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Original Contribution

Amyotrophic Lateral Sclerosis and Exposure to Diesel Exhaust in a Danish Cohort

Aisha S. Dickerson*, Johnni Hansen, Ole Gredal, and Marc G. Weisskopf

* Correspondence to Dr. Aisha S. Dickerson, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Building 1, 665 Huntington Avenue, Suite 1402, Boston, MA 02115 (e-mail: adickerson@hsph.harvard.edu).

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Previous studies have suggested an increased risk of amyotrophic lateral sclerosis (ALS) and other motor neuron diseases for persons in occupations commonly involving exposure to diesel exhaust (DE). In this study, we investigated the association between occupational exposure to DE and odds of ALS. ALS cases were identified from the Danish National Patient Registry (1982–2013) and individually matched to 100 controls per case on the basis of birth year and sex. Using information on occupational history from 1964 onward obtained from the Danish Pension Fund, we estimated cumulative DE exposures using a job exposure matrix. We evaluated associations using conditional logistic regression analyses and stratified the analyses by sex. Using a 10-year lag period, DE exposure was positively associated with ALS among men who had ever been exposed (adjusted odds ratio (aOR) = 1.20, 95% confidence interval (CI): 1.05, 1.38). For men with greater than 50% probability of DE exposure, we observed a positive association between ALS and highest-quartile exposure during the 5-year (aOR = 1.35, 95% CI: 1.07, 1.70) and 10-year (aOR = 1.41, 95% CI: 1.11, 1.79) lag periods. Our study suggests an association between consistently higher exposures to DE and ALS in men, but not in women. These findings support previous reports of associations between ALS and occupations commonly involving DE exposure.

ALS; amyotrophic lateral sclerosis; diesel exhaust; motor neuron disease; occupational exposure

Abbreviations: ALS, amyotrophic lateral sclerosis; aOR, adjusted odds ratio; CI, confidence interval; DE, diesel exhaust; JEM, job exposure matrix; SES, socioeconomic status.

As a progressively paralytic neurodegenerative disease, amyotrophic lateral sclerosis (ALS) has a notably brief average survival time of 3–5 years (1). Reports from the United States and Europe indicate an annual incidence of 1–2 new ALS cases per 100,000 people (2–4). Although approximately 10% of ALS cases are attributed to genetic inheritance (5), about 90% of ALS cases are sporadic. Overall the male:female ratio is skewed towards men (1), but more recently this ratio has been approaching unity (6, 7). Generally, the etiology of ALS is not well understood, but some researchers have suggested that preexisting genetic risk may be influenced by environmental exposures (1, 6, 8).

Some lines of evidence suggest that exposure to diesel exhaust (DE) might be a risk factor for ALS. Several studies have linked various components of DE, including hexane (9) and formaldehyde (10–13), to ALS, although 1 only suggested an association with formaldehyde (9) and 1 other study found no association (14). Many occupational studies, though not all (7, 15), have found increased risk of ALS among persons in occupations with high exposure to DE, such as truck drivers (16, 17), construction workers (9), machine operators (18), bus drivers (18), and military servicemen (19).

The observed genotoxicity resulting from DE exposure (20), along with the proposed associations of mutations and polymorphisms (1, 21) and oxidative stress (22, 23) with ALS, suggests biological plausibility of a relationship between DE exposure and ALS. Despite these lines of evidence leading to the hypothesis that DE exposure may be a risk factor for ALS and 1 study of occupations in which the investigators theorized a link with DE (17), no study, to our knowledge, has directly assessed the association between an estimate of DE exposure specifically and ALS. In this study, we used a job exposure matrix (JEM) to investigate the relationship between occupational DE exposure and ALS in a case-control study nested within the

entire population of Denmark, using data from nationwide Danish registries.

METHODS

Study participants

We identified ALS cases via *International Classification of Diseases, Eighth Revision* (pre-1994) and *International Classification of Diseases, Tenth Revision* (1994 and after) codes acquired from patient records included in the Danish National Patient Registry from its inception in 1977 (24, 25) through 2013. The Danish National Patient Registry originally included only inpatient data; outpatient data were later added, beginning in 1995 (24). Patients with a primary discharge diagnosis of amyotrophic lateral sclerosis (*International Classification of Diseases, Eighth Revision*, code 348.0) or motor neuron disease (*International Classification of Diseases, Tenth Revision*, code G12.2) were designated as ALS cases. The date of the first recorded ALS diagnosis was defined as the index date. The primary diagnosis in the Danish National Patient Registry is designated as the diagnosis associated with the initial hospital visit, while the secondary diagnosis indicates other diseases that may be underlying causes for the primary diagnosis (24). For each case, records for 100 individually birth-year- and sex-matched controls who were alive on the case's index date were randomly selected using the Danish Central Person Register (26), which was founded in 1968 and keeps track of vital status, including dates of death and emigration, and assigned the same index date. Because the Danish National Patient Registry was created in 1977 (24, 25), we limited our analysis to persons who had a first recorded diagnosis on January 1, 1982, or later, to exclude potential prevalent cases (see Figure 1).

Exposure assessment

We used unique residential Central Person Register numbers to link the above-mentioned diagnosis and demographic data to the Danish Pension Fund, which has maintained data on the

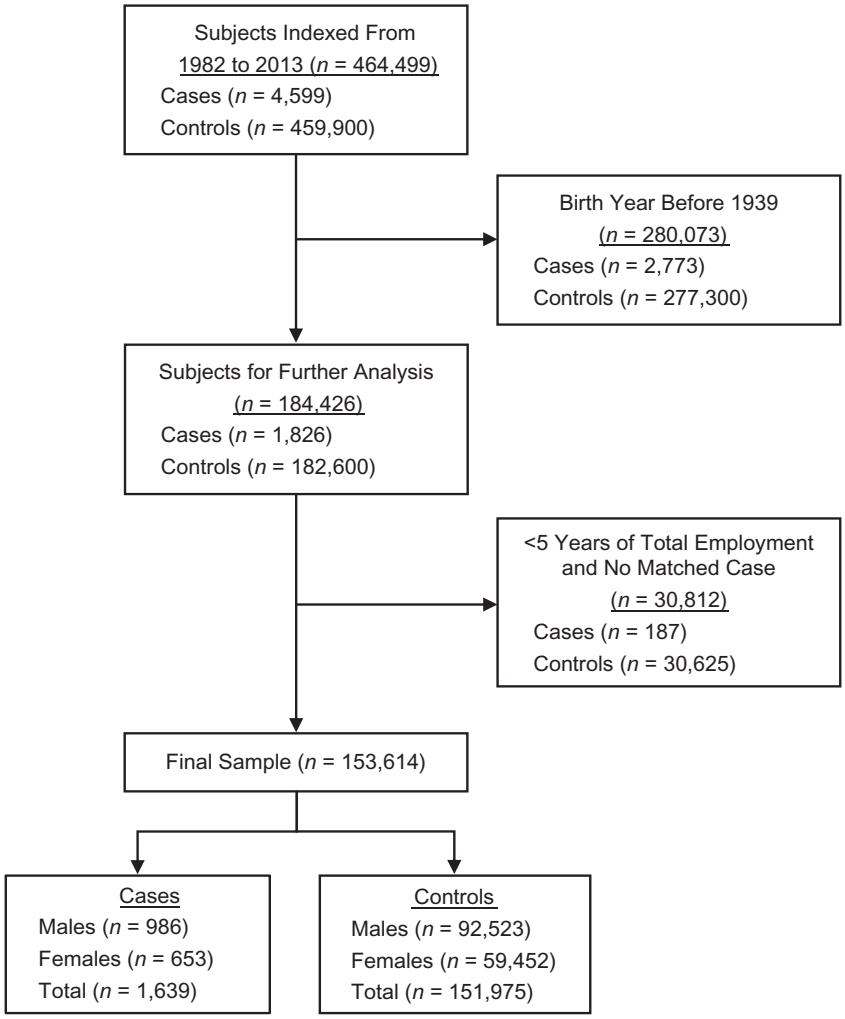

Figure 1. Process of study subject selection and exclusion for analyses of diesel exhaust exposure and amyotrophic lateral sclerosis, Denmark, 1982–2013.

employment history of all residents of Denmark aged 16–66 years since April 1, 1964 (27). Employment records were based on 8-digit employer tax identification numbers indicating the companies for which study participants worked and 5-digit industry codes from an extended version of the International Standard Industrial Classification codes compiled by Statistics Denmark (more detailed codes introduced after 1992 were recoded to the original International Standard Industrial Classification codes for comparability) (27). Each company in Denmark is assigned a specific industry code. In some cases these codes are relatively descriptive for larger groups of occupational exposures (e.g., service station attendants, miners and quarrymen, railway engine and truck drivers); others (e.g., general public services) are relatively broad.

For this study, we used a JEM constructed for Denmark by investigators in the Nordic Occupational Cancer Study, for which methods for development have already been reported (28). In summary, the Finnish version of this JEM was modified by one of the authors (J.H.) for relevance to the population of Denmark on the basis of industrial measurements of DE from Finland and Denmark. The expected measurements in the JEM used in this study are also time-specific, with time periods of 1960–1974, 1975–1984, and after 1984 for probability and intensity (mg/m^3) of exposure for each of the 5-digit industry codes (see Web Table 1, available at https://academic.oup.com/aje, for the list of industries with DE exposure). Using this DE JEM, we found an association between DE and chronic obstructive pulmonary disease similar to what has previously been reported (Web Appendix).

In our initial analysis, we calculated time-specific exposure by multiplying the probability (range, 0–0.90) and intensity (range, 0–0.88 mg/m^3) of exposure associated with each industry in which a subject worked (28). The results were then multiplied by the duration of time spent working in specific occupations and summed to determine the cumulative expected exposure of each participant. In secondary analyses, we limited exposure calculations to occupations in industries with at least a 50% probability of exposure, with persons having a <50% probability of exposure designated as unexposed. We then calculated exposure by multiplying the intensity of exposure for each industry by the number of days employed in each occupation to explore an exposure variable focused more on intensity of exposure. Total length of employment in diesel-exposed industries ranged from 5 days to 3,926 days (10.7 years), with cases working an average of 2,123 days (5.8 years) and controls an average of 2,074 days (5.7 years).

We also explored 5- and 10-year exposure lag periods before the index date (i.e., excluding exposures that occurred within those time periods) to exclude exposures that could have occurred during any time of undiagnosed ALS, examine possible variations in associations due to timing, and mitigate potential healthy-worker survivor bias. Furthermore, to diminish exposure misclassification and potential left-truncation bias as a result of work performed prior to the creation of the Danish Pension Fund in 1964 (29), we excluded study subjects who were older than age 25 years in 1964 (i.e., born in 1940 or earlier) (26). Additionally, in an attempt to avoid healthy-worker hire bias, participants with less than 5 years of total work experience (short-term employment) were removed from the analysis (30). Cases and controls with no matches were also removed from the analysis. The process of exclusions made to arrive at the final analytical study sample is presented in Figure 1.

Covariates

Covariates in adjusted analyses included socioeconomic status (SES) and residential area on the index date. SES was categorized into 5 ordered groups based on tax-recorded occupational title: 1) academics and corporate managers; 2) people with high-salary positions (entrepreneurs, managers, and teachers); 3) people with low-salary positions (nurses and technicians); 4) skilled workers; and 5) unskilled workers. SES for married subjects was based on the highest SES of the participant or spouse. SES was designated as "unknown" when individuals were suspected to be unemployed (unemployment was suspected because neither the participant nor the spouse had a tax-recorded job title in the Central Person Register at that time). Categories for area of residence included Copenhagen (capital), Copenhagen suburbs, Aarhus/Odense, provincial towns, rural areas, and Greenland. Information for the covariates was obtained from the Central Person Register and updated on a daily basis. Values that were unknown for covariates were set to "missing" for analyses.

Statistical analysis

We used conditional logistic regression to obtain odds ratios and 95% confidence intervals. ALS cases and controls were classified as ever or never exposed to DE. Additionally, expected cumulative exposure (or our intensity measure) to DE greater than zero was categorized into quartiles based on the distribution in controls for 10-year-lagged exposures, which was determined to have better fit than a model with the continuous exposure measure according to the Akaike Information Criterion; persons with no exposure served as the reference group. For comparability, we kept the same exposure categories for the other lag periods. These models adjusted for SES categories and geographic location; age was accounted for in the matching process. Because of likely differences in exposure assignment with the JEM by sex—due to differences in jobs and tasks performed by men and women in the same industry, especially in earlier time periods—we stratified the analyses by sex. We conducted linear trend tests using continuous DE exposure and intensity measures.

All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina) (31). Due to the secondary nature of this analysis, the requirement of informed consent was waived. The study was exempt from full review by the institutional review board of the Harvard T.H. Chan School of Public Health and was approved by the Danish Data Protection Agency.

RESULTS

The demographic characteristics of our analytical study population by DE exposure are displayed in Table 1. We analyzed data for 1,639 ALS cases and 151,975 controls. Among males, large portions of both ALS cases and controls had been occupationally exposed to DE (85% and 83%, respectively). With regard to socioeconomic categories, the greatest proportions of DE-exposed ALS cases (34%) and controls (35%) belonged to the "skilled workers" group.

Table 1. Characteristics of Amyotrophic Lateral Sclerosis Cases ($n = 1,639$) and Matched Controls ($n = 151,975$) on the Index Date, by Diesel Exhaust Exposure, Denmark, 1982–2013

Characteristic	Controls				Cases			
	Unexposed to DE ($n = 95,440$)		Exposed to DE ($n = 56,535$)		Unexposed to DE ($n = 1,041$)		Exposed to DE ($n = 598$)	
	No.	%	No.	%	No.	%	No.	%
Male sex	45,712	47.90	46,811	82.80	480	46.11	506	84.62
Age, years								
<45	11,357	11.90	6,878	12.17	145	13.93	59	9.87
45–54	23,975	25.12	15,025	26.58	244	23.44	172	28.76
55–64	38,798	40.65	23,316	41.24	421	40.44	243	40.64
65–74	21,310	22.33	11,316	20.02	231	22.19	124	20.74
Socioeconomic status[a]								
Academics and managers	12,651	13.26	4,659	8.24	153	14.70	50	8.36
High-salary positions	15,019	15.74	7,351	13.00	166	15.95	77	12.88
Low-salary positions	18,557	19.44	8,775	15.52	202	19.40	105	17.56
Skilled workers	27,707	29.03	19,727	34.89	280	26.90	203	33.95
Unskilled workers	12,609	13.21	11,162	19.74	139	13.35	118	19.73
Unknown	8,897	9.32	4,861	8.60	101	9.70	45	7.53
Residence at diagnosis/index date								
Copenhagen	9,882	10.35	5,219	9.23	112	10.76	58	9.70
Copenhagen suburbs	23,045	24.15	13,649	24.14	251	24.11	142	23.75
Aarhus/Odense	9,520	9.97	5,405	9.56	103	9.89	42	7.02
Provincial towns	38,910	40.77	23,007	40.70	441	42.36	259	43.31
Rural areas	13,815	14.48	8,999	15.92	132	12.68	92	15.38
Greenland	67	0.07	69	0.12	0	0.00	2	0.33
Unknown	201	0.21	187	0.33	2	0.19	3	0.50
Marital status								
Married	65,745	68.89	36,837	65.16	718	68.97	403	67.39
Unmarried	11,570	12.12	8,359	14.79	115	11.05	82	13.71
Divorced	12,771	13.38	9,166	16.21	146	14.02	94	15.72
Widowed	5,179	5.43	2,097	3.71	59	5.67	19	3.18
Unknown	175	0.18	76	0.13	3	0.29	0	0
Cumulative estimated DE exposure, mg/m^3[b]								
No lag			65.19 (13.79–208.65)				67.75 (14.20–217.26)	
5-year lag			40.78 (10.00–128.57)				43.44 (10.13–130.31)	
10-year lag			39.28 (9.73–122.72)				40.81 (9.54–126.73)	

Abbreviation: DE, diesel exhaust.

[a] Where a spouse's job title was available, socioeconomic status was based on the highest status of the study participant or his/her spouse.

[b] Values are expressed as median (interquartile range).

In our analysis of occupational DE exposure among males in our study population, the effect estimate for ever exposure increased with increasing exposure lags from none to 10 years (Table 2). The adjusted odds ratio for ALS among men who had ever experienced occupational DE exposure at least 10 years prior to the index date was 1.20 (95% confidence interval (CI): 1.05, 1.38). Additionally, when we limited exposures to industries in which men were employed at least 10 years prior to the index date, the adjusted odds ratio increased by quartile of exposure; the adjusted odds ratio for the lowest quartile of exposure (<11.55 mg/m^3) was 1.23 (95% CI: 1.03, 1.50), although the overall trend was not significant (aOR = 1.08, 95% CI: 0.99, 1.19). No such associations appeared among women (Table 3). Although risk was significantly decreased among

Table 2. Odds of Amyotrophic Lateral Sclerosis According to Cumulative Exposure to Diesel Exhaust Among Males ($n = 93,509$), Denmark, 1982–2013

Lag and Exposure Level	Controls ($n = 92,523$)		Cases ($n = 986$)		OR[a]	95% CI	aOR[b]	95% CI
	No.	%	No.	%				
No lag								
No exposure	45,712	49.41	480	48.68	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3 [c]	46,811	50.59	506	51.32	1.09	0.96, 1.24	1.13	0.99, 1.29
<11.55	9,331	10.09	106	10.75	1.08	0.88, 1.34	1.08	0.87, 1.33
11.55–45.62	9,293	10.04	94	9.53	0.97	0.77, 1.21	0.98	0.78, 1.22
45.63–135.40	10,263	11.09	107	10.85	1.00	0.81, 1.23	1.02	0.82, 1.26
≥135.41	17,924	19.37	199	20.18	1.06	0.90, 1.26	1.10	0.93, 1.30
Test for trend[d]					1.01	0.98, 1.04	1.02	0.99, 1.05
5-year lag								
No exposure	50,177	54.23	515	52.23	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3	42,346	45.77	471	47.77	1.10	0.97, 1.25	1.14	0.99, 1.30
<11.55	10,259	11.09	123	12.47	1.17	0.97, 1.44	1.15	0.93, 1.42
11.55–45.62	10,369	11.21	106	10.75	1.00	0.81, 1.24	1.04	0.83, 1.30
45.63–135.40	10,531	11.38	120	12.17	1.12	0.92, 1.37	1.17	0.94, 1.43
≥135.41	11,187	12.09	122	12.37	1.07	0.88, 1.31	1.16	0.95, 1.43
Test for trend					1.02	0.97, 1.07	1.03	0.98, 1.09
10-year lag								
No exposure	52,569	56.82	525	53.25	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3	39,954	43.18	461	46.75	1.17	1.03, 1.33	1.20	1.05, 1.38
<11.55	9,989	10.80	121	12.27	1.23	1.01, 1.50	1.23	1.03, 1.50
11.55–45.62	9,990	10.80	109	11.05	1.11	0.90, 1.36	1.12	0.91, 1.39
45.63–135.40	9,987	10.79	115	11.66	1.17	0.95, 1.43	1.20	0.97, 1.47
≥135.41	9,988	10.80	116	11.76	1.18	0.96, 1.44	1.22	0.99, 1.50
Test for trend					1.03	0.99, 1.09	1.08	0.99, 1.19

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.
[a] Controls were individually matched to cases on age and sex.
[b] Models adjusted for socioeconomic status and residential location.
[c] Cumulative exposure = [(level of exposure) × (probability of exposure)/100] × number of days employed.
[d] Tests for trend were conducted per 100-mg/m^3 increment of diesel exhaust exposure.

women in the second quartile in the analysis of 5-year-lagged exposure, there was no obvious trend, and results did not fit any clear pattern.

Results from our analysis of DE intensity in males, assigning industries with less than a 50% probability of DE exposure as involving no exposure, are shown in Table 4. The results showed overall larger effect estimates than those from analyses with cumulative expected exposure, but the pattern of increasing effect estimates with longer exposure lags was also present. The adjusted odds ratio for ever working in an industry with more than a 50% probability of DE exposure was 1.10 (95% CI: 0.95, 1.26) for no exposure lag, 1.16 (95% CI: 1.01, 1.35) for a 5-year lag, and 1.19 (95% CI: 1.03, 1.38) for a 10-year lag. Additionally, men with the highest quartile measurement of cumulative DE exposure intensity in the 10-year-lag analyses (≥141.96 mg/m^3) had 41% increased odds of ALS in adjusted analysis (adjusted odds ratio (aOR) = 1.41, 95% CI: 1.11, 1.79). The overall trends for 5-year and 10-year lags were also significant (aOR = 1.05 (95% CI: 1.01, 1.10) and aOR = 1.05 (95% CI: 1.00, 1.09), respectively). Among women, there was again no obvious pattern of association with DE; the adjusted odds ratios were slightly elevated in the highest exposure categories but not statistically significant (Table 5).

DISCUSSION

In our study of ALS cases diagnosed in Denmark from 1982 to 2013, we found an association between occupational DE exposure and odds of ALS in men. The results were stronger with longer exposure lags, which could relate to either a reduction in healthy-worker survivor bias with increasing exposure lag times (32) or the possibility that the relevant time window of exposure for the influence of DE on ALS risk is many years

Table 3. Odds of Amyotrophic Lateral Sclerosis According to Cumulative Exposure to Diesel Exhaust Among Females ($n = 60,105$), Denmark, 1982–2013

Lag and Exposure Level	Controls ($n = 59,452$)		Cases ($n = 653$)		OR[a]	95% CI	aOR[b]	95% CI
	No.	%	No.	%				
No lag								
No exposure	49,728	83.64	561	85.91	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3 [c]	9,724	16.36	92	14.09	0.85	0.68, 1.06	0.82	0.65, 1.03
<4.58	2,111	3.55	19	2.91	0.80	0.51, 1.27	0.78	0.48, 1.27
4.58–17.51	2,152	3.62	14	2.14	0.58	0.34, 0.99	0.55	0.30, 0.96
17.52–64.57	2,322	3.91	26	3.98	1.00	0.67, 1.48	0.95	0.63, 1.45
≥64.58	3,139	5.28	33	5.05	0.94	0.66, 1.34	0.93	0.64, 1.34
Test for trend[d]					0.99	0.90, 1.10	1.00	0.90, 1.10
5-year lag								
No exposure	51,009	85.80	570	87.29	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3	8,443	14.20	83	12.71	0.89	0.71, 1.12	0.84	0.66, 1.08
<4.58	2,074	3.49	18	2.76	0.79	0.49, 1.26	0.76	0.46, 1.25
4.58–17.51	2,129	3.58	16	2.45	0.68	0.41, 1.12	0.58	0.34, 1.01
17.52–64.57	2,097	3.53	25	3.83	1.08	0.72, 1.61	1.06	0.70, 1.61
≥64.58	2,143	3.60	24	3.68	1.01	0.67, 1.51	0.98	0.64, 1.49
Test for trend					1.08	0.95, 1.24	1.09	0.95, 1.24
10-year lag								
No exposure	51,716	86.99	578	88.51	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3	7,736	13.01	75	11.49	0.88	0.69, 1. 12	0.84	0.65, 1.08
<4.58	1,929	3.24	18	2.76	0.85	0.53, 1.3	0.80	0.49, 1.32
4.58–17.51	1,939	3.26	13	1.99	0.61	0.35, 1.05	0.54	0.30, 0.98
17.52–64.57	1,934	3.25	24	3.68	1.12	0.74, 1.69	1.08	0.71, 1.67
≥64.58	1,934	3.25	20	3.06	0.94	0.60, 1.47	0.92	0.58, 1.47
Test for trend					1.08	0.93, 1.24	1.08	0.93, 1.24

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.
[a] Controls were individually matched to cases on age and sex.
[b] Models adjusted for socioeconomic status and residential location.
[c] Cumulative exposure = [(level of exposure) × (probability of exposure)/100] × number of days employed.
[d] Tests for trend were conducted per 100-mg/m^3 increment of diesel exhaust exposure.

prior to ALS clinical onset. We did not see any associations among women, other than reduced odds in the second quartile of the 10-year-lagged analysis of cumulative expected DE exposure, which most likely was a chance finding. Previous mouse models of neurodegeneration have indicated sex differences and sex-dependent susceptibility to neurotoxicity from air pollution exposures (33, 34). Other than a difference in underlying biological response to DE exposure, it is likely that the types of jobs and tasks men and women perform in a given industry may differ. This would lead to the JEM not capturing exposures among men and women in the same way, which also would produce differences by sex. However, we had many fewer exposed female cases than male cases, which could also have contributed to the differences seen. Future studies with more exposed women are warranted.

Diesel engines are used in a variety of machinery and transport vehicles (35), with diesel-powered cars being highly popular in European countries due to their fuel efficiency (36). DE is composed of several toxic gaseous and particulate compounds, including carbon dioxide (CO_2), carbon monoxide (CO), nitrogen dioxide (NO_2), elemental carbon (C), and sulfur dioxide (SO_2) (35), and has been linked directly and indirectly to various adverse health outcomes (37). It is a well-known irritant and carcinogen (38), and it has also been found to be positively associated with lung cancer (39, 40), chronic obstructive pulmonary disease (41), and adverse cardiovascular events (42, 43).

Air pollution has been implicated as a risk factor for brain inflammation and neurodegenerative disorders (33, 44–46). With DE being a major component of traffic-related air pollution, it has been suggested that this particular air pollutant could be related to the etiology of ALS (17, 45). Specifically, the ability of DE to influence oxidative stress has been implicated as a potential mechanism for neurotoxicity and subsequent degeneration (22, 23, 33, 45). Furthermore, cigarette smoking has genotoxic properties that have been suggested to underlie observed associations with ALS (47), and DE has genotoxic properties

Table 4. Odds of Amyotrophic Lateral Sclerosis According to Intensity of Cumulative Diesel Exhaust Exposure Among Males ($n = 93,509$), Denmark, 1982–2013

Lag and Exposure Level	Controls ($n = 92,523$)		Cases ($n = 986$)		OR[a]	95% CI	aOR[b]	95% CI
	No.	%	No.	%				
No lag								
No exposure	66,109	71.45	690	69.98	1.00	Referent		Referent
Ever exposure, mg/m^3 [c]	26,414	28.55	296	30.02	1.08	0.94, 1.24	1.10	0.95, 1.26
<11.55	5,642	6.10	70	7.10	1.19	0.93, 1.53	1.19	0.93, 1.52
11.55–42.30	5,514	5.96	51	5.17	0.89	0.67, 1.18	0.90	0.68, 1.20
42.31–141.60	5,728	6.19	58	5.88	0.97	0.74, 1.27	1.00	0.76, 1.31
≥141.61	9,530	10.30	117	11.87	1.18	0.97, 1.44	1.22	1.00, 1.50
Test for trend[d]					1.01	0.99, 1.03	1.01	0.99, 1.04
5-year lag								
No exposure	69,023	74.60	714	72.41	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3	23,500	26.68	272	27.59	1.13	0.98, 1.30	1.16	1.01, 1.35
<11.55	5,747	6.21	72	7.30	1.22	0.96, 1.56	1.22	0.95, 1.60
11.55–42.30	5,715	6.18	54	5.48	0.92	0.70, 1.21	0.94	0.71, 1.24
42.31–141.60	5,833	6.30	63	6.39	1.05	0.81, 1.36	1.08	0.83, 1.40
≥141.61	6,205	6.71	83	8.42	1.30	1.03, 1.64	1.35	1.07, 1.70
Test for trend					1.04	1.00, 1.09	1.05	1.01, 1.10
10-year lag								
No exposure	70,580	76.28	725	73.53	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3	21,943	23.72	261	26.47	1.17	1.01, 1.35	1.19	1.03, 1.38
<11.55	5,491	5.93	68	6.90	1.22	0.95, 1.56	1.22	0.95, 1.56
11.55–42.30	5,481	5.92	53	5.38	0.95	0.72, 1.26	0.97	0.73, 1.28
42.31–141.60	5,484	5.93	64	6.49	1.15	0.89, 1.48	1.18	0.91, 1.53
≥141.61	5,487	5.93	76	7.71	1.36	1.07, 1.73	1.41	1.11, 1.79
Test for trend					1.04	1.00, 1.09	1.05	1.00, 1.09

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

[a] Controls were individually matched to cases on age and sex.

[b] Models adjusted for socioeconomic status and residential location.

[c] Cumulative exposure intensity = level of exposure × number of days employed in jobs with a >50% probability of exposure.

[d] Tests for trend were conducted per 100-mg/m^3 increment of diesel exhaust exposure.

that are similar to those of cigarette smoking (20). Several studies have investigated associations between employment in certain occupations and risk of ALS (11, 48–52). Many investigators have reported positive associations with ALS and working in occupations that can have a high probability of DE exposure, including driving buses and trucks (16–18), working in construction (9, 48), farming (15, 49, 53), operating machinery (15, 18), and serving in the military (19, 48, 54, 55). However, our study is the first to have specifically targeted DE exposure, by using a JEM with prospectively collected information on occupations.

Use of a JEM to estimate subjects' exposures to DE before ALS diagnoses allows for a more individualized marker of cumulative exposure than simply relating different occupations to ALS. Additionally, the objective collection of occupational data prospectively through the registry is probably better than self-reported occupational history, although whether assigning exposures based on industry groupings rather than self-reported specific jobs and tasks is more accurate is not clear. However, the ability to have each subject's full employment history certainly allows for a better estimate of cumulative exposure at different times prior to a possible ALS diagnosis than relying only on the longest-held occupation or the job held at 1 specific time point, as in several previous studies.

Despite the strength of using prospectively collected occupational data to estimate cumulative DE exposure prior to ALS diagnosis using individual exposure estimates, there were some limitations to this study. We did not have information on the smoking status of participants in this study; thus, we could not adjust for smoking as a potential confounder. However, smoking was common among men in Denmark at the time most of

Table 5. Odds of Amyotrophic Lateral Sclerosis According to Intensity of Cumulative Diesel Exhaust Exposure Among Females ($n = 60,105$), Denmark, 1982–2013

Lag and Exposure Level	Controls ($n = 59,452$)		Cases ($n = 653$)		OR[a]	95% CI	aOR[b]	95% CI
	No.	%	No.	%				
No lag								
No exposure	55,882	94.00	613	93.87	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3 [c]	3,570	6.00	40	6.13	1.03	0.75, 1.42	1.04	0.75, 1.43
<8.36	764	1.29	6	0.92	0.72	0.32, 1.61	0.67	0.28, 1.61
8.36–29.81	754	1.27	10	1.53	1.22	0.65, 2.29	1.31	0.70, 2.46
29.82–100.42	818	1.38	6	0.92	0.68	0.30, 1.51	0.61	0.25, 1.47
≥100.43	1,234	2.08	18	2.76	1.34	0.84, 2.15	1.41	0.88, 2.26
Test for trend[d]					1.01	0.94, 1.08	1.01	0.94, 1.08
5-year lag								
No exposure	56,457	94.96	621	95.10	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3	2,995	5.04	32	4.90	0.98	0.69, 1.40	0.99	0.69, 1.42
<8.36	742	1.25	5	0.77	0.62	0.26, 1.50	0.63	0.26, 1.51
8.36–29.81	748	1.26	8	1.23	0.98	0.49, 1.98	0.99	0.49, 2.00
29.82–100.42	744	1.25	8	1.23	0.99	0.49, 1.99	1.00	0.50, 2.01
≥100.43	761	1.28	11	1.68	1.33	0.73, 1.99	1.33	0.73, 2.43
Test for trend					1.10	0.97, 1.25	1.10	0.97, 1.25
10-year lag								
No exposure	56,707	95.38	623	95.41	1.00	Referent	1.00	Referent
Ever exposure, mg/m^3	2,745	4.62	30	4.59	1.00	0.70, 1.45	1.01	0.70, 1.47
<8.36	687	1.16	5	0.77	0.67	0.28, 1.62	0.63	0.26, 1.51
8.36–29.81	683	1.15	8	1.23	1.08	0.53, 2.17	0.99	0.49, 2.00
29.82–100.42	689	1.16	8	1.23	1.07	0.53, 2.15	1.08	0.53, 2.18
≥100.43	686	1.15	9	1.38	1.20	0.63, 2.33	1.20	0.62, 2.35
Test for trend					1.10	0.96, 1.27	1.10	0.96, 1.27

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

[a] Controls were individually matched to cases on age and sex.

[b] Models adjusted for socioeconomic status and residential location.

[c] Cumulative exposure intensity = level of exposure × number of days employed in jobs with a >50% probability of exposure.

[d] Tests for trend were conducted per 100-mg/m^3 increment of diesel exhaust exposure.

these subjects were exposed to DE; prevalence was more than 70% in the 1960s but had declined to slightly less than 30% by 2010 (56). There would have to have been a higher prevalence of smoking among persons working in DE-exposed jobs to explain any observed increase in ALS risk due to smoking (57). Additionally, considering that SES in Denmark has been correlated with smoking habits (58), we may have indirectly adjusted for smoking status by adjusting for SES in our analyses. In addition, while there is evidence that smoking is related to risk of ALS (59–62), that increased risk may be more prominent among women than among men (63, 64). Given that our current results were essentially only among men, this argues somewhat against smoking's accounting for our findings (65).

Because ALS diagnosis was determined using both inpatient and outpatient hospital records, there was a small risk of ALS case-status misclassification (66). Such misclassification would have to have been strongly related to DE exposure to account for our findings, which we have no reason to suspect. In addition, because the employment history registry used for our analysis was created in 1964, we were unable to determine exposures for any jobs held before that time point. Thus, some exposure misclassification may have been present. However, there is no reason to suspect that such misclassification would have differed by case status and so, if anything, this would have likely biased our results towards the null. We also attempted to minimize such bias by restricting the analysis to persons who were 25 years of age or younger at the start of the occupational registry.

The Danish JEM used in our study was based on the template of a Finnish JEM, FINJEM (28), and Danish measurements of DE were used when available; if not, measurements were adopted from FINJEM and adjusted based on experts' assessments. As Nordic countries, Denmark and Finland are in many ways very similar in terms of socioeconomic equality,

including occupational exposure levels. Lastly, despite targeting DE exposure specifically, JEMs still involve measurement error relative to actual personal exposures. Some additional error of this sort may have been introduced because of changes in the Pension Fund codes after 1992, although the JEMs attempted to minimize this by recoding the more detailed later classifications into the broader earlier ones. These errors, however, were probably unrelated to ALS status (partly because information was collected prior to disease onset), and so they would also likely have biased our results towards the null, if anything.

We observed an association between DE exposure at least 10 years prior to index dates and a higher risk of ALS among males. These findings, particularly given the mutagenic potential of DE and the potential role of mutations (1, 67) and oxidative stress (23) in ALS, suggest that this is an exposure which warrants more attention in ALS etiology. Although our assessment was of occupational exposures, widespread population exposures to DE do occur, particularly from some traffic pollution, though most often at a lower level than the occupational exposures. Studies of exposure to DE in the general population are warranted. Given the widespread nature of DE exposure but the rarity of ALS, an association with DE could suggest that only certain people are sensitive to DE exposure, possibly determined by genetic profile.

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Author affiliations: Departments of Epidemiology and Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Aisha S. Dickerson, Marc G. Weisskopf); and Danish Cancer Society Research Center, Copenhagen, Denmark (Johnni Hansen, Ole Gredal).

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