Exposure to Diesel Motor Exhaust and Lung Cancer Risk in a Pooled Analysis from Case-Control Studies in Europe and Canada

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Rationale: **Diesel motor exhaust is classified by the International Agency for Research on Cancer as probably carcinogenic to humans. The epidemiologic evidence is evaluated as limited because most studies lack adequate control for potential confounders and only a few studies have reported on exposure–response relationships.**
Objectives: **Investigate lung cancer risk associated with occupational exposure to diesel motor exhaust, while controlling for potential confounders.**
Methods: **The SYNERGY project pooled information on lifetime work histories and tobacco smoking from 13,304 cases and 16,282 controls from 11 case–control studies conducted in Europe and Canada. A general population job exposure matrix based on ISCO-68 occupational codes, assigning no, low, or high exposure to diesel motor exhaust, was applied to determine level of exposure.**
Measurements and Main Results: **Odds ratios of lung cancer and 95% confidence intervals were estimated by unconditional logistic regression, adjusted for age, sex, study, ever-employment in an occupation with established lung cancer risk, cigarette pack-years, and time-since-quitting smoking. Cumulative diesel exposure was associated with an increased lung cancer risk highest quartile versus unexposed (odds ratio 1.31; 95% confidence interval, 1.19–1.43), and a significant exposure–response relationship (*P* value < 0.01). Corresponding effect estimates were similar in workers never employed in occupations with established lung cancer risk, and in women and never-smokers, although not statistically significant.**
Conclusions: **Our results show a consistent association between occupational exposure to diesel motor exhaust and increased risk of lung cancer. This association is unlikely explained by bias or confounding, which we addressed by adjusted models and subgroup analyses.**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Diesel motor exhaust is currently classified as a probable lung carcinogen.

What This Study Adds to the Field

Our results from a very large pooled study show a small, consistent association between occupational exposure to diesel motor exhaust and lung cancer, after adjusting for potential confounders, such as smoking and other occupational exposures. The effect is similar for non–small cell and small cell lung carcinoma.

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Diesel motor exhaust (DME) consists of a complex mixture of components in gas or particulate form. The particulates are mainly composed of cores of elemental carbon; traces of metallic compounds; and adsorbed organic materials including aromatic hydrocarbons, polycyclic aromatic hydrocarbons, aldehydes, and nitrogen oxides (1, 2). The composition of DME has changed over time as a result of improvements in engine technology and type of fuels. The highest levels of occupational DME exposure have been reported among workers engaged in underground mining, tunnel construction, and underground mine maintenance (3).

Regulations for diesel engine emissions were established in the United States in the 1960s (4), and have thereafter been introduced in Europe and around the world (5). The legislative limits for particulate matter in the European Union have until today referred to the particulate matter mass and not the number of particles. Because most of the particles are small in size (<100 nm) the corresponding mass is low and a large number of ultrafine particles may remain even when the legislative limit of mass is respected (6). A particle number limit is planned to be introduced in the EURO 6 legislative limits, due to enter into force from the end of 2012 (7).

Diesel particles are, because of their small size, highly respirable and can penetrate deep into the lungs and so cause temporary exposure-related symptoms, chronic respiratory effects, and probably lung cancer (8). A large number of individual cohort and case–control studies have suggested an association between DME exposure and increased lung cancer risk (9–13). Nevertheless, lack of dose–response within and across occupations, and incomplete adjustment for smoking and other confounders, have not allowed a conclusion regarding the presence of a casual relationship (14, 15).

The International Agency for Research on Cancer (IARC) classified DME as probably carcinogenic to humans (group 2A) in 1989, based on limited evidence in humans and sufficient evidence in experimental animals for whole DME and for extracts of DME particles. For the carcinogenicity of gas-phase DME (with particles removed) in experimental animals the evidence was classified as inadequate (16).

Our objective was to study the association between occupational DME exposure and lung cancer risk by duration and level of exposure, and cumulative dose, in a very large dataset including individual data on occupational history and smoking habits.

Some of the results of this study have been previously reported in the form of abstracts (17, 18).

METHODS

The SYNERGY project represents a pooling of data from 11 lung cancer case–control studies from Europe and Canada where the primary objective is to study joint effects of exposure to concurrent occupational lung carcinogens (asbestos, polycyclic aromatic hydrocarbons, nickel, chromium, and silica) and smoking. The studies included in SYNERGY are well-designed population- or hospital-based case–control studies, and in one case a nested case–control study, that have collected lifetime tobacco history and occupational data. The inclusion of studies in SYNERGY was also determined by the availability of exposure data for the selected agents in respective country or region. The SYNERGY project is coordinated by IARC, the Institute for Prevention and Occupational Medicine of the DGUV (IPA), and the Institute for Risk Assessment Sciences at Utrecht University (IRAS). More information about the SYNERGY project is available (http://synergy.iarc.fr). The present analysis on DME is based on the same pooled studies.

The studies that have contributed data to the present analysis are described in Table 1. In most studies, cases and controls were frequency-matched for variables, such as sex and age. Most interviews (84%) were conducted face to face with the subjects. The LUCAS and LUCA studies were restricted to men and the PARIS study included only regular smokers. MORGEN is a case-control study nested in the prospective EPIC cohort in The Netherlands and the subjects filled in a questionnaire at recruitment. Thus, smoking data and occupational information in the MORGEN study are lacking for the time interval between enrolment and diagnosis or end of follow-up (mean interval 5.3 yr; SD 2.7). Besides MORGEN, all studies have provided data on lifetime smoking habits and complete occupational history. The occupational data were originally mostly coded according to national classifications, and therefore had to be recoded into the International Standard Classification of Occupations (ISCO-68) (19). A conversion table from the Nordic occupational classification (NYK-83) codes to ISCO-68 was created and validated at Karolinska Institute and thereafter applied to the Swedish data. The countries participating in the IARC multicenter study on lung cancer in Central and Eastern Europe and the United Kingdom (INCO) are included as individual studies in these analyses.

Ethical approvals were obtained in accordance with legislation in each country, and in addition by the Institutional Review Board at IARC.

Exposure Assessment

DME exposure was estimated by using a general population job-exposure matrix (DOM-JEM) based on five-digit ISCO-68 codes. The DOM-JEM for DME was created by three occupational exposure experts (H.K., R.V., and S.P.) and assigns scores of no exposure = 0, low = 1, or high = 4 exposure levels of DME to each ISCO code. The assignment of DME exposure to each ISCO code was initially performed independently, and for conflicting scores a consensus was achieved. Initial agreement for the three experts was 92% (20). Out of

TABLE 1. DESCRIPTION OF THE STUDIES INCLUDED IN THE POOLED ANALYSES ON OCCUPATIONAL DIESEL MOTOR EXHAUST EXPOSURE AND LUNG CANCER RISK

Study Acronym	Country	Cases (*n* = *13,304*)	Participation Rate (*%*)	Controls (*n* = *16,282*)	Participation Rate (*%*)	Data Collection (*between yrs*)	Diesel Motor Exhaust Exposure (*between yrs*)	Source of Controls
AUT	Germany	3,180	77	3,249	41	1990–1995	1931–1995	Population
EAGLE	Italy	1,921	87	2,089	72	2002–2005	1932–2005	Population
HdA	Germany	1,004	69	1,002	68	1988–1993	1926–1993	Population
INCO_Cz. Rep	Czech Republic	304	94	452	80	1998–2002	1936–2002	Hospital
INCO_Hungary	Hungary	391	90	305	100	1998–2001	1931–1999	Hospital
INCO_Poland	Poland	793	88	835	88	1999–2002	1933–2002	Hospital and population
INCO_Romania	Romania	179	90	225	99	1998–2001	1943–2001	Hospital
INCO_Russia	Russia	599	96	580	90	1998–2000	1937–2000	Hospital
INCO_Slovakia	Slovakia	345	90	285	84	1998–2002	1936–2002	Hospital
INCO_UK	UK	442	78	917	84	1998–2005	1932–2005	Population
LUCA	France	294	98	292	98	1989–1992	1927–1992	Hospital
LUCAS	Sweden	1,014	87	2,307	85	1985–1990	1923–1990	Population
MONTREAL	Canada	1,176	85	1,505	69	1996–2002	1934–2002	Population
MORGEN*	The Netherlands	64	N/A	187	N/A	1993–1997	1945–1994	Population
PARIS	France	169	95	227	95	1988–1992	1931–1992	Hospital
ROME	Italy	329	74	324	63	1993–1996	1926–1996	Hospital
TURIN/VENETO	Italy	1,100	79	1,501	80	1990–1994	1922–1994	Population

* Nested case–control study.

1,840 job codes in ISCO-68, 202 (11%; e.g., drivers, engineers, technicians, and farmers) were assigned low DME levels and 27 (1.5%; e.g., miners, mechanics for agricultural machinery and diesel engines, and railway and road vehicle loaders) were assigned high levels of DME exposure (more information about the DOM-JEM is available on request). Linkage of the job histories with the DOM-JEM assigned a DME exposure level to each job period.

We created two indices of DME exposure: duration across all job periods for the two exposure levels (low and high) separately; and an indicator of cumulative dose based on the intensity score (low = 1, high = 4), multiplied by duration for each job period, summed over all job periods of a subject. The cumulative index was thereafter categorized according to the quartiles of the exposure distribution among controls.

Statistical Analyses

Logistic regression models were fitted to calculate odds ratios (OR) and 95% confidence intervals (CI) of lung cancer associated with indices of DME exposure. To further explore residual confounding we repeated the analyses on cumulative DME exposure in never-smokers and among subjects who had never been employed in a "List A" job. A "List A" job represents a list of occupations and industries known to present an excess risk of lung cancer, which was identified by Ahrens and Merletti in 1998 (21) and updated by Mirabelli and coworkers in 2001 (22). We also investigated the DME effect in women separately. Additional sensitivity analyses consisted of (*1*) excluding the AUT-Munich study because of a low response rate (41%) among controls; (*2*) comparing the results of studies with controls recruited from the population versus the studies using hospital controls because the latter possibly are more prone to selection bias in case of different study bases for cases and controls; and (*3*) excluding "ever-farmers" because farmers may be particularly inclined to this kind of selection bias (23). The subjects unexposed to DME were the reference category in each of the analyses.

P values for linear trend were obtained by applying a logistic regression model including respective continuous variable. The trend was calculated among all subjects.

We made three levels of adjustment: (*1*) adjusting for age group (<45, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and 75+), sex, and study; (*2*) additionally adjusted for ever-employment in a "List A" job (yes/no); and (3) additionally adjusted for tobacco smoking (log[cigarette pack-years+1]) and time-since-quitting smoking cigarettes (current smokers; stopping smoking 2–7, 8–15, 16–25, 26+ yrs before interview/diagnosis; and never-smokers). Current smokers were persons who had smoked greater than or equal to one cigarette per day for greater than or equal to 1 year, and included those who had stopped smoking in the last 2 years before diagnosis or interview. The cigarette pack-year was calculated as follows: $\sum$duration × average intensity per day/20.

Meta regression models were used to explore study-specific ORs and extent and sources of heterogeneity, and forest plots were used to visualize the results. We compared the DME effect in small versus large studies (> /< 1,500 subjects); old versus recent studies (end of data collection before or after 1995); hospital-based versus population-based case–control studies; and by study and region according to Globocan for Western Europe, Northern Europe, Central Europe, Eastern Europe, Southern Europe, and Northern America (24). The heterogeneity was assessed using a chi-squared test with inverse variance weights. The extent of heterogeneity between OR estimates was assessed as a percentage (I^2) (25).

All analyses were conducted using Stata v.11.0 for Windows (StataCorp LP, College Station, TX). We used the Stata command "metan" for the meta regression analyses.

RESULTS

The study sample comprised 13,479 cases and 16,510 controls. Subjects providing incomplete information for calculating duration of jobs or cumulative smoking were omitted (175 cases and 228 controls), leaving 13,304 cases and 16,282 controls for these analyses.

The data were collected in 41 centers in 13 countries between 1985 and 2005. The response rates ranged between 68% (HdA) and 98% (LUCA) among cases, and 41% (AUT-Munich) and 100% (INCO-Hungary) among controls. The hospital-based case–control studies generally achieved a higher response rate. The overall response rate weighted by the size of the study population was 82% among cases and 67% among controls. The MORGEN study is derived from a prospective cohort study conducted in The Netherlands. After invitation by letter 45% agreed to participate in the cohort study and completed a baseline questionnaire; the mean follow-up time until diagnosis was 5.3 years (SD 2.7).

Table 2 describes characteristics of the study population. The median age was 64 years in men and 62 years in women. Six percent of cases were never-smokers, versus almost 30% among the controls. The PARIS study was restricted to smokers. The proportion of current smokers was 65.2% among cases and 31.6% among controls. The mean of cumulative tobacco consumption (cigarette pack-years) was 38.9 (SD 27.8) in cases and 19.2 (SD 23.2) in controls. The mean time since quitting smoking was 4.6 (SD 8.7) years among cases and 11.6 (SD 13.5) years among controls. Twelve percent of the cases (14.1% men and 2.7% women) and 7.8% of controls (9.4% men and 1.4% women) have held a job known to entail an excess risk of lung cancer ("List A" job). Based on the DOM-JEM assignment, the lifetime prevalence of occupational DME exposure among control subjects was 13.6% in women and 42.4% in men.

TABLE 2. DESCRIPTION OF THE STUDY POPULATION

Characteristics	Cases (*n* = *13,304*)	%	Controls (*n* = *16,282*)	%
Sex				
Men	10,812	81.3	13,031	80
Women	2,492	18.7	3,251	20
Age, yr				
<45	499	3.8	662	4.1
45–49	752	5.7	849	5.2
50–54	1,330	10	1,669	10.3
55–59	2,087	15.7	2,385	14.6
60–64	2,610	19.6	3,098	19
65–69	2,892	21.7	3,686	22.6
70–74	2,375	17.9	3,145	19.3
75+	759	5.7	788	4.8
Smoking status				
Never smokers*	801	6	4,773	29.3
Former smokers	3,827	28.8	6,369	39.1
Current smokers	8,676	65.2	5,137	31.6
Unknown/missing	0	0	3	0
"List A" job, occupation with known lung cancer risk				
Never	11,714	88	15,018	92.2
Ever	1,590	12	1,264	7.8
Lifetime prevalence of occupational diesel motor exhaust exposure				
OVERALL	5,628	42.3	5,962	36.6
AUT	1,604	50.4	1,295	39.9
EAGLE	592	30.8	624	29.9
HdA	635	63.3	577	57.6
INCO_Cz. Rep	132	43.4	137	30.3
INCO_Hungary	181	46.3	146	47.9
INCO_Poland	247	31.2	233	27.9
INCO_Romania	36	20.1	46	20.4
INCO_Russia	196	32.7	203	35
INCO_Slovakia	146	42.3	94	33
INCO_UK	199	45	408	44.5
LUCA	137	46.6	132	45.2
LUCAS	335	33	682	29.6
MONTREAL	427	36.3	506	33.6
MORGEN	13	20.3	27	14.4
PARIS	67	39.6	76	33.5
ROME	146	44.4	128	39.5
TURIN	535	48.6	648	43.2

* The PARIS study included only smokers.

TABLE 3. LUNG CANCER RISK ASSOCIATED WITH CUMULATIVE DIESEL MOTOR EXHAUST EXPOSURE

Subjects	Cumulative Diesel Motor Exhaust Exposure (*unit-years*)*	Cases	%	Controls	%	OR1†	95% CI	OR2‡	95% CI
All	Never	7,676	57.7	10,320	63.4	1.00	Reference	1.00	Reference
	<6	1,269	9.5	1,513	9.3	1.04	0.96–1.13	0.98	0.89–1.08
	6–17.33	1,325	10	1,497	9.2	1.13	1.04–1.23	1.04	0.95–1.14
	17.34–34.5	1,440	10.8	1,502	9.2	1.23	1.13–1.33	1.06	0.97–1.16
	>34.5	1,594	12	1,450	8.9	1.42	1.31–1.54	1.31	1.19–1.43
	Test for trend, P value					<0.01§		<0.01§	
Women	Never	2,144	86	2,810	86.4	1.00	Reference	1.00	Reference
	<6	146	5.9	198	6.1	0.85	0.68–1.07	0.83	0.64–1.08
	6–17.33	116	4.7	127	3.9	1.07	0.82–1.39	1.27	0.94–1.71
	17.34–34.5	51	2	71	2.2	0.87	0.60–1.26	0.94	0.62–1.42
	>34.5	35	1.4	45	1.4	1.03	0.66–1.63	1.58	0.96–2.59
	Test for trend, P value					0.83§		0.20§	
Never-smokers	Never	614	76.7	3,486	73	1.00	Reference	N/A	
	<6	44	5.5	334	7	0.74	0.52–1.05		
	6–17.33	63	7.9	328	6.9	1.22	0.90–1.65		
	17.34–34.5	33	4.1	305	6.4	0.85	0.57–1.26		
	>34.5	47	5.9	320	6.7	1.26	0.90–1.78		
	Test for trend, P value					0.28§			
Workers never employed in a "List A" job	Never	6,954	59.4	9,764	65	1.00	Reference	1.00	Reference
	<6	1,034	8.8	1,320	8.8	1.05	0.96–1.15	0.98	0.89–1.09
	6–17.33	1,091	9.3	1,309	8.7	0.15	1.06–1.26	1.07	0.97–1.18
	17.34–34.5	1,223	10.4	1,324	8.8	1.28	1.17–1.39	1.10	1.00–1.21
	>34.5	1,412	12.1	1,301	8.7	1.49	1.37–1.62	1.35	1.23–1.49
	Test for trend, P value					<0.01§		<0.01§	

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
* The categories represent the quartile distribution of cumulative diesel motor exhaust exposure among exposed controls.
† OR1 is adjusted for age, sex, study, and ever-employment in a "List A" job (*see* text for details).
‡ OR2 is additionally adjusted for pack-years and time-since-quitting smoking.
§ Test for trend, *P* value obtained using the continuous variable for cumulative exposure.

Among women, the highest proportion of DME-exposed controls was found in Germany (24.2%) and the lowest in France (0%), whereas in men the highest proportion was found in the United Kingdom (66.1%) and the lowest in Romania (23.9%). Among control subjects, very few women (<1%) had experienced high levels of occupational DME exposure, versus 8.3% among men. The proportion of highly exposed men among control subjects was particularly high in the United Kingdom (20.6%); Germany (11.5%); Hungary (10.6%); and Canada (9.7%).

Risk estimates as shown in Tables 3–5 were based on models adjusting for age, sex, study, and ever-employed in a job known to entail an increased lung cancer risk (OR1); and OR2 additionally adjusted for cigarette pack-years, and time-since-quitting smoking cigarettes. In the subsequent text we refer to the results adjusted for smoking (i.e., OR2) or else we indicate what adjustments were made.

Table 3 shows the OR for lung cancer associated with cumulative DME exposure. We observed a significant dose–response trend (P value < 0.01). In the analysis by exposure category the CI of the OR for the highest exposure category excluded unity (OR, 1.31; 95% CI, 1.19–1.43). A random effects meta regression rendered essentially similar results (OR, 1.26; 95% CI, 1.14–1.40) (Figure 1). The OR for the highest quartile of DME exposure, when only adjusted for age, sex, and study, was 1.42 (95% CI, 1.31–1.54).

Figure 1 illustrates the study-specific OR for the highest quartile of cumulative DME exposure versus the never DME exposed. INCO-Romania, INCO-UK, LUCA, EAGLE, and MORGEN showed OR less than 1, whereas the OR in the other studies ranged between 1.16 (INCO-Czech Republic) and 1.77 (INCO-Poland). The OR decreased 10–20% in most countries, and the heterogeneity between the studies expressed as I^2 decreased from 32.5% to 13.8%, when adjusting for smoking (pack-years and time-since-quitting smoking).

In subgroups analyses, the OR for lung cancer among never-smokers was 1.26 (95% CI, 0.90–1.78) in the highest exposure category of cumulative DME exposure; no trend was observed

TABLE 4. LUNG CANCER RISK BY YEARS AMONG WORKERS ONLY EXPOSED TO LOW LEVELS OF DIESEL MOTOR EXHAUST EXPOSURE

Duration of Diesel Motor Exhaust Exposure (*yrs*)	Case/Control	OR1*	95% CI	OR2†	95% CI
0	7,676/ 10,320	1.00	Reference	1.00	Reference
1–10	1,576/1,897	1.05	0.97–1.13	1.00	0.92–1.09
11–20	785/937	1.08	0.98–1.20	0.98	0.88–1.10
21–30	660/723	1.18	1.06–1.33	1.03	0.91–1.17
>30	1,246/1,292	1.28	1.18–1.40	1.17	1.07–1.29
Test for trend, P value		<0.01‡		<0.01‡	

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
* OR1 is adjusted for age, sex, study, and ever-employment in a "List A" job (*see* text for details).
† OR2 is additionally adjusted for smoking pack-years, time-since-quitting smoking.
‡ Test for trend, *P* value obtained by using respective continuous variable.

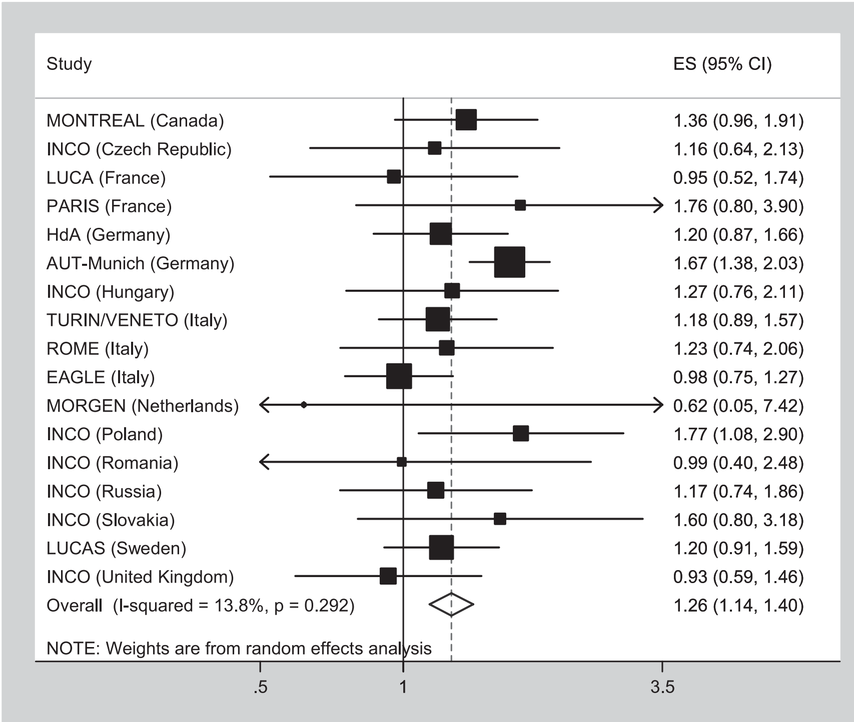

Figure 1. Study-specific odds ratios for the highest quartile of cumulative diesel motor exhaust exposure compared with never-exposed, adjusted for age, sex, cigarette pack-years, time-since-quitting smoking, and ever-employment in a "List A" job. CI = confidence interval; ES = odds ratio.

(P = 0.28). The results in workers never employed in "List A" jobs were comparable with the overall results (i.e., an increased OR for lung cancer in the highest exposure category; OR, 1.35; 95% CI, 1.23–1.49, with a significant exposure–response trend [P value < 0.01]). Among women, the OR for lung cancer in the highest DME exposure category was 1.58 (95% CI, 0.96–2.59). In men, an OR 1.28 (95% CI, 1.17–1.41) for the fourth quartile was observed, with a significant exposure–response trend (P < 0.01).

The risk estimates were very similar for population-based and hospital-based case–control studies: for the highest quartile of cumulative DME exposure OR 1.30 (95% CI, 1.17–1.44) versus 1.31 (95% CI, 1.09–1.59). Excluding the AUT-Munich study lowered the OR for lung cancer to 1.22 (95% CI, 1.10–1.35), whereas excluding ever-farmers resulted in an OR 1.28 (95% CI, 1.15–1.42). The significant exposure–response trends remained (excluding AUT-Munich P value < 0.01; excluding farmers P value < 0.01).

The effect of cumulative DME exposure was similar for different types of lung cancer (*see* Table E1 in the online supplement). The OR for non–small cell lung carcinoma among men was 1.27 (95% CI, 1.14–1.40) in the highest exposure category of cumulative DME exposure, whereas it was 1.44 (95% CI, 0.83–2.50) among women. For small cell lung carcinoma, the OR in the highest exposure category was 1.31 (95% CI, 1.10–1.55) in men and 3.82 (95% CI, 1.51–9.67) in women.

In Tables 4 and 5, we estimated lung cancer risk in relation to duration of exposure. The OR for lung cancer associated with only low levels of DME exposure (Table 4) was close to 1, until 30 years of duration. The OR associated with greater than 30 years of exposure to low levels of DME exposure versus never-exposed was 1.17 (95% CI, 1.07–1.29). Workers exposed to high levels of DME exposure (Table 5) experienced an increased risk of lung cancer within a short period of high exposure (<10 yr; OR 1.28; 95% CI, 1.14–1.45). The highest risk was observed after 21–30 years of high level exposure (OR 1.52; 95% CI, 1.15–2.02).

We observed no significant heterogeneity for the effect of DME in the highest quartile of cumulative exposure versus the never-exposed across studies (I^2 13.8%; P value = 0.29). However, when exploring other potential sources of heterogeneity we found a difference in the effect of DME in the studies completed before 1995 (OR 1.49; 95% CI, 1.32–1.68) compared with the more recent studies (OR 1.19; 95% CI, 1.04–1.36); with a pooled OR 1.34 (95% CI, 1.07–1.67), I^2 = 83.9%, and P value 0.01. Geographic region was also associated with significant heterogeneity, with the highest risk estimate in Western Europe (OR 1.51; 95% CI, 1.30–1.76) and the lowest in Southern Europe (OR 1.07; 95% CI, 0.90–1.28). The pooled OR for the highest quartile of cumulative DME exposure across regions was 1.29 (95% CI, 1.11–1.50), I^2 = 59.8%, and P value 0.04. The effect of DME in large and small studies was not significantly different (P value = 0.13) with the pooled OR 1.33 (95% CI, 1.14–1.54). Likewise, the effect of DME was not influenced by the type of controls (P value = 0.82) with the pooled OR 1.36 (95% CI, 1.24–1.48).

DISCUSSION

We used the recently established database from the SYNERGY project to explore the possible association between occupational DME exposure and lung cancer. The SYNERGY database is unique in the sense that it comprises lifetime occupational data and detailed smoking information for more than 13,000 cases and 16,000 controls from 11 case–control studies in Europe and Canada. We found an exposure–response relationship between occupational DME exposure, measured by a semiquantitative score of cumulative exposure, and lung cancer. In the analysis by categories of the cumulative dose score, the conventional limit for statistical significance of the OR was reached in the fourth quartile of cumulative dose. The results were similar in women, in never-smokers, and in workers never employed in jobs known to entail increased lung cancer risk, although the ORs in the highest quartile did not attain statistical significance in all subgroup analyses. Whereas subgroup analyses are helpful in limiting residual confounding, they lead to considerable loss of power. This is especially true for women and never-smokers

TABLE 5. LUNG CANCER RISK BY YEARS OF EXPOSURE TO HIGH LEVELS OF DIESEL MOTOR EXHAUST

Duration of Diesel Motor Exhaust Exposure (*yrs*)	Case/Control	OR1*	95% CI	OR2†	95% CI
0	7,676/10,320	1.00	Reference	1.00	Reference
1–10	858/696	1.48	1.33–1.65	1.28	1.14–1.45
11–20	228/208	1.34	1.10–1.62	1.21	0.98–1.51
21–30	149/108	1.75	1.36–2.26	1.52	1.15–2.02
>30	126/101	1.59	1.22–2.08	1.45	1.07–1.96
Test for trend, P value		<0.01‡		<0.01‡	

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
* OR1 is adjusted for age, sex, study, and ever-employment in a "List A" job (*see* text for details).
† OR2 is additionally adjusted for smoking pack-years, time-since-quitting smoking.
‡ Test for trend, *P* value obtained by using respective continuous variable.

and makes the OR estimates unstable and the interpretation of the confidence intervals in the individual categories of exposure difficult. When we distinguished workers with low-intensity exposure from those with high exposure, the latter showed excess risks with as low as 10 years duration, although those with low-intensity exposure showed elevated risks only after 30 years and more of exposure. Our results are to a large extent in line with previous research (8, 16), although most previous studies could not control for major potential confounders, such as cigarette smoking and occupational exposures, and have not had as large sample sizes as ours to assess risks in different subgroups.

Three papers on lung cancer risk after diesel exposure have been published from the studies included in this pooled analysis (9, 26, 27). Exposure to DME in these studies was assessed on a case-by-case basis by local experts. An increased risk of lung cancer and a dose–response trend was observed in Germany (AUT-Munich and HdA combined; OR 1.43; 95% CI, 1.23–1.67) and Sweden (LUCAS; OR 1.40; 95% CI, 0.90–2.19), but not in Italy (Turin/Veneto; OR 1.04; 95% CI, 0.79–1.37) (9, 26, 27). Our country-specific results for ever high exposure obtained by using the DOM-JEM were similar to those reported in these previous studies: Germany (OR 1.54; 95% CI, 1.31–1.81); Sweden (OR 1.10; 95% CI, 0.65–1.85); and Italy (OR 1.00; 95% CI, 0.80–1.24).

The prevalence of DME exposure was higher in the current analysis compared with the original studies that had estimated diesel exposure using expert case-by-case assessment, or specific project JEMs. This is a consequence of the ratings in the DOM-JEM (e.g., farmers are assigned low DME exposure and represent a relatively large proportion of the exposed population in some of the studies). In the INCO-Hungary study the prevalence of DME exposure decreased by 19% when farmers were excluded, whereas the decrease was only 1% in INCO-UK. The high prevalence of exposure is also a consequence of the nature of a JEM, namely to assign everybody in a given job code the same exposure, whereas individual assessments give the opportunity for attributing exposure to some people in a job but not others, and to take into account an increasing trend of diesel engines over time. This may contribute to multiple dimensions of exposure misclassification, but is not related to disease status and thus would most often lead to an attenuation of the OR estimates.

We excluded farmers in sensitivity analyses assuming that farmers living in rural areas may belong to specialized cancer hospitals with a larger catchments area than the region from which hospital controls were enrolled, and which could cause selection bias as has been shown in a previous small case–control study (23). The OR for low DME exposure greater than 30 years decreased from OR 1.17 (95% CI, 1.07–1.29) to 1.07 (95% CI, 0.95–1.20) when excluding farmers. The OR for the fourth quartile of cumulative DME exposure changed from OR 1.31 (95% CI, 1.19–1.43) to OR 1.28 (95% CI, 1.15–1.42). The corresponding risk estimates when comparing studies with population controls versus hospital controls were virtually the same, *P* value for heterogeneity 0.82. Thus, these data do not show an important selection bias as a result of potentially different study bases for cases and controls.

A large group of workers with DME exposure are drivers; more than 20% of the study population has worked as driver during their working life. Drivers are exposed to high exposure levels of hazardous substances when they smoke in their vehicles, and are exposed to second-hand smoke from coworkers or other passengers (28). This residual confounding by tobacco smoke among drivers could contribute, even if minimally, to the increased risk seen among low-exposed workers.

In most scenarios nondifferential exposure misclassification leads to attenuation of OR estimates; however, our large study size and the high prevalence of DME exposure may have given SYNERGY enough power to detect a statistically significant OR, even in the presence of underestimation (29, 30). The DOM-JEM is based on job titles only and is therefore a highly standardized tool (31, 32), which diminishes the likelihood of both potential recall and reporting bias. Selection bias has been discussed previously in relation to farmers, but can also occur if participation differed by other subgroups of cases and controls with different probability of DME exposure. We assessed this by excluding the AUT-Munich study (the largest individual study with low response rate among controls); the ORs decreased slightly but did not change the overall results. Thus, a strong selection bias as a result of differences in nonparticipation among cases and controls is unlikely.

Heterogeneity of relative risk estimates may result from variation in many factors, including the background risks of lung cancer. The most influential risk factor for lung cancer is the smoking pattern in respective country (33). Indeed, lung cancer mortality varies largely in the countries included in the analyses and has changed dramatically over the last 50 years; lung cancer mortality peaked around 1970 in the United Kingdom, whereas it peaked as late as around 2000 in Poland and Hungary (34). Exposure to other lung carcinogens may also have differed as a result of the level of industrialization in each local setting. The frequency of employment in jobs known to entail increased lung cancer risk among the controls in the current study, ranging from 3% in MORGEN (The Netherlands) to 16% in HdA (Germany), was approximately controlled for in the analyses.

Among the strengths of this analysis are the large sample size, the good quality of data on occupational history and smoking, and the fact that the exposure assignment for DME was based on a JEM created by experts. Among the limitations are that some of the centers used hospital-based control selection, the JEM did not take into account the changes in the use of diesel engines over time, and it was not possible to estimate absolute concentration levels for DME.

Our results reflect the effects of the DME exposure present before and up to the time when the studies were conducted. Modern engine emissions have become cleaner in the last 20 years (e.g., by the use of low-sulfur fuel and particle traps on vehicles) (35). However, the number of emitted particles may still be high and the consequences on the potential carcinogenicity are not clear. In addition, old types of engines and other sources of DME (e.g., ships, generators, diesel powered tools, paving equipment, and so forth) continue to lead to DME exposure; our results suggest that DME exposure may contribute to the current lung cancer burden.

Conclusions

Our results show a small consistent association between occupational exposure to DME and lung cancer risk, and significant exposure–response trends. When the exposure score was categorized in quartiles, the OR associated with the highest quartile was statistically significant. This association is unlikely to be entirely explained by bias or confounding, which we addressed by adjusted models and analyses in subgroups not exposed to potential confounders. Cohort studies among heavily exposed occupations with quantitative exposure measurements may shed further light on the risk assessment.

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