REVIEW

Diesel Exhaust Exposure and Lung Cancer

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We evaluated the relation between occupational exposure to diesel exhaust and cancer of the lung in a meta-analysis of 29 published cohort and case-control studies. Twenty-one of the 23 studies meeting the inclusion criteria had observed relative risk estimates greater than one. Pooled effect measures weighted by study precision indicated an increased relative risk (RR) for lung cancer from occupational exposure to diesel exhaust [RR = 1.33; 95% confidence interval (CI) = 1.24–1.44]. Subanalysis of case-control (RR = 1.33; 95% CI = 1.18–1.51) *vs* cohort studies (RR = 1.33; 95% CI = 1.21–1.47) and of studies that controlled for smoking (RR = 1.35; 95% CI = 1.20–1.52) *vs* those that did not (RR = 1.33; 95% CI = 1.20–1.47) produced results that did not differ from those of the overall analysis. On the other hand, cohort studies using internal comparisons (RR = 1.43; 95% CI = 1.29–1.58) showed higher relative risks than those using external comparisons (RR = 1.22; 95% CI = 1.04–1.44). Heterogeneity between studies was reduced when we stratified studies by the occupational setting in which exposure occurred. A positive duration-response relation was evident in those studies that were stratified by employment duration. This meta-analysis supports a causal association between increased risks for lung cancer and exposure to diesel exhaust. (Epidemiology 1998;9: 84–91)

Keywords: lung cancer, diesel exhaust, meta-analysis.

Studies of exposure to diesel exhaust and lung cancer have included diverse occupational groups and research methods. Few of these studies have had the benefit of individual-level exposure estimation; relative risk estimates are generally less than two. Such studies are particularly susceptible to biases, including confounding. Given these recognized limitations, the interpretation of these studies has been challenging and controversial. In 1989, the International Agency for Research on Cancer classified the evidence for the human carcinogenicity of diesel exhaust as limited.[1] In this article, we combine results from published data of lung cancer mortality among workers with potential exposure to diesel exhaust fumes. The objective of this analysis is to evaluate quantitatively the epidemiologic evidence that exposure to diesel exhaust is a cause of lung cancer. We attempt to answer the following questions: (1) Are the risks of lung cancer in these observational studies likely to be due to chance? (2) Is confounding due to smoking a likely explanation for the increased observed risks? (3) Do differences in study methods or exposure settings explain differences in observed risks?

Methods

We followed the general principles of meta-analysis, such as those outlined by L'Abbe *et al*[2] as well as those discussed by Greenland.[3] We searched the epidemiologic literature for all studies concerning lung cancer and occupational diesel exhaust exposure. Within most of these studies, exposure was defined as work in an occupation or industry in which diesel engines and equipment were in use; however, a few of the studies benefited from quantitative exposure measures. In addition to looking for primary references using resources such as Melvyl MEDLINE, we surveyed reviews on the subject for secondary references. We included only studies reported in peer-reviewed journals.

Although the use of diesel engines in the coal and metal mining industries is common, we chose to exclude occupational studies of miners because of the potential role of multiple occupational carcinogens, including radon and silica. When different updates of a study had been published in more than one journal, we used the most recent report. Similarly, when a study population had been followed for different time intervals, we used the analysis based on the longest period of follow-up.

We extracted effect measures [relative risks (RRs), odds ratios, and standardized mortality ratios (SMRs)] and their confidence intervals (CI) for lung cancer mortality among diesel exhaust-exposed workers from each

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Support for the initial stages of this work was provided by Grant 93-E0023 from the California Environmental Protection Agency. Additional support came from the National Institute of Environmental Health Sciences (Grant P30-ESO1896) and the University of California Center for Occupational and Environmental Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the funding agencies.

Submitted January 7, 1997; final version accepted July 7, 1997.

Editors' note: See related editorial on page 4 of this issue.

study. We estimated missing confidence intervals by Byar's approximation for the cohort studies,[4] or by calculating the variance of the log of the odds ratio using unadjusted data for the case-control studies.[5] If information on lung cancer mortality was not provided, we used the data on total respiratory cancer mortality.

We reviewed studies for inclusion into a pooled analysis, based on their validity. We excluded (1) studies in which inadequate latency for lung cancer after exposure to diesel exhaust was likely; and (2) studies in which work with diesel equipment or engines could not be confirmed or reliably inferred.

We chose a period of 10 years as a minimum interval time from first exposure to end of follow-up. If studies were conducted at or near the time of transition to diesel fuels in an industry, we defined the time of potential first exposure as the midpoint between the year when diesel fuels were introduced and the year that the transition to diesel was completed. If a study did not provide sufficient information to estimate latency for the entire cohort, yet it was apparent that at least some of the subjects had been followed for 10 years after first exposure, we included these studies in the analysis.

If a study presented risk estimates for more than one specific occupational category of diesel exhaust-exposed workers, we used the subgroup risk estimates in the meta-analysis. If a study considered data on duration of exposure or employment, we used the risk estimates from the longest exposure stratum. If more than one stratum represented 20 or more years of diesel exposure, these strata were combined. In cohort studies in which both national and regional populations were used to calculate the expected deaths, we used results based on the regional rates in the meta-analysis. We always used smoking-adjusted effect measures when present.

We used the method of weighting by precision to calculate the pooled estimates.[3] We calculated the weight or inverse variance ($\omega_i = 1/SE_i^2$) of each study using a standard error equal to the natural log of the ratio of the upper to lower 95% confidence intervals divided by 3.92 [$SE = \ln(RR_{upper}/RR_{lower})/3.92$]. The value 3.29 replaced 3.92 in the formula if 90% confidence intervals were presented. For each study, the weight (ω_i) was multiplied by the natural log of the effect measure ($\beta_i = \log RR_i$) to give a summary measure ($\omega_i\beta_i$) for the ith study. We calculated a weighted mean or pooled summary estimate (B) by dividing the weighted sum of the results by the sum of the weights ($B = \Sigma\omega_i\beta_i/\Sigma\omega_i$). The variance of this pooled estimate is simply $1/\Sigma\omega_i$.

We estimated pooled summaries for all studies combined and separately for cohort studies and case-control studies. We further subdivided cohort studies into those that used internal reference populations and those that did not. We also calculated pooled estimates for studies that statistically adjusted for smoking and for those that did not have available smoking data. We estimated summaries for occupational categories when more than two studies in that category met the criteria for inclusion. We converted all pooled estimates into rate ratios ($RR = \exp B$) with 95% confidence intervals.

We evaluated heterogeneity among studies with the statistic $\chi^2 = \omega_i(B - \beta_i)^2$, with degrees of freedom (df) equal to one less than the number of studies combined. Where evidence for heterogeneity was present, it was reflected in the confidence interval by adjusting the variance of the pooled relative risk estimate using a factor derived from the heterogeneity test. The method used was originally suggested by Armitage and described by Shore *et al.*[6] The variance of the log of the relative risk estimate is adjusted by multiplying it by the ratio of the heterogeneity χ^2 to its degrees of freedom ($Var_{Adj} = Var \times \chi^2/df$ when $\chi^2 > df$). The adjusted variance is then used to calculate the adjusted confidence interval.

In cohort studies that used external reference populations, we examined potential bias from the healthy worker by a simple adjustment of the lung cancer SMR by the SMR for all causes excluding lung cancer in those studies in which data were available. Briefly, we recalculated the SMR for all causes of death after removing observed and expected cases of lung cancer. Then, we adjusted the expected number of lung cancer deaths by multiplying the general population expected number by the SMR for all causes excluding lung cancer. We then calculated an adjusted lung cancer SMR with the observed lung cancer deaths and the adjusted expected number of deaths.

To assess the studies for evidence of dose-response relations, we examined those studies that had data for exposure duration and which used internal reference groups. As exposure duration categories were defined differently in the various studies, we were not able to pool the risk estimates by duration of exposure.

Results

We found 35 studies in the published literature with data concerning exposure to diesel exhaust and lung cancer. Six pairs of studies represented analyses of the same study population. Burns and Swanson,[7] Hall and Wynder,[8] Schenker *et al*,[9] and Damber and Larsson[10] presented preliminary results of data later re-analyzed by Swanson *et al*,[11] Boffetta *et al*,[12] Garshick *et al*,[13] and Damber and Larsson.[14] We used the later publications in the meta-analysis. The paper by Siemiatycki[15] was a re-analysis of a 1988 publication; however, we used the earlier study, since the later analysis presented only a subset of the earlier data. Emmelin *et al*[16] presented a nested case-control analysis of the cohort studied by Gustafsson *et al*[17]; we used the original cohort study owing to uncertainty in the methods of exposure categorization in the later analysis.

The study of Hayes *et al*[18] presented a secondary analysis of three pooled case-control studies of lung cancer examining the effect of occupation in diesel exhaust-exposed trades. The original studies were case-control studies of lung cancer that had not focused on diesel exhaust exposure.[19–21] The data we used in the pooled analysis were derived from the analysis presented by Hayes *et al.*

We excluded two case-control studies because of uncertain exposure to diesel exhaust. These included the

TABLE 1. Studies Included in Meta-Analysis

Authors and Year	Type*	Smoking Adjusted	Occupation	Exposure or Duration Category	Cases	RR	95% CI
Ahlberg *et al*,[50] 1981	RC	No	Truck driver		161	1.3	1.1–1.6
Boffetta *et al*,[42] 1988	PC	Yes	Truck driver		48	1.24	0.93–1.66
			Equipment operator		5	2.6	1.12–6.06
			Railroad worker		14	1.59	0.94–2.69
Boffetta *et al*,[12] 1990	CC	Yes	Diesel-exposed	>30 years	17	1.49	0.72–3.11
Coggon *et al*,[29] 1984	CC	No	Diesel-exposed		172	1.3	1.0–1.6
Damber & Larsson,[14] 1987	CC	Yes	Professional driver	>20 years	37	1.2	0.6–2.2
Edling *et al*,[36] 1987	RC	No	Bus worker		6	0.67	0.24–1.46†
Garshick *et al*,[41] 1987	CC	Yes	Railroad worker	>20 years	117	1.64	1.18–2.20
Garshick *et al*,[13] 1988	RC	No	Railroad worker	>15 years	N/A‡	1.72	1.27–2.33
Gustafsson *et al*,[17] 1986	RC	No	Dock worker		70	1.32	1.05–1.66
Gustavsson *et al*,[40] 1990	RC	No	Bus garage worker	High exposure	12	2.0	1.43–2.81†
Hansen,[51] 1993	RC	No	Truck driver		76	1.6	1.26–2.0
Hayes *et al*,[18] 1989	CC	Yes	Bus driver	>10 years	38	1.6	0.9–2.8
			Truck driver	>10 years	147	1.5	1.1–1.9
			Equipment operator	>10 years	14	1.3	0.6–3.1
Howe *et al*,[35] 1983	RC	No	Railroad worker	Probable exposure	279	1.35	1.2–1.52†
Lerchen *et al*,[30] 1987	CC	Yes	Diesel mechanic		7	0.6	0.2–2.0
Menck & Henderson,[38] 1976	RC	No	Truck driver		109	1.65	1.35–1.99†
Raffle,[27] 1957	RC	No	Bus & trolley worker		30	1.4	0.94–2.0†
Rafnsson & Gunnarsdottir,[43] 1991	RC	No	Truck driver	>30 years	24	2.32	0.85–5.04
Rushton *et al*,[28] 1983	RC	No	Bus mechanic		102	1.01	0.82–1.22
Siemiatycki *et al*,[31] 1988	CC	Yes	Diesel-exposed		76	1.08	0.92–1.27
Steenland *et al*,[39] 1990	CC	Yes	Diesel truck driver	>25 years	128	1.60	1–2.3
Swanson *et al*,[11] 1993	CC	Yes	Truck driver	>20 years	121	2.44	1.43–4.16
			Railroad worker	>10 years	40	2.46	1.24–4.87
Williams *et al*,[32] 1977	CC	Yes	Truck driver		22	1.52	0.9–2.56†
			Railroad worker		12	1.40	0.74–2.64†
Wong *et al*,[37] 1985	RC	No	Equipment operator	>20 years	163	1.07	0.91–1.24†

* RC = retrospective cohort study; PC = prospective cohort study; CC = case-control study.
† Confidence intervals are calculated from the published data as described in Methods.
‡ N/A = not available.

studies by Benhamou *et al*[22] and Buiatti *et al*,[23] who studied professional drivers and transportation workers, respectively, but did not provide information on vehicle or engine types. We included, however, the case-control study of professional drivers by Damber and Larsson,[14] as a majority of the lung cancer deaths were among truck drivers who would have been exposed to diesel exhaust.

We excluded two studies because the follow-up period would not allow for a 10-year latency interval. Kaplan[24] studied a cohort of railroad workers from 1953 to 1958. The midpoint for transition to diesel fuels in the United States was 1952, and the transition was complete in 1959.[13] Milne *et al*[25] looked at occupations and lung cancer in Alameda County, CA, from 1958 to 1962. Risk estimates were provided for truck drivers, yet diesel trucks were not introduced until the late 1950s.[26]

We included several studies with possibly adequate latency. Raffle[27] followed a cohort of bus company employees from 1950 to 1954. Diesel buses were introduced in England in the mid-1930s, and 85% of buses were using diesel by the end of World War II. It is likely that many of these workers would have been exposed for at least 10 years. In the Rushton *et al*[28] cohort of bus garage maintenance workers, the follow-up averaged about 6 years, but no data on duration of employment were available. The Coggon *et al*[29] case-control study of lung cancer restricted cases to men under 40 years of age and did not provide any data on duration of employment. The case-control studies of Lerchen *et al*,[30] Siemiatycki *et al*,[31] and Williams *et al*[32] also did not provide sufficient data to make a good estimate of latency, but in each of these studies, subjects were ascertained well after the transitions to diesel fuels were completed.

We excluded the studies of Waller[33] and Luepker and Smith[34] because of the selection bias that would likely result from restricting the cohort to actively employed workers. We included the study of Williams *et al*[32] although it had only a 57% response rate to questionnaires.[1] The authors note that the response rate among cancer subjects with the more aggressive sites including lung, pancreas, and esophagus was slightly lower than the rate among subjects with the less aggressive cancers; still, as all other cancers were used as the controls for the lung cancer cases, we considered a large selection bias to be unlikely.

The 23 studies that we included in the pooled analysis are presented in Table 1, and those that we excluded are presented in Table 2. The tables include information on occupation, whether statistical adjustment for smoking was done, effect measures, and confidence intervals. Missing confidence intervals have been calculated for several studies.[24,25,27,28,32–38]

In some cases, we found it necessary to pool data reported within an individual study. Siemiatycki *et al*[31] presented odds ratios for four histologic categories of lung cancer separately; we combined these estimates into a single odds ratio using the weighting by precision technique described in the Methods. For

TABLE 2. Studies Excluded From Pooled Analysis

Authors and Year	Type*	Smoking Adjusted	Occupation	Cases	RR	95% CI	Comments
Benhamou *et al*,[22] 1988	CC	Yes	Professional driver	128	1.42	1.07–1.89	Uncertain exposure
Buiatti *et al*,[23] 1985	CC	Yes	Transportation	45	1.1	0.7–1.6	Uncertain exposure
Kaplan,[24] 1959	RC	No	Railroad worker	49	0.88	0.65–1.16†	Inadequate latency
Leupker & Smith,[34] 1978	RC	No	Truck driver	34	1.21	0.84–1.69†	Excluded retirees
Milne *et al*,[25] 1983	CC	No	Truck driver	36	1.6	0.97–2.62†	Inadequate latency
Waller,[33] 1981	RC	No	Bus company worker	677	0.79	0.73–0.85†	Excluded retirees

* RC = retrospective cohort study; PC = prospective cohort study; CC = case-control study.
† Confidence intervals are calculated from the published data as described in Methods.

Swanson *et al*,[11] we pooled the race-stratified odds ratios for white men and black men. For Steenland *et al*,[39] we combined the odds ratios for the strata 25–34 and ≥35 years employment, and for the nested case-control study of Gustavsson *et al*,[40] we combined the strata for cumulative exposure indices of 20–30 and >30.

The case-control study of Garshick *et al*[41] stratified the analysis by age, as they demonstrated a lower prevalence of diesel exposure in employees older than 64 years. The data shown in Table 1 and used in the pooled analysis are for workers less than 64 years old.

The studies done by Williams *et al*,[32] Boffetta *et al*,[42] and Swanson *et al*[11] included data for more than one occupational group; we used the effect measures for each group in the pooled analysis. Although the case-control study of Boffetta *et al*[12] presented a separate analysis for truck drivers, no separate result for any other occupational group was presented. In the analysis, we use the data for all "probably exposed" occupations.

We observed relative risks of less than one in only two of the 23 studies meeting our inclusion criteria. These studies by Edling *et al*[36] and Lerchen *et al*[30] were also the two smallest studies, each with less than 10 lung cancer cases. No study that included more than 10 lung cancer cases had relative risks of less than one.

We conducted pooled analyses for the following subgroups of studies: (1) all included studies; (2) case-control studies; (3) cohort studies; (4) cohort studies using internal reference populations; (5) cohort studies making external comparisons; (6) studies adjusted for smoking; (7) studies not adjusted for smoking; and (8) studies by occupational groups.

The results of the pooled analyses are presented in Table 3 and in Figure 1. Statistical tests for heterogeneity and adjusted and unadjusted confidence intervals are also presented in Table 3. The pooled relative risk estimate for lung cancer from exposure to diesel exhaust using all studies was 1.33 (95% CI = 1.24–1.44). Subanalyses of studies stratified on study methods showed similar results. Stratification of studies by exposure setting revealed greater effects among railroad workers (RR = 1.44; 95% CI = 1.30–1.60) and truck drivers (RR = 1.49; 95% CI = 1.36–1.65) than equipment operators (RR = 1.11; 95% CI = 0.89–1.38) and bus workers (RR = 1.24; 95% CI = 0.93–1.64).

Statistical evidence for heterogeneity was present among all studies combined, case-control studies, cohort studies, studies adjusted and not adjusted for smoking, and studies of bus employees (Table 3). Cohort studies and studies not adjusted for smoking showed relatively more heterogeneity than did the case-control and smoking-adjusted studies. When we subdivided cohort studies by comparison population, studies using external comparisons accounted for a larger proportion of the heterogeneity than those using internal comparisons. There was little statistical evidence of heterogeneity for the studies of railroad workers, equipment operators, and truck drivers.

Seven studies included in our analysis presented standard mortality rate based on external comparison populations.[17,27,28,36–38,43] Four of the seven studies presented sufficient information to adjust the lung cancer mortality for the healthy worker effect, as described in the Methods. The calculations and results for the four studies with available data are presented in Table 4. For the four adjusted studies, the pooled RR before adjustment was 1.09 (95% CI = 0.98–1.22; heterogeneity $\chi^2 = 4.42$, $df = 3$, $P = 0.22$) and after adjustment was 1.33 (95% CI = 1.19–1.48; heterogeneity $\chi^2 = 2.66$, $df = 3$, $P = 0.45$).

Nine studies included in the pooled analysis presented data for years of exposure or for years of employment.

TABLE 3. Summary of Pooled Relative Risks

Group	Number	RR	95% CI	χ^2 Heterogeneity	Adjusted 95% CI*
All studies	29	1.33	1.27–1.40	58.0	1.24–1.44
Case-control studies	14	1.33	1.21–1.47	20.5	1.18–1.51
Cohort studies	15	1.33	1.26–1.42	37.5	1.21–1.47
Internal comparison group	8	1.43	1.32–1.55	11.0	1.29–1.58
External comparison group	7	1.22	1.12–1.34	20.0	1.04–1.44
Smoking adjusted	16	1.35	1.22–1.49	23.4	1.20–1.52
Smoking not adjusted	13	1.33	1.25–1.41	34.5	1.20–1.47
Subanalysis by occupation	24	1.37	1.30–1.46	48.4	1.27–1.49
Railroad workers	6	1.44	1.30–1.59	5.6	1.30–1.60
Equipment operators	3	1.11	0.95–1.29	4.3	0.89–1.38
Truck drivers	10	1.49	1.36–1.64	9.8	1.36–1.65
Bus workers	5	1.24	1.07–1.43	14.8	0.93–1.64

* Heterogeneity-adjusted confidence intervals using method described by Shore *et al*.[6]

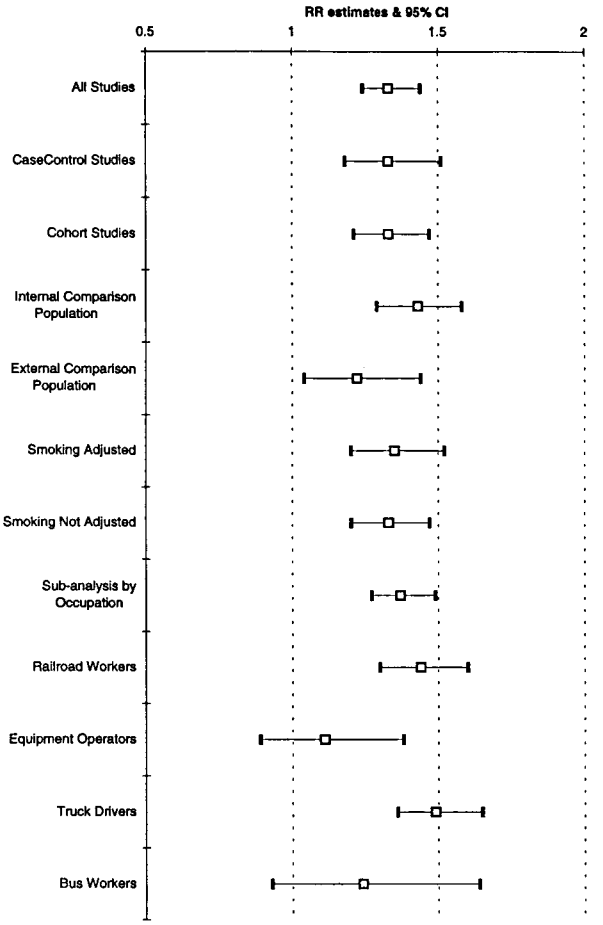

FIGURE 1. Pooled relative risk estimates and heterogeneity-adjusted 95% confidence intervals for all studies and subgroups of studies included in the meta-analysis.

The employment duration-stratified data from seven of these studies that used internal reference groups are presented in Table 5. Except in the subanalysis of equipment operators by Hayes *et al*,[18] the relative risk estimates consistently increase with duration of exposure.

TABLE 4. Adjustment of Studies with External Reference Populations for the Healthy Worker Effect

Study	Cause of Death	Observed	Expected	SMR
Edling *et al*,[36] 1987	All causes	195	237.0	0.82
	All causes excluding lung cancer	189	228.0	0.83
	Lung cancer	6	9.0	0.67
	Lung cancer (adjusted)	6	7.5	0.80
Gustafsson *et al*,[17] 1986	All causes	1,062	1,190.5	0.89
	All causes excluding lung cancer	991	1,135.4	0.87
	Lung cancer	71	55.1	1.29
	Lung cancer (adjusted)	71	48.1	1.48
Rushton *et al*,[28] 1983	All causes	705	836.6	0.84
	All causes excluding lung cancer	603	735.3	0.82
	Lung cancer	102	101.3	1.01
	Lung cancer (adjusted)	102	83.1	1.23
Wong *et al*,[37] 1985*	All causes	1,526	1,855.7	0.82
	All causes excluding lung cancer	1,363	1,703.8	0.80
	Lung cancer	163	151.9	1.07
	Lung cancer (adjusted)	163	121.5	1.34

* Adjustments using data from >20 years employment duration.

In 10 of the studies included in our pooled analysis, statistical adjustment for confounding from smoking was done. Three of these studies used continuous measures of smoking in the analysis,[11,12,41] and five reduced the data to categories of cigarette consumption.[14,18,30,39,42] The form of the smoking covariate was not presented in the study of Siemiatycki *et al*[31] or the study of Williams *et al*.[32] In Table 6, we present the forms of the smoking data used for statistical adjustment in 5 of the 10 studies that presented both smoking-adjusted and -unadjusted risk estimates for diesel exhaust. (Smoking-adjusted RRs presented in Table 6 are not necessarily the same as those presented in Table 1, as the unadjusted RRs presented in the papers did not always correspond to the exposure categories selected for the pooled analysis.)

Discussion

This analysis shows a small but consistent increase in the risk for lung cancer among workers with exposure to diesel exhaust. Of the 23 publications included in our analysis, only two present relative risks of less than one, and both of these were very small studies. Such a finding is extremely unlikely to be due to chance.

The pooled relative risk estimates center around 1.33 (95% CI = 1.24–1.44). Given the low relative risks observed in these studies, bias from known causes of lung cancer, such as smoking, is an important concern. In the pooled analyses, we found that the studies that adjusted for smoking had a similar pooled relative risk estimate (RR = 1.35) as the studies that did not control for smoking (RR = 1.33) (Table 3.) This result gives some assurance that smoking does not explain the observed increased risks for diesel exhaust. A preferred method to assess confounding from a covariate is to compare crude and adjusted risk estimates within studies.[44] As shown in Table 6, in four of five studies in which data on adjusted and unadjusted risk were presented, adjustment for smoking resulted in a decrease in the observed relative risk. In these five studies, the pooled smoking-unadjusted RR for all occupation and exposure duration categories was 1.34 (95% CI = 1.24–1.44; heterogeneity $\chi^2 = 1.39$, $df = 4$, $P = 0.84$), and the smoking-adjusted pooled RR was 1.26 (95% CI = 1.12–1.41; heterogeneity $\chi^2 = 10.87$, $df = 4$, $P = 0.03$). This small reduction in the pooled RR estimates would not be consistent with a major effect from residual confounding.

The study by Garshick *et al*[41] found little difference in the lung cancer risk estimate due to diesel exhaust exposure in models treating smoking as pack-years as a continuous and categorical variable, cigarettes per day, years of smoking, or pack-years categories considering years since quitting smoking, showing that the classification scheme for smoking did not

TABLE 5. Observed Risks by Employment Duration in Studies Using Internal Comparisons

Reference	Type	Smoking Adjusted	Occupation	Subgroup (Years)	RR	95% CI
Boffetta *et al*,[12] 1990	CC	Yes	Diesel-exposed	1–15	0.52	0.15–1.86
				16–29	0.7	0.34–1.44
				≥30	1.49	0.72–3.11
Damber & Larsson,[14] 1987	CC	Yes	Driver	1–19	1	0.7–1.5
				≥20	1.2	0.6–2.2
Garshick *et al*,[41] 1987	CC	Yes	Railroad worker	5–19	1.02	0.72–1.4
				≥20	1.64	1.18–2.2
Garshick *et al*,[13] 1988	RC	No	Railroad worker	1–4	1.2	1.01–1.44
				5–9	1.24	1.06–1.44
				10–14	1.32	1.13–1.56
				≥15	1.72	1.27–2.33
Hayes *et al*,[18] 1989	CC	Yes	Equipment operator	<10	1.5	0.4–4.3
				≥10	1.3	0.6–3.1
			Truck driver	<10	1	0.8–1.3
				≥10	1.5	1.1–1.9
			Bus driver	<10	1.1	0.6–2.1
				≥10	1.6	0.9–2.8
Steenland *et al*,[39] 1990	CC	Yes	Diesel truck driver	1–24	1.27	0.7–2.27
				25–34	1.26	0.74–2.16
				≥35	1.89	1.04–3.42
Swanson *et al*,[11] 1993	CC	Yes	Railroad worker	1–9	1.57	0.8–3.11
				≥10	2.46	1.24–4.87
			Heavy truck driver	1–9	1.56	0.95–2.58
				10–19	1.67	0.87–3.18
				≥20	2.44	1.43–4.16

change estimates of main effects. In this study, the lung cancer relative risk was 1.39 before and 1.41 after adjusting for smoking using a pack-year measure (Table 6). Other studies did not include such detailed consideration of smoking.

For the eight cohort studies that had internal comparison populations, the pooled RR was 1.43 (95% CI = 1.29–1.58; heterogeneity $\chi^2 = 11.0$, $df = 7$, $P = 0.14$). Although the use of an internal comparison group does not eliminate the potential for confounding bias from smoking, smoking prevalence is more likely to be similar among individuals within an industry or occupation.

TABLE 6. Treatment of Smoking Data for Studies Included in Pooled Analysis and Smoking-Adjusted and -Unadjusted RR Where Available

Study	Treatment of Smoking Data in Main Analysis	Crude RR (95% CI)	Adjusted RR (95% CI)
Boffetta *et al*,[42] 1988	Categorical Never-smoker Current 1–20 cigarettes/day Current ≥21 cigarettes/day Ex-smoker Pipe or cigar smoker	1.41 (1.19–1.66)	1.31 (1.10–1.54)
Boffetta *et al*,[12] 1990	Continuous: cigarettes/day	1.31 (1.09–1.57)	0.95 (0.78–1.16)
Damber & Larsson,[14] 1987	Dichotomous: smoker *vs* nonsmoker	1.5 (0.9–2.6)	1.2 (0.6–2.2)
Garshick *et al*,[41] 1987	Continuous: pack-years	1.39 (1.05–1.83)	1.41 (1.06–1.88)
Lerchen *et al*,[30] 1987	Categorical Never-smoker Ex-smoker Current smoker	1.0 (0.34–2.90)*	0.6 (0.2–2.0)

* Confidence intervals are calculated from the published data as described in Methods.

Thus, we note three reasons why it is unlikely that the increased risks observed in these studies are due to smoking: (1) The pooled RR for studies adjusted for smoking was the same as for those studies not adjusted for smoking. (2) In those studies giving both smoking-unadjusted and -adjusted risk estimates, there was only a small reduction in the pooled RR from diesel exhaust exposure. (3) In studies with internal comparison populations, in which confounding is less likely, the pooled RR estimate was 1.43.

Lack of exposure data is another limitation of this meta-analysis. Only three of the studies included in the pooled analysis examined quantified exposure measures,[13,39,41] and none of these had access to historical exposure measures. The studies of Coggon *et al*[29] and Gustavsson *et al*[40] made use of job-exposure matrices to evaluate exposure. In the remainder of studies considered in this report, occupation or industry of work is used as a surrogate measure of exposure to diesel exhaust. In cohort studies using general population comparison groups and in population-based case-control studies, a classification scheme based on occupation alone is likely to include those not exposed to diesel exhaust along with those exposed and thus may dilute the observed effect. In all of the studies, nondifferential exposure misclassification due to crude exposure definitions would also likely dilute any observed effects. Thus, although measures of exposure in these studies are limited, bias from exposure misclassification is unlikely to create an observed effect artificially.

A healthy worker effect for cancer has been observed in a number of studies.[45,46] In re-analysis of lung cancer risk in an occupational cohort exposed to arsenic, Arrighi and Hertz-Picciotto[45] showed that diverse methods for the control of the healthy worker effect enhanced the observed effect of exposure. Although the data available within the published reports included in this meta-analysis only allowed us to use a simple method to account for the health worker effect, we felt it important to demonstrate the potential magnitude and direction of this bias in our analysis.

For instance, the pooled analysis was heavily weighted by the study of Wong *et al*,[37] in which the low all-cause SMR of 0.81 indicated the presence of a healthy worker effect. Although the lung cancer SMR for the longest duration of union membership was only 1.07, a trend was evident for

increasing lung cancer risk both by duration of union membership and by latency period. As shown in Table 4, in the Wong *et al* study, adjustment of the lung cancer SMR for >20 years of employment (SMR = 1.07) by the SMR for all causes (SMR = 0.82) produces an adjusted lung cancer SMR of 1.34 that is consistent with the pooled estimate using all studies. Thus, the healthy worker effect is a potential source of bias that would tend to underestimate the risks of diesel exhaust exposure in cohort studies with external comparison populations.

We did not find large differences in the pooled relative risk estimates after stratification of the studies on their design, on occupations studied, or on control for a smoking covariate. Heterogeneity was present, however, between studies in many of the pooled analyses. Studies stratified by industry or occupation tended to have less evidence for heterogeneity than either all studies or those stratified by study design. Differences in exposure to diesel exhaust are likely to explain some of the differences in results among studies. Studies of truck drivers and railroad workers were relatively homogeneous, but studies among bus company workers found dissimilar effects. The studies of bus company workers included several occupational categories, including mechanics, drivers, and other service workers.

Fixed effects methods as used in this analysis weight the studies on the within-study variance, which is primarily determined by study size. We did not attempt to account for the heterogeneity among studies with a random effects model, as described by DerSimonian and Laird.[47] Such methods have been used to account for interstudy variation in the pooling of summary statistics and generally produce wider confidence intervals than the fixed effects model used in this analysis. Random effects models postulate that interstudy variation can be estimated by a single value and have been criticized for the assumption that studies are representative of a hypothetical population of studies. We felt that major sources of heterogeneity could be predicted from the study methods and populations. Thus, the underlying assumption that interstudy variance was constant was unlikely to be met. Furthermore, since the component of interstudy variation is assumed constant for all studies, smaller studies would be given a relatively larger weight than they would receive by fixed effects methods. Given these issues, we chose to use a model in which studies were weighted primarily on precision.

Publication bias is another potential limitation to meta-analysis.[48] The tendency to not publish negative or null results is of particular concern and is thought to be more likely for small studies. Several small studies were included in our analysis. In the review by Steenland,[49] we identified several studies of lung cancer among truck drivers that were presented as agency reports or documents. These unpublished studies were not included in our analysis; however, the risk ratios of these studies are similar to the those in published studies among truck drivers.

Funnel plots can be used to estimate whether a publication bias exists.[48] The risk estimates are plotted against a measure of the study precision, such as the logarithm of the standard error. The scattering of the point estimates should decrease as the precision of the studies increases. A publication bias is suggested when larger studies having greater precision observe no effect. In Figure 2, we present a funnel plot of all studies included in the analysis. As study precision increases, the point estimates appear to congregate just below 1.5. Overall, the funnel plot supports our overall finding of an average relative risk estimate around 1.3 and does not indicate publication bias.

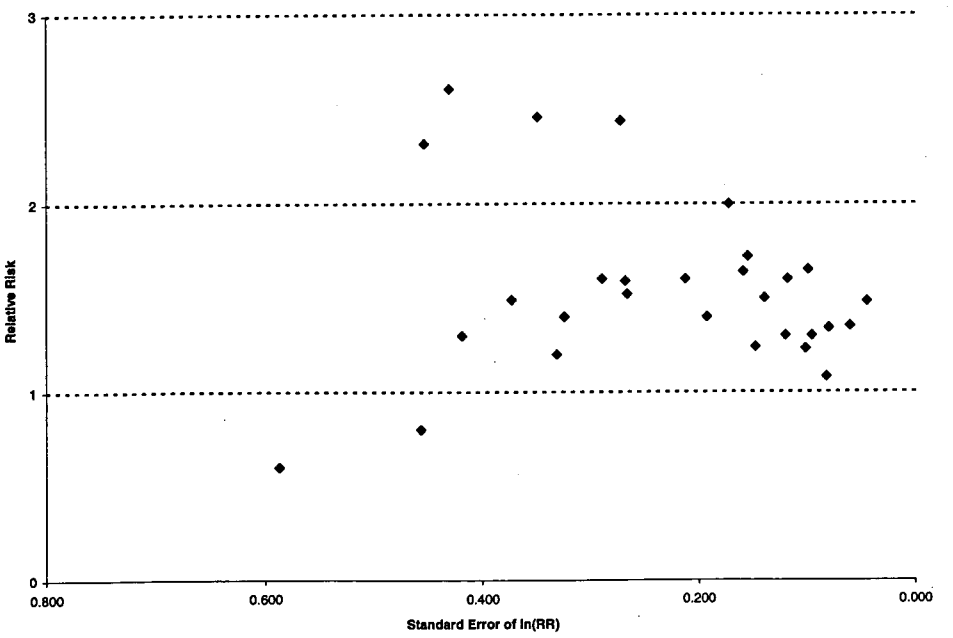

FIGURE 2. Plot of observed relative risks of studies included in the meta-analysis against the standard error of the natural logarithm of the relative risk. Studies with available data are adjusted for the healthy worker effect.

The possible causal association between exposure to diesel exhaust and lung cancer is an important public health question. Animal evidence has indicated that inhaled diesel exhaust may produce tumors of the lung in rats.[1] The interpretation of occupational epidemiology in this field has been limited by the lack of quantitative exposure data in many of the studies and the potential for confounding from smoking given the relatively low risk estimates. This quantitative analysis of pub-

lished occupational studies indicates that although the risk estimates for diesel exhaust exposure are small, they are consistently above one and are, in aggregate, unlikely to be due to chance. Confounding from smoking is also unlikely to explain all of the increased risks among diesel exhaust-exposed workers. The heterogeneity in observed relative risk estimates may be explained by differences between studies in methods, in populations studied and comparison groups used, in latency intervals, in intensity and duration of exposure, and in the chemical and physical characteristics of diesel exhaust.

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