	13 706	68.00
Female	45 362	48.43	8292	20.84	6451	32.00
Age (years)						
<45	11 337	12.10	4862	12.22	2240	11.11
45–54	23 686	25.29	10 506	26.40	5224	25.92
55–64	37 838	40.40	16 416	41.26	8524	42.29
65–74	20 805	22.21	8006	20.12	4169	20.68
Socioeconomic status *						
Academics and managers	12 894	13.77	3003	7.55	1616	8.02
High-salary positions	15 296	16.33	4664	11.721	2653	13.16
Low-salary positions	17 761	18.96	6441	16.19	3437	17.05
Skilled workers	25 454	27.18	14 979	37.65	7484	37.13
Unskilled workers	13 575	14.49	7070	17.77	3383	16.78
Unknown	8686	9.27	3633	9.13	1584	7.86
Residence at diagnosis/index date						
Copenhagen	9606	10.26	3328	8.36	2337	11.59
Copenhagen suburbs	22 226	23.73	88581	22.26	6003	29.78
Aarhus/Odense	9166	9.79	3939	9.90	1965	9.75
Provincial towns	38 703	41.32	17 001	42.73	6913	34.30
Rural areas	13 664	14.59	6553	16.42	2840	14.09
Greenland	81	0.09	31	0.08	26	0.13
Unknown	220	0.23	100	0.25	73	0.36
Marital status						
Married	64 619	68.99	26 123	65.65	12 961	64.30
Unmarried	11 755	12.55	5805	14.59	2565	12.73
Divorced	12 193	13.02	6281	15.79	3703	18.37

Characteristic	Lead unexposed (n=93 773)		Lead exposed <50% probability (n=39 877)		Lead exposed ≥50% probability (n=20 203)	
	n	%	n	%	n	%
Widowed	4918	5.25	1539	3.87	897	4.45
Unknown	181	0.19	42	0.11	31	0.15

* SES for married subjects was based on the highest SES of the participant or spouse.

Table 2

Analyses of cumulative estimated exposure to lead and ALS case status in men

	Controls N (%)	Cases N (%)	OR (95% CI)*	aOR (95% CI)†
No lag (n=93 508)				
No exposure	48 802 (51.67)	502 (50.91)	1.00 (Ref)	1.00 (Ref)
Ever exposure (μmol/L)‡	44 720 (48.33)	484 (49.09)	1.03 (0.91 to 1.17)	1.07 (0.93 to 1.22)
<23.87	9 030 (10.73)	119 (12.07)	1.20 (0.97 to 1.48)	1.20 (0.97 to 1.49)
23.87–102.90	10 044 (10.86)	111 (11.26)	1.02 (0.82 to 1.28)	1.04 (0.83 to 1.20)
>102.90	24 746 ()	254 (25.76)	0.98 (0.84 to 1.15)	1.02 (0.87 to 1.20)
Test for trend			1.00 (0.98 to 1.01)	1.00 (0.99 to 1.02)
5-year lag				
No exposure	53 250 (57.55)	558 (56.59)	1.00 (Ref)	1.00 (Ref)
Ever exposure (μmol/L)‡	39 272 (42.45)	428 (43.41)	1.05 (0.92 to 1.19)	1.08 (0.94 to 1.24)
<23.87	1 1 337 (12.25)	128 (12.98)	1.08 (0.89 to 1.32)	1.14 (0.93 to 1.39)
23.87–102.90	1 1 365 (12.28)	119 (12.07)	1.01 (0.82 to 1.23)	1.05 (0.85 to 1.29)
>102.90	16 570 (17.91)	181 (18.36)	1.05 (0.89 to 1.24)	1.06 (0.89 to 1.27)
Test for trend			1.00 (0.99 to 1.01)	1.01 (0.98 to 1.04)
10-year lag				
No exposure	55 274 (59.74)	575 (58.32)	1.00 (Ref)	1.00 (Ref)
Ever exposure (μmol/l)‡	37 248 (40.26)	411 (41.68)	1.07 (0.94 to 1.22)	1.10 (0.96 to 1.26)
<23.87	1 1 186 (12.09)	127 (12.88)	1.10 (0.91 to 1.34)	1.14 (0.93 to 1.40)
23.87–102.90	11 161 (12.06)	120 (12.17)	1.04 (0.86 to 1.27)	1.09 (0.88 to 1.34)
>102.90	14 901 (16.11)	164 (16.63)	1.07 (0.90 to 1.27)	1.08 (0.90 to 1.30)
Test for trend			1.01 (0.97 to 1.04)	1.01 (0.97 to 1.05)

*Controls were individually matched to cases on age and sex.

†Models adjusted for SES and residential location.

‡Cumulative estimated exposure = [(level of exposure)*(probability of exposure)/100]*(days employed).

ALS, amyotrophic lateral sclerosis; aOR, adjusted OR; SES, socioeconomic status.

Table 3

Analyses of cumulative expected lead and ALS case status in men

	Controls N (%)	Cases N (%)	OR (95% CI)*	aOR (95% CI)†
No lag (n=93 508)				
No exposure	78 975 (85.36)	827 (83.87)	1.00 (Ref)	1.00 (Ref)
Ever exposure (µmol/L)‡	13 547 (14.64)	159 (16.13)	1.13 (0.95 to 1.33)	1.15 (0.96 to 1.38)
<50.00	3172 (3.43)	37 (3.75)	1.19 (0.85 to 1.68)	1.20 (0.85 to 1.69)
50.00–222.00	3269 (3.53)	33 (3.35)	0.92 (0.63 to 1.34)	0.93 (0.63 to 1.35)
>222.00	7106 (7.68)	89 (9.30)	1.22 (0.97 to 1.53)	1.23 (0.99 to 1.55)
Test for trend			1.01 (0.99 to 1.02)	1.00 (0.99 to 1.02)
5-year lag				
No exposure	81 107 (87.66)	848 (86.00)	1.00 (Ref)	1.00 (Ref)
Ever exposure (µmol/L)‡	11 415 (12.34)	138 (14.00)	1.16 (0.97 to 1.39)	1.19 (0.98 to 1.44)
<50.00	3276 (3.54)	39 (3.96)	1.14 (0.83 to 1.58)	1.22 (0.87 to 1.70)
50.00–222.00	3348 (3.62)	32 (3.25)	0.92 (0.65 to 1.31)	0.93 (0.64 to 1.35)
>222.0	4791 (5.18)	67 (6.80)	**1.35 (1.05 to 1.73)**	**1.35 (1.04 to 1.76)**
Test for trend			1.02 (0.99 to 1.04)	1.01 (0.99 to 1.04)
10-year lag				
No exposure	81 802 (88.41)	858 (87.02)	1.00 (Ref)	1.00 (Ref)
Ever exposure (µmol/L)‡	10 720 (11.59)	128 (12.98)	1.15 (0.95 to 1.38)	1.16 (0.95 to 1.41)
<50.00	3208 (3.47)	37 (3.75)	1.11 (0.80 to 1.54)	1.16 (0.83 to 1.64)
50.00–222.00	3223 (3.48)	32 (3.25)	0.95 (0.67 to 1.36)	0.95 (0.65 to 1.38)
>222.00	4289 (4.64)	59 (5.98)	**1.32 (1.01 to 1.73)**	**1.33 (1.03 to 1.72)**
Test for trend			1.01 (0.99 to 1.05)	1.01 (0.98 to 1.04)

Bold values are statistically significant (p <0.05)

*Controls were individually matched to cases on age and sex.

†Models adjusted for SES and residential location.

‡Cumulative expected exposure=level of exposure*days employed for jobs with >50% probability of exposure.

ALS, amyotrophic lateral sclerosis; aOR, adjusted OR; SES, socioeconomic status.

Table 4

Analyses of cumulative estimated exposure to lead and ALS case status in women

	Controls N (%)	Cases N (%)	OR (95% CI)*	aOR (95% CI)†
No lag (n=60 105)				
No exposure	44 867 (75.47)	495 (75.80)	1.00 (Ref)	1.00 (Ref)
Ever exposure (μmol/L)‡	14 585 (24.53)	158 (24.20)	0.99 (0.82 to 1.18)	1.01 (0.83 to 1.21)
<17.40	3566 (6.00)	37 (5.67)	0.95 (0.68 to 1.33)	0.94 (0.66 to 1.34)
17.40–72.89	3663 (6.16)	39 (5.97)	0.97 (0.70 to 1.34)	1.03 (0.74 to 1.31)
>72.89	7356 (12.37)	82 (12.56)	1.01 (0.80 to 1.28)	1.03 (0.80 to 1.31)
Test for trend			1.00 (0.97 to 1.04)	1.00 (0.97 to 1.04)
5-year lag				
No exposure	46 938 (78.95)	514 (78.71)	1.00 (Ref)	1.00 (Ref)
Ever exposure (μmol/L)‡	12 514 (21.05)	139 (21.29)	1.00 (0.84 to 1.20)	1.02 (0.85 to 1.24)
<17.40	3675 (6.18)	40 (6.13)	1.00 (0.73 to 1.39)	0.99 (0.70 to 1.39)
17.40–72.89	3678 (6.19)	44 (6.74)	1.10 (0.81 to 1.50)	1.14 (0.83 to 1.56)
>72.89	5161 (8.68)	55 (8.42)	0.98 (0.74 to 1.30)	1.00 (0.75 to 1.34)
Test for trend			1.01 (0.95 to 1.07)	1.02 (0.95 to 1.08)
10-year lag				
No exposure	47 637 (80.13)	520 (79.63)	1.00 (Ref)	1.00 (Ref)
Ever exposure (μmol/L)‡	11 815 (19.87)	133 (20.37)	1.04 (0.86 to 1.26)	1.04 (0.85 to 1.27)
<17.40	3544 (5.96)	39 (6.73)	1.02 (0.74 to 1.36)	1.00 (0.71 to 1.41)
17.40–72.89	3545 (5.96)	44 (6.74)	1.15 (0.84 to 1.56)	1.17 (0.85 to 1.61)
>72.89	4726 (7.95)	50 (7.66)	0.98 (0.73 to 1.31)	0.98 (0.72 to 1.32)
Test for trend			1.00 (0.93 to 1.07)	1.01 (0.94 to 1.08)

*Controls were individually matched to cases on age and sex.

†Models adjusted for SES and residential location.

‡Cumulative estimated exposure=[(level of exposure)*(probability of exposure)/100]*(days employed).

ALS, amyotrophic lateral sclerosis; aOR, adjusted OR; SES, socioeconomic status.

Table 5

Analyses of cumulative expected lead and ALS case status in women, Denmark, 1982–2013

n=60 105	Controls N (%)	Cases N (%)	OR (95% CI)*	aOR (95% CI)†
No lag				
No exposure	53 073 (89.27)	581 (88.97)	1.00 (Ref)	1.00 (Ref)
Ever exposure (µmol/L)‡	6379 (10.73)	72 (1 1.03)	1.04 (0.81 to 1.33)	1.07 (0.83 to 1.38)
<46.00	1560 (2.62)	20 (3.06)	1.18 (0.75 to 1.84)	1.17 (0.73 to 1.88)
46.00–178.50	1638 (2.76)	17 (2.60)	0.95 (0.59 to 1.54)	1.07 (0.66 to 1.73)
>178.50	3181 (5.35)	35 (5.36)	1.01 (0.72 to 1.43)	1.04 (0.73 to 1.48)
Test for trend			1.00 (0.99 to 1.03)	1.01 (0.98 to 1.03)
5-year lag				
No exposure	53 952 (90.75)	590 (90.35)	1.00 (Ref)	1.00 (Ref)
Ever exposure (µmol/L)‡	5500 (9.25)	63 (9.65)	1.05 (0.81 to 1.37)	1.08 (0.82 to 1.42)
<46.00	1590 (2.67)	21 (3.22)	1.21 (0.78 to 1.88)	1.20 (0.76 to 1.91)
46.00–178.50	1620 (2.72)	18 (2.76)	1.02 (0.64 to 1.46)	1.06 (0.65 to 1.73)
>178.20	2290 (3.85)	24 (3.68)	0.97 (0.64 to 1.46)	1.00 (0.66 to 1.53)
Test for trend			1.00 (0.96 to 1.05)	1.00 (0.96 to 1.05)
10-year lag				
No exposure	54 274 (91.29)	595 (91.12)	1.00 (Ref)	1.00 (Ref)
Ever exposure (µmol/L)‡	5178 (8.71)	58 (8.88)	1.03 (0.79 to 1.35)	1.04 (0.78 to 1.37)
<46.00	1549 (2.61)	19 (2.91)	1.13 (0.71 to 1.79)	1.09 (0.67 to 1.78)
46.00–178.50	1555 (2.61)	18 (2.76)	1.06 (0.66 to 1.71)	1.09 (0.67 to 1.78)
>178.50	2074 (3.49)	21 (3.22)	0.93 (0.60 to 1.44)	0.95 (0.60 to 1.49)
Test for trend			0.98 (0.93 to 1.04)	1.00 (0.93 to 1.05)

*Controls were individually matched to cases on age and sex.

†Models adjusted for SES and residential location.

‡Cumulative expected exposure=level of exposure*days employed for jobs with >50% probability of exposure.

ALS, amyotrophic lateral sclerosis; aOR, adjusted OR; SES, socioeconomic status.