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Published on: 01 Aug 2020 - American Journal of Respiratory and Critical Care Medicine (American Thoracic Society)

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Diesel Engine Exhaust Exposure, Smoking, and Lung Cancer Subtype Risks: A Pooled Exposure-response Analysis of 14 Case-control Studies

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Author contribution: Authors #1-6 & 42-44 contributed significantly in data analysis, results interpretation, and original drafting of the work. Authors #42-44 additionally contributed to the original conception of the project and secured project funding. Authors 7-44 participated in data acquisition and data analysis design of the project. All authors participated in critical revision of the manuscript and provided approval of the finalized submitted version.

Funding: This work was funded by the German Social Accident Insurance (DGUV).

Running head: Workplace diesel exhaust exposure and lung cancer

Subject category: 6.12 Lung Cancer Epidemiology: Occupational and Environmental Factors

Body word count: 3680

Supplement statement: This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

ABSTRACT:

Rationale and objectives: We expanded upon a previous pooled case-control analysis on diesel engine exhaust and lung cancer by including 3 additional studies and quantitative exposure assessment to evaluate lung cancer and subtype risks associated with occupational exposure to diesel exhaust, characterized by elemental carbon (EC) concentrations.

Methods: We used a quantitative EC job-exposure matrix for exposure assessment. Unconditional logistic regression models were used to calculate lung cancer odds ratios (ORs) and 95% confidence intervals (CI) associated with various metrics of EC exposure. Lung cancer excess lifetime risks (ELR) were calculated using life-tables accounting for all-cause mortality. Additional stratified analyses by smoking history and lung cancer subtypes were performed in men.

Results: Our study included 16,901 cases and 20,965 controls. In men, exposure-response between EC and lung cancer was observed: ORs ranged from 1.09 (95% CI 1.00, 1.18) to 1.41 (95% CI 1.30, 1.52) for the lowest and highest cumulative exposure groups, respectively. EC-exposed men had elevated risks in all lung cancer subtypes investigated; associations were strongest for squamous and small cell carcinomas and weaker for adenocarcinoma. EC-lung cancer exposure-response was observed in men regardless of smoking history, including among never smokers. ELR associated with 45 years of EC exposure at 50, 20, and 1 $\mu\text{g}/\text{m}^3$ were 3.0%, 0.99%, and, 0.04%, respectively, for both sexes combined.

Conclusion: We observed a consistent exposure-response relationship between EC exposure and lung cancer in men. Reduction of workplace EC levels to background environmental levels will further reduce lung cancer ELR in exposed workers.

(Abstract word count 248)

Key words: Occupational exposure, diesel exhaust, lung neoplasms, epidemiology

INTRODUCTION

The International Agency for Research on Cancer (IARC) classifies diesel engine exhaust (hereafter: diesel exhaust) as a Group 1 human carcinogen ¹. Previous studies have provided consistent epidemiological evidence that lung cancer is associated with occupational exposure to diesel exhaust ²⁻⁵. Positive exposure-response relationships of diesel exhaust exposure and lung cancer were also reported by studies with quantitative exposure assessment for elemental carbon (EC), which is a measure of diesel exhaust exposure ⁴⁻⁷.

However, few studies have explored the risk of lung cancer associated with low exposure levels and none have observed a positive association at lifetime cumulative EC exposure levels below 50 $\mu\text{g}/\text{m}^3$ -years. Questions also remain regarding the role of cigarette smoking as a potential confounder or effect modifier in the relationship between EC exposure and lung cancer. For instance, although a handful of studies have shown suggestive elevated lung cancer risks in diesel exhaust-exposed workers who were never smokers ^{2,8,9}, only one study reported a significant effect ⁴. The same study also reported attenuated lung cancer risk in subjects who were heavy smokers and highly exposed to diesel exhaust (i.e. a negative interaction). Finally, results reported by studies on risks of major lung cancer subtypes associated with diesel exhaust exposure have been inconsistent. Some studies reported the strongest association in large cell carcinoma compared to other major lung cancer subtypes ^{2,9}, whereas others observed higher risks in squamous cell carcinoma ^{8,10}.

Previously we published a study with pooled subjects from 11 lung cancer case-control studies from Europe and Canada³. In the current study we increased the study population by including three additional studies (3,663 cases; 4,805 controls).

Occupational exposure assessment was also enhanced with the use of a new job-exposure matrix (JEM), where EC exposure was estimated quantitatively based on subject occupations. The purposes of our work were to evaluate: 1) the lung cancer risks associated with various indices of occupational diesel exhaust exposure by sex; 2) the associations between diesel exhaust exposure and lung cancer by smoking status and cancer subtype in men; 3) the joint effects of diesel exhaust exposure and smoking on the risk of lung cancer and its major subtypes on the additive and multiplicative scale in men; and 4) the excess lifetime lung cancer risks associated with various levels of occupational diesel exhaust exposure in both sexes combined.

METHODS

Study population

Subjects from 14 hospital- and population-based lung cancer case-control studies in 13 European countries and Canada were pooled. Detailed description of the original study population is available elsewhere³. The current study updated the population with 3,663 cases and 4,805 controls from the TORONTO, CAPUA, and ICARE studies in Canada, Spain, and France respectively (Table E1 in online supplement). The project received ethical approvals from all participating countries and the IARC institutional review board. More information about the SYNERGY project is available online: <http://synergy.iarc.fr>.

Job-exposure matrix and exposure assessment

A quantitative diesel engine exhaust job-exposure matrix (DEE-JEM) was developed by CG and RV. The DEE-JEM consists of EC exposure (in $\mu\text{g}/\text{m}^3$) assigned to all 1,506 five-digit International Standard Classification of Occupations (version 1968, or ISCO-68)¹¹ and was constructed based on 4,417 occupational EC measurements (data sources available in Supplementary Methods and Table E6 in online supplement). For occupations represented in the EC exposure measurements, the mean exposure concentrations were directly assigned. For occupations without measurement data, exposure concentrations from similar occupations with measurement data were assigned using expert decisions. An exposure probability factor was also assigned by expert decision to each exposed job (details on probability factors available in Supplementary Methods in online supplement). The DEE-JEM was linked to study participant job histories by ISCO-68 occupations. Probability-weighted cumulative EC exposure (hereafter: cumulative EC, expressed in $\mu\text{g}/\text{m}^3\text{-years}$) was calculated as the sum of the product of exposure levels, probabilities, and duration (in years) across all reported job periods for each subject. The DEE-JEM is available upon request from the corresponding author.

Main Statistical analysis

Separately for men and women, unconditional logistic regression models were used to calculate the odds ratios (ORs) and 95% confidence intervals (CI) of lung cancer associated with various categorical EC exposure metrics, including ever/never exposure, duration of exposure (<10; 10–19; 20–29; >29 years), and cumulative exposure (quartiles of exposure distribution among controls: >0–22; 23–70; 71–178; >178 $\mu\text{g}/\text{m}^3\text{-years}$).

Trends were assessed using p-values from the respective indices of EC exposure as continuous variables for all subjects and for exposed subjects only. Adjustments for the main analyses were determined *a priori* within the SYNERGY consortium and identical with our previous occupational exposure publications^{3,12}; these adjustments included study, age group (<45; 45–49; 50–54; 55–59; 60–64; 65–69; 70–74; >74 years), smoking ($\log(\text{cigarette pack-years}+1)$), smoking cessation prior to interview/diagnosis (current smokers; >0-7; 8-15; 16-25; >25 years; never smokers), and having been ever employed in occupations with known lung cancer risks (List A jobs ever/never; full list in Table E7 in online supplement). First published in 1982, List A jobs include occupations with definite lung cancer risks according to the IARC Monographs; the list was updated in 1995 and 2000 to cover all IARC-reviewed agents up to volume 75 of the Monographs^{13,14}. Smokers were defined as smoking more than one cigarette per day for more than one year. Smoking pack-year was calculated by summing the products of average daily smoking amount in 20-cigarettes packs and smoking duration in years. Association between lung cancer and cumulative EC exposure as a continuous metric was assessed with a logistic linear regression model for men, women, and all subjects with identical adjustments as the categorical models.

Models with various cumulative EC exposure lag times (i.e. omitting exposure in the last 5, 10, 15, or 20 years, or no omission at all) were constructed. Model fit was the best, according to minimized Akaike information criterion value, when lag time was 10 years – therefore only results from models with a 10-year lag are presented.

Using the lung cancer risk from our linear continuous exposure model with all subjects, we calculated lung cancer excess lifetime risks (ELR) at age 80 associated with 45 years of occupational EC exposure at 50, 20, and 1 $\mu\text{g}/\text{m}^3$ using life-table methods accounting for all-cause mortality outlined by Vermeulen and colleagues ⁷. The selected exposure levels at 50, 20, and 1 $\mu\text{g}/\text{m}^3$ represented recommended limit values from: 1) the German Committee for Hazardous Substances (AGS) in 2017 based on a study on lung irritation after controlled human exposure ¹⁵; 2) the US National Institute of Occupational Safety and Health (NIOSH) in 2003 that was later withdrawn ¹⁶; and 3) the Health Council of the Netherlands in 2019 based on exposure-response estimates from Vermeulen and colleagues ^{7,17}, respectively. 2008 European data on mortality from all causes and lung cancer were used in our calculations ¹⁸.

Extended analysis for male subjects

To further investigate the exposure-response relationship between EC exposure and lung cancer in men, stratified analyses were performed to calculate lung cancer ORs associated with cumulative EC exposure categories with different major lung cancer subtypes and smoking histories. In addition, non-parametric thin-plate regression splines were created, as implemented in the R package *mgcv*, to visualize the shape of the exposure-response relationships between EC exposure and lung cancer subtypes in men. The number of basis functions was limited to three ($k=3$) and the smoothing parameter was estimated using the relative maximum likelihood method. Spline model results were truncated at the 99th percentile of EC exposure to emphasize on results with greater data support.

Additive interactions of cigarette smoking and EC exposure on lung cancer and subtype risks in men were assessed by calculating the excess risks due to interaction (RERI) using ORs from our logistic models as defined by Rothman and Greenland¹⁹ and as implemented in the *epi.interaction* package in R. RERI values measure departure from additivity with 0 representing no interaction on the additive scale²⁰. Interactions in men on the multiplicative scale were assessed using p-values obtained from the cross products of smoking and EC exposure in the adjusted logistic models.

Statistical analyses were conducted using SAS (version 9.3, SAS Institute, Cary, NC) and R (version 3.6).

RESULTS

37,866 subjects (16,901 cases; 20,965 controls) were included in our final analyses (Table 1). Among the lung cancer cases there were 4,752 adenocarcinomas, 810 large cell carcinomas, 2,730 small cell carcinomas, 6,503 squamous cell carcinomas, 2,012 other lung cancers, and 94 cases without subtype information.

In men, we observed elevated ORs for subjects with ever occupational exposure to EC (OR 1.22; 95% CI 1.15, 1.29; Table 2). Increasing trends in lung cancer risks in men were associated with increases in both exposure duration and cumulative exposure (p-trends<0.01). Elevated male lung cancer ORs were also observed in the lowest categories of exposure duration (1-9 years; OR 1.07; 95% CI 1.00, 1.16) and cumulative exposure (>0–22 $\mu\text{g}/\text{m}^3\text{-years}$; OR 1.09; 95% CI 1.00, 1.19). In our female population, we observed no associations between lung cancer and different EC exposure metrics.

Our continuous EC exposure models show that one $\mu\text{g}/\text{m}^3$ -year increase in cumulative exposure was associated with an increase in lung cancer OR by a factor of 1.00001 (95% CI 0.9987, 1.00131) for women. The corresponding results for men and for all subjects were identical: lung cancer OR increased by a factor of 1.00034 (95% CI 1.00021, 1.00048) per $\mu\text{g}/\text{m}^3$ -year increase in cumulative EC exposure. Lung cancer ELR associated with lifetime occupational EC exposure at 50, 20, and 1 $\mu\text{g}/\text{m}^3$ were 3.0%, 0.99%, and, 0.04%, respectively, for both sexes combined.

By lung cancer subtype, increasing cumulative EC exposure was associated with increasing ORs of squamous cell (p-trend<0.01) and small cell carcinomas (p-trend 0.02) in men (Table 3). For squamous cell carcinoma, all categories of cumulative EC exposure were associated with elevated ORs in males, including the lowest (OR 1.13; 95% CI 1.01, 1.26). The highest risks for both adenocarcinoma (OR 1.23; 95% CI 1.09, 1.39) and large cell carcinoma (OR 1.31; 95% CI 1.02, 1.67) were also observed in men in the highest exposed group.

Results from the non-parametric spline analyses for male subjects show monotonic increases in cancer risks for overall lung cancer and all four included subtypes (Figure 1). Among the lung cancer subtypes, squamous cell and small cell carcinomas show the strongest association with cumulative EC exposure, followed by large cell carcinoma and adenocarcinoma.

In our analyses stratified by smoking status, exposure-response associations between cumulative EC exposure and lung cancer were observed in men regardless of smoking history (Table 4). Lung cancer risks were similar for men in the highest EC

exposure group who were never smokers (OR 1.41; 95% CI 1.04, 1.88), former smokers (OR 1.47; 95% CI 1.31, 1.65), and current smokers (OR 1.40; 95% CI 1.24, 1.57).

Super-additive joint effects of smoking and EC exposure were observed in men for overall lung cancer and all four cancer subtypes (Table 5). Suggestive super-multiplicative joint effects of smoking and EC exposure were observed for large cell carcinoma in men ($p=0.05$).

DISCUSSION

In a large pooled case-control population, we observed in men positive associations between lung cancer and different occupational EC exposure metrics, including ever EC exposure, exposure duration, and cumulative exposure. Increasing exposure duration and cumulative exposure were associated with increases in lung cancer risks in men, exhibiting monotonic exposure-response relationships. Our results are in accordance, and further expand upon, results from our earlier analysis within the SYNERGY study with 11 studies and semi-quantitative exposure assessment, where we reported a consistent exposure-response relationship between lung cancer and EC exposure³. Additional evidence of the exposure-response relationship between diesel exhaust exposure and lung cancer is provided by studies on workers in highly exposed industries such as mining^{4,21-23} and trucking^{5,6}.

In a meta-regression analysis of the exposure-response relationship of lung cancer and diesel exhaust exposure based on data from three occupational cohort studies, Vermeulen and colleagues estimated that each $\mu\text{g}/\text{m}^3$ -year increase in cumulative EC

exposure results in a lung cancer relative risk (RR) of 1.00098⁷. A subsequent sensitivity analysis reported a range of lung cancer RR of 1.0006 to 1.0012 per $\mu\text{g}/\text{m}^3$ -year increase in cumulative EC exposure from several alternative models²⁴. These exposure-response slope estimates are approximately 2-3 times higher than our present linear model estimate of 1.00034 for all subjects. This difference may be due to factors such as occupational cohorts having higher cumulative EC exposures and more accurate exposure assessment in specific industries. Despite the differences on the exact risk magnitude, a consistent exposure-response trend between occupational diesel exhaust exposure and lung cancer was reported by studies with different designs among different populations.

We did not observe an exposure threshold for diesel exhaust-related lung cancer in males within the cumulative EC exposure ranges we investigated; increased lung cancer risk in men was observed in the lowest cumulative EC exposure group with a median exposure of 11 $\mu\text{g}/\text{m}^3$ -years. An additional sensitivity analysis with 10 cumulative exposure groups suggested (naturally, with less precision) an increased risk among the lowest exposure group with a median EC exposure of 3.3 $\mu\text{g}/\text{m}^3$ -years (Table E2 in online supplement). Few other studies investigated lung cancer risks in similar cumulative EC exposure ranges quantitatively. In occupational cohorts with higher EC exposures, one study reported a lung cancer OR of 1.31 (95% CI 1.01, 1.71) in US trucking workers with a cumulative exposure of approximately 51 $\mu\text{g}/\text{m}^3$ -years⁶, while another reported a lung cancer OR of 0.74 (95% CI 0.40, 1.38) for US miners with a cumulative EC exposure around 37 $\mu\text{g}/\text{m}^3$ -years⁴.

We found that diesel exhaust exposure was associated with all four major lung cancer subtypes in men, although differential risks were observed by subtype. Both our logistic regression and spline models showed that the associations were the strongest for squamous cell and small cell carcinomas, moderate for large cell carcinoma, and weakest for adenocarcinoma. Similar findings supportive of a stronger link between diesel exhaust exposure and lung squamous cell carcinoma were reported in populations in Canada⁸⁻¹⁰, Finland²⁵ and Sweden^{2,26}. This is the first report of a positive exposure-response relationship for diesel exhaust exposure and lung small cell carcinoma in men. Guo and colleagues observed a small cell carcinoma OR of 2.31 (95% CI 1.02, 5.25) for female Finnish workers in the low diesel exhaust exposure category, based on six exposed cases²⁵. Elevated point estimates of small cell carcinoma risks were also observed in population-based studies from different countries^{2,10,25}. For adenocarcinoma, in accordance with our current observations, previous studies were consistent in reporting ORs that were lower than overall lung cancer risks^{2,8-10,25,26}. Information on risk of large cell carcinoma related to diesel exhaust exposure is limited; only two previous studies included large cell carcinoma in subtype analyses^{2,9}. These studies reported exposure-response relationships for duration, intensity, and lifetime cumulative exposure to diesel exhaust and large cell carcinoma. In our male population we observed a clear increased large cell carcinoma risk only in the group with the highest cumulative EC exposure (>178 $\mu\text{g}/\text{m}^3\text{-years}$), with a suggestive elevated OR estimate for the second highest exposed group.

We observed a lung cancer exposure-response risk trend in never smoking males who were exposed to EC. Similarly, Silverman and colleagues reported a significant lung cancer OR of 7.30 (95% CI 1.46, 36.57) among highly exposed US miners who never

smoked⁴. The very high risk observed in the US miners may be attributable to higher cumulative EC exposure in mining occupations or the fact that the estimate was based on only seven exposed cases.

The observed super-additive joint effects between EC exposure and smoking for overall lung cancer and its subtypes in men indicated that the absolute risk of cancer for men exposed to both EC and smoking was higher than the sum of the absolute risks of cancer from EC exposure and smoking alone²⁷. Only one other study in Swedish dock workers investigated EC and smoking interaction on the additive scale and similarly reported a super-additive effect²⁸. Interaction in other studies were assessed on the multiplicative scale, where super-multiplicative interaction represents a scenario where the risk ratios (e.g. OR) of cancer for those exposed to both EC and smoking was higher than the product of cancer risk ratios from EC exposure and smoking alone²⁷. In two non-overlapping Canadian population-based case-control studies, no significant multiplicative interaction was observed^{9,10}. Lastly, in the US Miners Study Silverman and colleagues reported a suggestive sub-multiplicative interaction, where high exposure to both EC and cigarette smoke resulted in an attenuation of lung cancer risk increase⁴. In additional analyses where we explored cancer risks in four groups of male smokers (<10, 10-19, 20-39 and >39 pack-years, respectively) with cumulative EC exposures similar to those in Silverman and colleagues, we did not observe sub-multiplicative interactive effects and found consistent risk increases across all EC exposure categories for subjects with increasing pack-years of smoking (Table E3 in online supplement).

Strengths of our study include a large pooled population with detailed smoking and occupational histories. Our sample size allowed for stratified analyses to explore the exposure-response relationship in different subgroups, while high-quality smoking and occupational histories allowed for the control of important potential confounders such as smoking and exposure to other occupational carcinogens. Exposure assessment was performed with a quantitative JEM developed using a combination of exposure measurements and expert assessment. The current DEE-JEM was developed independently from the DOM-JEM (Domtoren-JEM), an expert judgment JEM we used in an earlier analysis³. Despite this difference, results of both analyses showed consistent exposure-response between occupational exposure to diesel exhaust and lung cancer. Reliability studies on occupational exposure assessment also suggested that incorporating measurements in the exposure assessment process may improve expert judgment^{29,30}. Finally, the exposure-response between EC exposure and lung cancer in our male population was robust and present in various sensitivity analyses, including when we limited analyses to a more homogenous group of studies, when we limited our analyses to blue-collar workers only, and when we assessed EC exposure with alternative JEM configurations (Tables E4.1-4.9 in online supplement).

There are also limitations in our work. Our DEE-JEM did not account for changes in exposure in different time periods and therefore may underestimate exposure for earlier periods when exposure was likely higher³¹. The EC measurements used in our JEM were collected from 1985 to 2016 (median: 2002) whereas our subjects were assessed as exposed from 1923 to 2020 (median: 1968). However, the association between EC exposure and lung cancer was still present when we restricted our analyses to subjects

exposed after 1960 (Table E4.2 in online supplement). Because List A jobs included some jobs with potential diesel exhaust exposure, adjustment for ever-employment in any List A jobs in our main model may represent over-adjustment for co-exposures to other lung carcinogens. Removing all jobs with EC exposure from List A, however, may lead to under-adjustment as many EC-exposed jobs have concurrent exposures to other lung carcinogens. We explored the co-exposure adjustments using two additional sensitivity models: one with no adjustment and another adjusting for ever exposure to crystalline silica, asbestos, polycyclic aromatic hydrocarbons (PAHs), and hexavalent chromium as assessed by the DOM-JEM (Table E4.4 in online supplement). All three categorical EC models (i.e. main model plus the two sensitivity models) showed the EC-lung cancer exposure response among men, suggesting that the association is unlikely to be fully explained by confounding due to exposures to other occupational lung carcinogens. Further, because our JEM assigned EC exposures based on job titles, individual exposures may be misclassified in occupations with large exposure variability. This misclassification, however, was not likely to be differential by case status and introduced Berkson-like error that likely affected the precision, but not magnitude, of our risk estimates^{32,33}. Exposure misclassification of jobs within the DEE-JEM may also have occurred due to the fact that our EC exposure data was limited and did not represent all jobs in all study regions. If present, this would introduce classical error in our work and bias the observed effect towards the null, meaning that the true effect of diesel exhaust exposure on lung cancer may be stronger than our observed results. However, the aforementioned shortcomings related to retrospective exposure assessment are almost inevitable due to our study design and size. We have provided

details on all data sources, assessment procedures, and various sensitivity analyses in an effort to maximize transparency.

Another notable limitation of our study is the lower statistical power to assess risk in female workers (390 exposed cases) compared to males (7,843 exposed cases). Our results on female cancer risks may also have been affected by more exposure misclassification of women compared to men, since the supporting EC exposure data were collected almost exclusively among male workers. Adenocarcinoma, for which we observed the weakest association with diesel exhaust exposure among the lung cancer subtypes, were also more common in women than in men. However, our results should not be interpreted as diesel exhaust having no effect on lung cancer risks in women. A sensitivity analysis among women with lung cancer subtypes other than adenocarcinoma showed increased OR point estimates for cancer for all cumulative EC exposure groups, albeit with larger uncertainties (Table E4.9 in online supplement).

In risk assessment for occupational carcinogen exposure, definitions for “tolerable” ELR range from 4 in 1,000 (0.4%) in the Netherlands and Germany to 1 in 1,000 (0.1%) in the US ^{17,34,35}. Of our three ELR estimates derived from different exposure limits, only the scenario with 1 $\mu\text{g}/\text{m}^3$ EC exposure and 0.04% ELR is below these levels. Another study using data from the US trucking industry estimated that male workers exposed to 5 $\mu\text{g}/\text{m}^3$ EC would have a lung cancer ELR of 1-2% ⁵. A separate study calculated a lung cancer ELR of 0.17% for workers exposed to 1 $\mu\text{g}/\text{m}^3$ EC using data from three US mining and trucking industry cohorts ⁷. Despite variations in the exact risk magnitude, estimates from different studies suggest that workplace EC levels should be at or near environmental background

levels in order to reduce the lung cancer ELR for workers with lifetime exposure to diesel exhaust to “tolerable levels” as defined by various national risk assessment agencies. Although multiple diesel engine emission control standards have been introduced in Europe since 2006 ¹⁷, these standards alone cannot be expected to reduce workplace EC exposure to environmental levels in the near future because they do not apply to the large number of existing diesel equipment that still is and will probably remain in use for many more years.

In summary, we observed a consistent exposure-response relationship between occupational diesel exhaust exposure and lung cancer in men in a large pooled analysis of case-control studies. Increased lung cancer risks were found in EC-exposed men who were never smokers and smokers. Increased risks in males were also observed for all lung cancer subtypes included, with associations strongest for squamous cell and small cell carcinomas and weaker for adenocarcinoma. The joint effects of EC exposure and smoking were super-additive on risks of overall lung cancer and all included subtypes. Our findings support efforts to further reduce workplace diesel exhaust exposure to protect workers against risks of lung cancer.

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FIGURE LEGEND:

Figure 1 Title: Spline analyses showing exposure-response relationships in men between cumulative elemental carbon (EC) exposure and risks of overall lung cancer plus subtypes.

Figure 1 Abbreviation: $\mu\text{g}/\text{m}^3\text{-years}$ = microgram per cubic metre years

FOOTNOTES: This work was supported by the German Social Accident Insurance (DGUV). The project is coordinated by the International Agency for Research on Cancer (IARC), the Institute for Prevention and Occupational Medicine of the DGUV, Institute of the Ruhr-University Bochum (IPA) and the Institute for Risk Assessment Sciences (IRAS) at Utrecht University. Where authors are identified as personnel of the International Agency for Research on Cancer /World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

The authors have no conflicts of interest to disclose. The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

TABLES

Table 1. Selected study population characteristics by lung cancer status and elemental carbon (EC) exposure

| Characteristic | Category | Ever exposed to EC | | Never exposed to EC | |
|---|-------------------------|--------------------|------------|---------------------|------------|
| | | Cases % | Controls % | Cases % | Controls % |
| Sex | Male | 8045 95.4 | 8181 94.1 | 5560 65.6 | 8270 67.4 |
| | Female | 386 4.6 | 512 5.9 | 2910 34.4 | 4002 32.6 |
| Age group | <45 years | 267 3.2 | 359 4.1 | 448 5.3 | 1012 8.2 |
| | 45-64 years | 4195 49.8 | 4120 47.4 | 4568 53.9 | 6234 50.8 |
| | >64 years | 3969 47.1 | 4214 48.5 | 3454 40.8 | 5026 41.0 |
| Smoking status | Never smoker | 379 4.5 | 2287 26.3 | 990 11.7 | 4866 39.7 |
| | Former smoker | 2966 35.2 | 3880 44.6 | 2466 29.1 | 4340 35.4 |
| | Current smoker | 5086 60.3 | 2526 29.1 | 5014 59.2 | 3066 25.0 |
| Smoking pack years | Never smoker | 379 4.5 | 2287 26.3 | 990 11.7 | 4866 39.7 |
| | <10 | 381 4.5 | 1287 14.8 | 428 5.1 | 1782 14.5 |
| | 10-19 | 765 9.1 | 1206 13.9 | 837 9.9 | 1656 13.5 |
| | >19 | 6906 81.9 | 3913 45.0 | 6215 73.4 | 3968 32.3 |
| Years-since- quitting- smoking | Never smoker | 379 4.5 | 2287 26.3 | 990 11.7 | 4866 39.7 |
| | >0-7 years | 1085 12.9 | 644 7.4 | 941 11.1 | 778 6.3 |
| | 8-15 years | 836 9.9 | 883 10.2 | 695 8.2 | 1015 8.3 |
| | 16-25 years | 637 7.6 | 1088 12.5 | 534 6.3 | 1258 10.3 |
| | >25 years | 408 4.8 | 1265 14.6 | 296 3.5 | 1289 10.5 |
| | Current smoker | 5086 60.3 | 2526 29.1 | 5014 59.2 | 3066 25.0 |
| 'List A' job | Ever employment | 1143 13.6 | 866 10.0 | 644 7.6 | 498 4.1 |
| | Never employment | 7288 86.4 | 7827 90.0 | 7712 92.4 | 11629 95.9 |
| Lung cancer subtype | Adenocarcinoma | 1953 23.2 | - | 2799 33.0 | - |
| | Large cell carcinoma | 390 4.6 | - | 420 5.0 | - |
| | Small cell carcinoma | 1427 16.9 | - | 1303 15.4 | - |
| | Squamous cell carcinoma | 3704 43.9 | - | 2799 33.0 | - |
| | Other/unspecified | 914 10.8 | - | 1098 13.0 | - |
| | Not available | 43 0.5 | - | 51 0.6 | - |

Table 2. Lung cancer odds ratios (OR) associated with categorical indices of occupational elemental carbon (EC) exposure

| Subject | Occupational EC exposure | Exposure category | Cases (%) | Controls (%) | OR* | 95% CI | |
|---------|--|----------------------|-------------|--------------|-------------|-----------------|-----------|
| Men | Reference | Never | 5560 (40.9) | 8270 (50.3) | 1.0 | Referent | |
| | | Ever exposure | Ever | 8045 (59.1) | 8181 (49.7) | 1.22 | 1.15–1.29 |
| | Duration (years) | 1–9 | 2346 (17.2) | 2750 (16.7) | 1.07 | 1.00–1.16 | |
| | | 10–19 | 1774 (13.0) | 1774 (10.8) | 1.23 | 1.13–1.34 | |
| | | 20–29 | 1578 (11.6) | 1471 (8.9) | 1.23 | 1.12–1.35 | |
| | | >29 | 2347 (17.3) | 2186 (13.3) | 1.39 | 1.28–1.51 | |
| | <i>Test for trend, p-value</i> | | | | | <i><0.01</i> | |
| | <i>Excl. never exposed</i> | | | | | <i><0.01</i> | |
| | Cumulative exposure ($\mu\text{g}/\text{m}^3$ -years) | >0–22 | 1684 (12.4) | 2002 (12.2) | 1.09 | 1.00–1.19 | |
| | | 23–70 | 1858 (13.7) | 2005 (12.2) | 1.10 | 1.02–1.20 | |
| | | 71–178 | 2113 (15.5) | 2074 (12.6) | 1.24 | 1.15–1.35 | |
| | | >178 | 2390 (17.6) | 2100 (12.8) | 1.43 | 1.32–1.54 | |
| | <i>Test for trend, p-value</i> | | | | | <i><0.01</i> | |
| | <i>Excl. never exposed</i> | | | | | <i><0.01</i> | |
| Women | Reference | Never | 2910 (88.3) | 4002 (88.7) | 1.0 | Referent | |
| | | Ever exposure | Ever | 386 (11.7) | 512 (11.3) | 1.00 | 0.85–1.18 |
| | Duration (years) | 1–9 | 235 (7.1) | 273 (6.0) | 1.02 | 0.83–1.26 | |
| | | 10–19 | 86 (2.6) | 112 (2.5) | 1.07 | 0.77–1.47 | |
| | | 20–29 | 25 (0.8) | 49 (1.1) | 0.69 | 0.39–1.17 | |
| | | >29 | 40 (1.2) | 78 (1.7) | 1.05 | 0.69–1.58 | |
| | <i>Test for trend, p-value</i> | | | | | <i>0.85</i> | |
| | <i>Excl. never exposed</i> | | | | | <i>0.74</i> | |
| | Cumulative exposure ($\mu\text{g}/\text{m}^3$ -years) | >0–22 | 165 (5.0) | 179 (4.0) | 1.03 | 0.80–1.33 | |
| | | 23–70 | 118 (3.6) | 162 (3.6) | 1.03 | 0.78–1.36 | |
| | | 71–178 | 64 (1.9) | 99 (2.2) | 0.92 | 0.64–1.31 | |
| | | >178 | 39 (1.2) | 72 (1.6) | 0.97 | 0.62–1.48 | |
| | <i>Test for trend, p-value</i> | | | | | <i>0.99</i> | |
| | <i>Excl. never exposed</i> | | | | | <i>0.82</i> | |

*OR adjusted for study, age group, smoking pack-years ($\log(\text{cigarette pack-years}+1)$), time-since-quit smoking, and List A jobs.

Table 3. Lung cancer major subtype risks (OR) associated with cumulative occupational elemental carbon (EC) exposure in men

| Lung cancer subtype | Cumulative EC exposure ($\mu\text{g}/\text{m}^3\text{-years}$) | Cases | OR* | 95% CI |
|--------------------------------|--|-------|-------------|-----------------|
| Adenocarcinoma | Never | 1513 | 1.0 | Referent |
| | >0-22 | 414 | 1.09 | 0.95-1.24 |
| | 23-70 | 415 | 1.00 | 0.88-1.14 |
| | 71-178 | 452 | 1.07 | 0.94-1.21 |
| | >178 | 531 | 1.23 | 1.09-1.39 |
| | <i>Test for trend, p-value</i> | | | <i>0.14</i> |
| | <i>Excl. never exposed</i> | | <i>0.49</i> | |
| Large cell carcinoma | Never | 257 | 1.0 | Referent |
| | >0-22 | 84 | 1.04 | 0.79-1.36 |
| | 23-70 | 76 | 0.90 | 0.68-1.18 |
| | 71-178 | 93 | 1.14 | 0.88-1.47 |
| | >178 | 109 | 1.31 | 1.02-1.67 |
| | <i>Test for trend, p-value</i> | | | <i>0.11</i> |
| | <i>Excl. never exposed</i> | | <i>0.14</i> | |
| Squamous cell carcinoma | Never | 2216 | 1.0 | Referent |
| | >0-22 | 742 | 1.13 | 1.01-1.26 |
| | 23-70 | 819 | 1.14 | 1.03-1.27 |
| | 71-178 | 982 | 1.37 | 1.24-1.52 |
| | >178 | 1069 | 1.54 | 1.39-1.70 |
| | <i>Test for trend, p-value</i> | | | <i><0.01</i> |
| | <i>Excl. never exposed</i> | | <i>0.01</i> | |
| Small cell carcinoma | Never | 850 | 1.0 | Referent |
| | >0-22 | 249 | 0.99 | 0.84-1.16 |
| | 23-70 | 334 | 1.20 | 1.03-1.39 |
| | 71-178 | 360 | 1.31 | 1.14-1.53 |
| | >178 | 407 | 1.53 | 1.32-1.76 |
| | <i>Test for trend, p-value</i> | | | <i>0.02</i> |
| | <i>Excl. never exposed</i> | | <i>0.39</i> | |

*OR adjusted for study, age group, smoking pack-years ($\log(\text{cigarette pack-years}+1)$), time-since-quitting smoking, and List A jobs.

Table 4. Lung cancer risks (OR) associated with cumulative occupational elemental carbon (EC) exposure by smoking status in men

| Cumulative EC exposure ($\mu\text{g}/\text{m}^3\text{-years}$) | Never smokers | | | Former smokers | | | Current smokers | | |
|--|---------------|-------------|-----------|----------------|-----------------|-----------|-----------------|-----------------|-----------|
| | Cases | OR* | 95% CI | Cases | OR† | 95% CI | Cases | OR‡ | 95% CI |
| Never | 256 | 1.0 | Referent | 1868 | 1.0 | Referent | 3436 | 1.0 | Referent |
| >0-22 | 66 | 1.40 | 1.03-1.88 | 624 | 1.11 | 0.98-1.26 | 994 | 1.04 | 0.92-1.18 |
| 23-70 | 41 | 0.94 | 0.65-1.33 | 656 | 1.23 | 1.09-1.40 | 1161 | 1.01 | 0.90-1.14 |
| 71-178 | 55 | 1.17 | 0.85-1.60 | 764 | 1.33 | 1.18-1.50 | 1294 | 1.15 | 1.03-1.29 |
| >178 | 72 | 1.41 | 1.04-1.88 | 875 | 1.47 | 1.31-1.65 | 1443 | 1.40 | 1.24-1.57 |
| <i>Test for trend, p-value</i> | | <i>0.03</i> | | | <i><0.01</i> | | | <i><0.01</i> | |
| <i>Excl. never exposed</i> | | <i>0.11</i> | | | <i>0.08</i> | | | <i>0.05</i> | |

*OR adjusted for study, age group and "List A" jobs.

†OR adjusted for study, age group, "List A" jobs, smoking pack-years ($\log(\text{cigarette pack-years}+1)$) and time-since-quitting smoking.

‡OR adjusted for study, age group, "List A" jobs, and smoking pack-years ($\log(\text{cigarette pack-years}+1)$).

Table 5: Interactions between occupational elemental carbon (EC) exposure and smoking for overall lung cancer and major subtypes in men

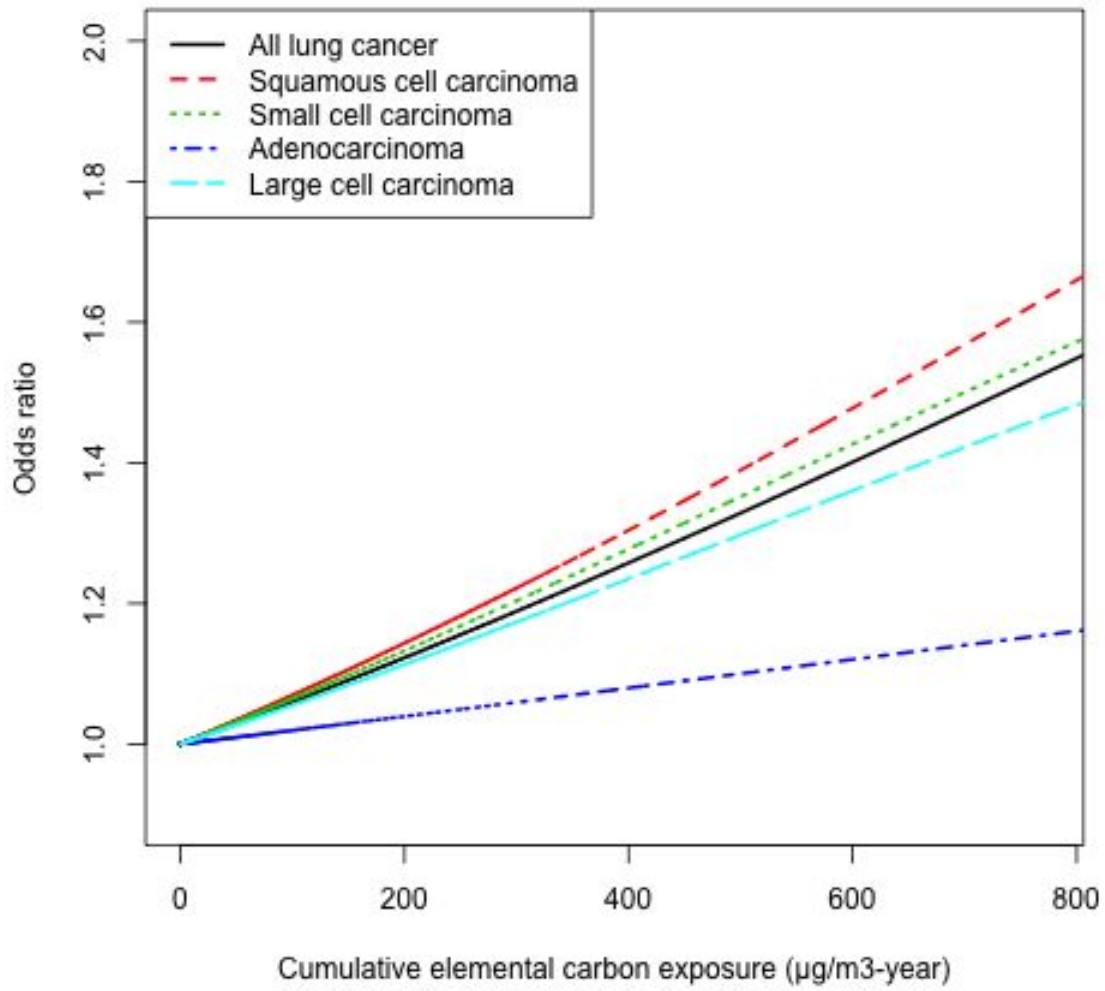
| Lung cancer subtype | Exposure status | Controls | Cases | OR* | 95%CI |
|--------------------------------|---------------------------------|----------|-------|-------------|------------------|
| All lung cancers | Never Smoker & Never EC | 2525 | 256 | 1.0 | Referent |
| | Never Smoker & Ever EC | 1912 | 234 | 1.14 | 0.95–1.38 |
| | Ever Smoker & Never EC | 5745 | 5304 | 8.71 | 7.62–10.0 |
| | Ever Smoker & Ever EC | 6269 | 7811 | 11.4 | 9.93–13.0 |
| | <i>p-value multiplicative</i> † | | | <i>0.18</i> | |
| | <i>RERI</i> ‡ | | | <i>2.49</i> | <i>1.92–3.07</i> |
| Adenocarcinoma | Never Smoker & Never EC | 2525 | 100 | 1.0 | Referent |
| | Never Smoker & Ever EC | 1912 | 79 | 1.05 | 0.77–1.42 |
| | Ever Smoker & Never EC | 5745 | 1413 | 6.14 | 4.99–7.63 |
| | Ever Smoker & Ever EC | 6269 | 1733 | 7.22 | 5.87–8.98 |
| | <i>p-value multiplicative</i> † | | | <i>0.47</i> | |
| | <i>RERI</i> ‡ | | | <i>1.03</i> | <i>0.43–1.63</i> |
| Large cell carcinoma | Never Smoker & Never EC | 2525 | 14 | 1.0 | Referent |
| | Never Smoker & Ever EC | 1912 | 5 | 0.43 | 0.14–1.14 |
| | Ever Smoker & Never EC | 5745 | 243 | 7.57 | 4.57–13.7 |
| | Ever Smoker & Ever EC | 6269 | 357 | 9.35 | 5.66–16.8 |
| | <i>p-value multiplicative</i> † | | | <i>0.05</i> | |
| | <i>RERI</i> ‡ | | | <i>2.34</i> | <i>0.67–4.02</i> |
| Squamous cell carcinoma | Never Smoker & Never EC | 2525 | 64 | 1.0 | Referent |
| | Never Smoker & Ever EC | 1912 | 77 | 1.38 | 0.98–1.94 |
| | Ever Smoker & Never EC | 5745 | 2152 | 13.4 | 10.5–17.1 |
| | Ever Smoker & Ever EC | 6269 | 3535 | 18.1 | 14.4–24.0 |
| | <i>p-value multiplicative</i> † | | | <i>0.99</i> | |
| | <i>RERI</i> ‡ | | | <i>4.66</i> | <i>3.23–6.09</i> |
| Small cell carcinoma | Never Smoker & Never EC | 2525 | 26 | 1.0 | Referent |
| | Never Smoker & Ever EC | 1912 | 30 | 1.38 | 0.81–2.36 |
| | Ever Smoker & Never EC | 5745 | 824 | 13.5 | 9.32–20.6 |
| | Ever Smoker & Ever EC | 6269 | 1320 | 18.5 | 12.8–28.1 |
| | <i>p-value multiplicative</i> † | | | <i>0.96</i> | |
| | <i>RERI</i> ‡ | | | <i>4.56</i> | <i>2.42–6.69</i> |

* OR adjusted for study, age group and "List A" jobs.

†RERI: Excess risks due to interaction. Interaction on the additive scale is present when RERI deviates from 0.

‡ p-value for the EC and smoking interaction cross product term coefficient in fully adjusted logistic models. Interaction on the multiplicative scale is present when $p < 0.05$.

FIGURE



Diesel Engine Exhaust Exposure, Smoking, and Lung Cancer Subtype Risks: A Pooled Exposure-response Analysis of 14 Case-control Studies

Online Data Supplement

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SUPPLEMENTARY METHODS

Elemental carbon (EC) data sources and additional description for the DEE-JEM

We chose EC as an exposure proxy for diesel engine exhaust because of its high specificity to diesel engine emissions and general acceptance as the best marker for diesel engine exhaust ^{E1}. The occupational EC exposure measurements for the JEM were obtained from three sources. Studies published from 1957 to 2007 that were included in an earlier review of EC occupational exposure by Pronk and colleagues ^{E2}. An additional literature review was performed in the MEDLINE database for studies with EC measurements published between January 1st 2008 and May 31st 2017. Specifically, Medical Subject Headings (MeSH) terms “vehicle emissions” and “occupational exposures” were used in conjunction with all fields keywords “elemental carbon” and “diesel” to search for studies containing EC measurements. The search resulted in 34 matches and 9 publications contained relevant EC measurements for extraction ^{E3-11}. Two additional reports on EC exposures in firefighters were also added ^{E11, E12}. Finally, occupational EC measurements from the UK Health and Safety Executive (HSE) National Exposure Database (NEDB) were also screened for extraction ^{E14}. For inclusion in our JEM, EC measurements had to be: 1) personal measurements or area measurements representative of personal exposure (e.g. inside a vehicle cabin); 2) sampled with duration longer than 1 hour; 3) representative of typical exposures experienced by workers (i.e. not worst-case or complaint-driven sampling); and 4) taken in actual workplaces rather than other simulated controlled settings. In total, 3,528 EC measurements were extracted from studies covered by the review by Pronk and colleagues, 700 were extracted from the additional literature review, and 189 were extracted from the NEDB. The EC measurements included 2,066 in the respirable

fraction, 1,333 in the submicron fraction, 665 in the inhalable fraction, and 353 with no size fraction information. Measurements of all size fractions were treated equally as studies suggest the submicron size fraction captures approximately 75% of EC particulates whereas respirable and larger size fractions captures nearly all EC ^{E15,E16}. Sampling year for EC measurements used to construct the JEM ranged from 1985 to 2016 (median: 2002). Additional information on all EC measurements used for the DEE-JEM, including occupation, country, and sampling year, is available in Supplementary Table E6.

Assigned probabilities in the DEE-JEM consisted of one of three values in 0.1, 0.25, 0.5 and were given based on expert decision by two experts (CG, RV) consecutively. Probabilities were only assigned to occupations where the experts were confident that EC exposure does not occur for all workers with the same job title. A few ISCO-68 occupations at the 2- or 3-digit level received probabilities of 0.4 (n=3) and 0.6 (n=4) as median values of probabilities assigned to their respective 5-digit daughter occupations. In total, the DEE-JEM assigned EC exposure to 248 of 1,506 ISCO-68 jobs. Probability factors for these jobs were: 0.1 for 12 jobs, 0.25 for 84 jobs, 0.4 for 3 jobs, 0.5 for 46 jobs, 0.6 for 4 jobs and 1.0 for 100 jobs.

Sensitivity analyses

Stratified models were used to assess if cancer risks associated with cumulative EC exposure categories differed between population- versus hospital-based case control studies in men. Restricted models were created for male blue-collar workers and workers employed after 1960 to investigate whether cancer risks differed for workers with lower socioeconomic status and for workers whose exposures were more recent when diesel equipment became more common in the workplace, respectively. Because

miners and farmers may account for large proportions of the exposed population and may have different exposure patterns than other occupations, restricted analyses were performed on the male study population without those ever-employed in mining and agriculture industries to see if risks differed compared to our main analyses. As an alternative to List-A job adjustment for exposures to other lung carcinogens, we controlled for ever exposure to asbestos, crystalline silica, hexavalent chromium, and polycyclic aromatic hydrocarbons (PAHs) as assessed by the DOM-JEM^{E17} in our main categorical exposure model for men. Heterogeneity in lung cancer ORs in men associated with ever EC exposure between 14 studies was measured using the p-value of the Cochran's Q statistic and as a percentage in I²^{E18}.

To assess the impact of various decisions during the development of the DEE-JEM, we also carried out multiple sensitivity analyses with different JEM configurations. In our male categorical cumulative EC exposure model, we tested the impact of including expert-assigned probabilities by using a JEM with no probabilities (i.e. all probabilities=1 for exposed job titles) and a JEM with no expert-assigned probabilities <1. We also tested the same model with a JEM with EC measurement data restricted in the respirable size fraction to see if this changes the findings obtained from the JEM with EC data in various size fractions.

To further explore lung cancer risks in women related to EC exposure, we limited our cumulative EC exposure model to women with lung cancer subtypes other than adenocarcinoma. Additional analysis to calculate lung cancer OR and 95% CIs associated with time-since-last-exposure (<10; 10–19; 20–29; 30–39; >39 years) for men and women separately, with similar adjustments as our main analyses. Trends

were assessed using p-values from the respective indices of EC exposure as continuous variables for exposed subjects only.

SUPPLEMENTARY RESULTS

Sensitivity analyses

We observed associations between cumulative EC exposure and lung cancer in all stratified and restricted sensitivity analyses in men (Tables E4.1-4.5). Associations were similar or stronger compared to our main models in models restricted to studies with population controls and models restricted to subjects who never worked in agriculture. Risk estimates were more attenuated and less precise in models restricted to studies with hospital controls, subjects who were blue-collar workers, workers employed after 1960, workers who were never-miners, as well as in the model with alternative control for exposure to other occupational lung carcinogens.

Heterogeneity was observed in the lung cancer ORs related to ever EC exposure in the 14 included studies ($I^2=50\%$; $Q=40$; $p<0.01$). Significant reduction in heterogeneity was observed ($I^2=18\%$; $Q=24$; $p=0.13$) in the remaining subgroup after excluding two studies: AUT and PARIS. Exposure-response patterns between lung cancer and cumulative EC exposure in this more homogeneous subgroup were attenuated, but the risk pattern was generally similar to those observed in the main analyses (Table E4.5).

All analyses involving alternative JEM configurations produced results that were more attenuated than results from the main analyses; however elevated lung cancer ORs and exposure-response between EC exposure and lung cancer were observed in all three alternative models (Tables E4.6-4.8).

For women with lung cancer subtypes other than adenocarcinoma, we observed elevated OR point estimates for all EC exposure categories compared with unexposed subjects (Table E4.9). However the uncertainties around these estimates were large due to limited statistical power. Among women we observed an indication of increasing risk trend ($p=0.04$) with longer time since last exposure (Table E5). No trends were observed in men.

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Table E1: Description of the studies included in these analyses in the SYNERGY project

| Study | Country | Data collection | Cases | | Controls | | EC exposure | Control source ^b | Interview ^c |
|---------------------|----------------|-----------------|--------|-------------------|----------|-------------------|-------------|-----------------------------|------------------------|
| | | | N | Response rate (%) | N | Response rate (%) | | | |
| AUT-Munich | Germany | 90-95 | 3180 | 77 | 3249 | 41 | 31-95 | P | S |
| CAPUA | Spain | 00-10 | 559 | 91 | 512 | 96 | 26-10 | H | S |
| EAGLE | Italy | 02-05 | 1908 | 87 | 2065 | 72 | 32-05 | P | S |
| HdA | Germany | 88-93 | 1004 | 69 | 1002 | 68 | 26-93 | P | S |
| ICARE | France | 01-07 | 2739 | 63 | 3449 | 77 | 37-07 | P | S & NOK |
| INCO | Czech Republic | 99-02 | 304 | 94 | 452 | 80 | 37-02 | H | S |
| INCO | Hungary | 98-01 | 391 | 90 | 305 | 100 | 31-99 | H | S |
| INCO | Poland | 98-02 | 793 | 88 | 835 | 88 | 33-01 | P & H | S |
| INCO | Romania | 98-02 | 179 | 90 | 225 | 99 | 43-01 | H | S |
| INCO | Russia | 98-01 | 599 | 96 | 580 | 90 | 38-00 | H | S |
| INCO | Slovakia | 98-02 | 345 | 90 | 285 | 84 | 37-02 | H | S |
| INCO/LLP | United Kingdom | 98-05 | 441 | 78 | 916 | 84 | 34-04 | P | S |
| LUCA | France | 89-92 | 280 | 98 | 282 | 98 | 27-92 | H | S |
| LUCAS | Sweden | 85-90 | 1014 | 87 | 2307 | 85 | 23-90 | P | S & NOK |
| MONTREAL | Canada | 96-02 | 1176 | 85 | 1505 | 69 | 36-99 | P | S & NOK |
| MORGEN ^a | Netherlands | 93-97 | 43 | N/A | 115 | N/A | 45-94 | P | S |
| PARIS | France | 88-92 | 169 | 95 | 227 | 95 | 29-92 | H | S |
| ROME | Italy | 93-96 | 326 | 74 | 321 | 63 | 26-95 | H | S |
| TORONTO | Canada | 97-02 | 365 | 62 | 844 | 71 | 29-02 | P & H | S |
| TURIN/ VENETO | Italy | 90-94 | 1086 | 79 | 1489 | 80 | 25-94 | P | S |
| Overall | 14 countries | 85-10 | 16 901 | 78% | 20 965 | 69% | 23-10 | P=79% | S=92.7 % |

a Nested case-control study: 45% of invited participants to the original cohort completed the baseline questionnaire.

b P = population controls; H = hospital controls

c S = subject; NOK = Next-of-kin

Table E2 Sensitivity analyses in men for the association between cumulative exposure to elemental carbon (EC) in decile groups and lung cancer

| Cumulative EC exposure | All studies | | |
|---------------------------------------|----------------|-------|-----------|
| $\mu\text{g}/\text{m}^3\text{-years}$ | Cases/controls | OR | 95%CI |
| Unexposed | 5560/8270 | 1.0 | Referent |
| >0-6.5 | 663/819 | 1.04 | 0.92-1.18 |
| 6.6-16 | 685/788 | 1.10 | 0.97-1.24 |
| 17-29 | 638/786 | 1.04 | 0.92-1.18 |
| 30-47 | 759/786 | 1.18 | 1.04-1.33 |
| 48-71 | 797/828 | 1.12 | 1.00-1.26 |
| 72-104 | 907/847 | 1.30 | 1.16-1.46 |
| 105-148 | 800/813 | 1.20 | 1.07-1.36 |
| 149-218 | 875/822 | 1.33 | 1.18-1.49 |
| 219-322 | 925/834 | 1.41 | 1.25-1.58 |
| >322 | 996/858 | 1.42 | 1.27-1.59 |
| <i>Test for trend, p-value§</i> | | <0.01 | |
| <i>Excl. never exposed</i> | | <0.01 | |

OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

Table E3: Odds ratios (OR) and 95% confidence intervals (CIs) of lung cancer for cumulative elemental carbon (EC) for male subjects with different smoking habits (packyears).

| <u>Smoking and EC exposure</u> | <u>Controls</u> | <u>Cases</u> | <u>OR</u> | <u>95% CI</u> | |
|-----------------------------------|-----------------|--------------|-----------|---------------|------|
| <u>Never smokers</u> | | | | | |
| Unexposed | 2525 | 256 | 1.0 | ref | |
| >0–22 µg/m ³ -years | 453 | 66 | 1.33 | 0.99 | 1.7 |
| 23–70 µg/m ³ -years | 445 | 41 | 0.88 | 0.61 | 1.2 |
| 71–178 µg/m ³ -years | 485 | 55 | 1.10 | 0.80 | 1.4 |
| 179–218 µg/m ³ -years | 95 | 17 | 1.60 | 0.91 | 2.6 |
| 219–261 µg/m ³ -years | 112 | 11 | 0.89 | 0.45 | 1.6 |
| 262–322 µg/m ³ -years | 115 | 10 | 0.79 | 0.39 | 1.4 |
| >322 µg/m ³ -years | 207 | 34 | 1.50 | 1.00 | 2.1 |
| <u><10 pack-years</u> | | | | | |
| Unexposed | 1226 | 244 | 1.91 | 1.58 | 2.3 |
| >0–22 µg/m ³ -years | 336 | 81 | 2.12 | 1.60 | 2.7 |
| 22–70.6 µg/m ³ -years | 302 | 76 | 2.28 | 1.70 | 3.0 |
| 70.6–178 µg/m ³ -years | 305 | 89 | 2.59 | 1.97 | 3.3 |
| 178–218 µg/m ³ -years | 69 | 18 | 2.28 | 1.29 | 3.8 |
| 218–261 µg/m ³ -years | 54 | 30 | 5.07 | 3.14 | 8.0 |
| 261–322 µg/m ³ -years | 61 | 18 | 2.60 | 1.47 | 4.4 |
| >322 µg/m ³ -years | 113 | 52 | 4.21 | 2.93 | 5.9 |
| <u>10-19 pack-years</u> | | | | | |
| Unexposed | 1245 | 494 | 3.78 | 3.20 | 4.4 |
| >0–22 µg/m ³ -years | 322 | 153 | 4.30 | 3.39 | 5.4 |
| 22–70.6 µg/m ³ -years | 287 | 168 | 5.25 | 4.16 | 6.6 |
| 70.6–178 µg/m ³ -years | 278 | 197 | 6.51 | 5.19 | 8.1 |
| 178–218 µg/m ³ -years | 59 | 45 | 6.76 | 4.46 | 10. |
| 218–261 µg/m ³ -years | 53 | 44 | 7.32 | 4.77 | 11. |
| 261–322 µg/m ³ -years | 65 | 38 | 5.14 | 3.34 | 7.8 |
| >322 µg/m ³ -years | 114 | 76 | 6.21 | 4.49 | 8.5 |
| <u>20-39 pack-years</u> | | | | | |
| Unexposed | 1934 | 1904 | 13.7 | 12.0 | 15. |
| >0–22 µg/m ³ -years | 509 | 603 | 14.6 | 12.5 | 17. |
| 22–70.6 µg/m ³ -years | 543 | 654 | 15.2 | 13.1 | 17. |
| 70.6–178 µg/m ³ -years | 572 | 749 | 16.6 | 14.3 | 19. |
| 178–218 µg/m ³ -years | 107 | 170 | 19.9 | 16.0 | 24. |
| 218–261 µg/m ³ -years | 103 | 159 | 18.8 | 15.1 | 23. |
| 261–322 µg/m ³ -years | 95 | 151 | 19.8 | 15.9 | 24. |
| >322 µg/m ³ -years | 236 | 316 | 18.5 | 15.5 | 22. |
| <u>>39 pack-years</u> | | | | | |
| Unexposed | 1340 | 2662 | 21.1 | 18.2 | 24.5 |
| >0–22 µg/m ³ -years | 382 | 781 | 20.5 | 17.1 | 24.6 |
| 22–70.6 µg/m ³ -years | 428 | 919 | 21.8 | 18.3 | 26.1 |
| 70.6–178 µg/m ³ -years | 434 | 1023 | 24.0 | 20.2 | 28.6 |
| 178–218 µg/m ³ -years | 78 | 219 | 30.0 | 22.5 | 40.4 |
| 218–261 µg/m ³ -years | 92 | 231 | 25.4 | 19.3 | 33.7 |
| 261–322 µg/m ³ -years | 84 | 233 | 28.0 | 21.1 | 37.3 |
| >322 µg/m ³ -years | 188 | 518 | 28.1 | 22.7 | 34.9 |

OR is adjusted for study, age group, and List A job

Supplementary Table E4: Sensitivity analyses for the association between cumulative exposure to elemental carbon (EC) and lung cancer

E4.1 Analyses in men by type of controls

| Cumulative EC exposure | Studies with population controls* | | | Studies with hospital controls* | | |
|---------------------------------|-----------------------------------|-----------------|-----------|---------------------------------|-------------|-----------|
| | Cases/controls | OR | 95%CI | Cases/controls | OR | 95%CI |
| Unexposed | 4001/6440 | 1.0 | Referent | 1571/1901 | 1.0 | Referent |
| >0–22 | 1302/1615 | 1.10 | 1.00–1.21 | 317/286 | 1.22 | 1.01–1.48 |
| 23–70 | 1368/1512 | 1.14 | 1.03–1.25 | 427/397 | 1.06 | 0.89–1.25 |
| 71–178 | 1535/1516 | 1.30 | 1.18–1.43 | 513/432 | 1.17 | 1.00–1.38 |
| >178 | 1723/1495 | 1.56 | 1.42–1.71 | 643/544 | 1.20 | 1.03–1.40 |
| <i>Test for trend, p-value§</i> | | <i><0.01</i> | | | <i>0.89</i> | |
| <i>Excl. never exposed</i> | | <i><0.01</i> | | | <i>0.37</i> | |

OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

*Subjects from the INCO Poland and Toronto studies were included in both analyses, since both types of controls were used

E4.2 Analyses restricted to male blue-collar workers and workers employed after 1960

| Cumulative EC exposure | Restricted to blue-collar workers | | | Restricted to workers employed after 1960 | | |
|---------------------------------|-----------------------------------|-----------------|-----------|---|-------------|-----------|
| | Cases/controls | OR | 95%CI | Cases/controls | OR | 95%CI |
| Unexposed | 3559/4828 | 1.0 | Referent | 1682/2825 | 1.0 | Referent |
| >0–22 | 1424/1567 | 1.01 | 0.92–1.11 | 342/460 | 0.98 | 0.82–1.17 |
| 23–70 | 1724/1762 | 1.00 | 0.92–1.10 | 443/466 | 1.25 | 1.05–1.48 |
| 71–178 | 1948/1830 | 1.10 | 1.01–1.21 | 403/429 | 1.17 | 0.98–1.39 |
| >178 | 2242/1906 | 1.27 | 1.16–1.38 | 329/351 | 1.24 | 1.02–1.50 |
| <i>Test for trend, p-value§</i> | | <i><0.01</i> | | | <i>0.18</i> | |
| <i>Excl. never exposed</i> | | <i>0.05</i> | | | <i>0.60</i> | |

OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

E4.3 Analyses restricted to male non-agricultural and non-mining workers

| Cumulative EC exposure | Subjects never employed in the mining industry | | | Subjects never employed in the agriculture industry | | |
|---------------------------------|--|-----------------|-----------|---|-----------------|-----------|
| | Cases/controls | OR | 95%CI | Cases/controls | OR | 95%CI |
| Unexposed | 5534/8220 | 1.0 | Referent | 5414/8044 | 1.0 | Referent |
| >0–22 | 1620/1943 | 1.08 | 0.99–1.18 | 1406/1666 | 1.09 | 1.00–1.20 |
| 23–70 | 1729/1919 | 1.09 | 1.00–1.18 | 1434/1496 | 1.13 | 1.03–1.24 |
| 71–178 | 1928/1957 | 1.22 | 1.12–1.32 | 1467/1387 | 1.28 | 1.17–1.41 |
| >178 | 2029/1881 | 1.38 | 1.27–1.50 | 1655/1405 | 1.43 | 1.31–1.57 |
| <i>Test for trend, p-value§</i> | | <i><0.01</i> | | | <i><0.01</i> | |
| <i>Excl. never exposed</i> | | <i><0.01</i> | | | <i><0.01</i> | |

OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

E4.4 Analyses in men with alternative model adjustments for exposure to other occupational lung carcinogens

| Cumulative EC exposure | No co-exposure adjustment* | | | Alternative adjustment† | | |
|---------------------------------------|----------------------------|-------|-----------|-------------------------|------|-----------|
| $\mu\text{g}/\text{m}^3\text{-years}$ | Cases/controls | OR | 95%CI | Cases/controls | OR | 95%CI |
| Unexposed | 5560/8270 | 1.0 | Referent | 5560/8270 | 1.0 | Referent |
| >0-22 | 1684/2002 | 1.11 | 1.02-1.21 | 1684/2002 | 1.00 | 0.91-1.09 |
| 23-70 | 1858/2005 | 1.13 | 1.04-1.22 | 1858/2005 | 0.99 | 0.90-1.08 |
| 71-178 | 2113/2074 | 1.25 | 1.16-1.36 | 2113/2074 | 1.09 | 0.99-1.19 |
| >178 | 2390/2100 | 1.43 | 1.32-1.55 | 2390/2100 | 1.23 | 1.13-1.35 |
| <i>Test for trend, p-value§</i> | | <0.01 | | | 0.03 | |
| <i>Excl. never exposed</i> | | <0.01 | | | 0.06 | |

* OR is adjusted for study, age group, and smoking (pack-years, time-since-quitting smoking).

† (OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and ever exposure to silica, asbestos, polycyclic aromatic hydrocarbons, and chromium.

E4.5 Analyses in men by homogenous group of studies (excluding AUT and PARIS)

| Cumulative EC exposure | All studies except AUT and PARIS | | |
|---------------------------------------|----------------------------------|-------|-----------|
| $\mu\text{g}/\text{m}^3\text{-years}$ | Cases/controls | OR | 95%CI |
| Unexposed | 4745/7056 | 1.0 | Referent |
| >0-22 | 1235/1481 | 1.10 | 0.99-1.21 |
| 23-70 | 1406/1563 | 1.09 | 1.00-1.20 |
| 71-178 | 1606/1687 | 1.19 | 1.09-1.30 |
| >178 | 1793/1746 | 1.29 | 1.18-1.40 |
| <i>Test for trend, p-value§</i> | | <0.01 | |
| <i>Excl. never exposed</i> | | 0.20 | |

OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

E4.6 Analyses in men with alternative JEM restricted to respirable EC data

| Cumulative EC exposure | All studies | | |
|---------------------------------------|----------------|-------|-----------|
| $\mu\text{g}/\text{m}^3\text{-years}$ | Cases/controls | OR | 95%CI |
| Unexposed | 5560/8270 | 1.0 | Referent |
| >0-24 | 1621/1971 | 1.07 | 0.98-1.17 |
| 25-73 | 1841/2024 | 1.09 | 1.01-1.19 |
| 74-193 | 2207/2071 | 1.30 | 1.20-1.41 |
| >193 | 2376/2115 | 1.39 | 1.29-1.51 |
| <i>Test for trend, p-value§</i> | | <0.01 | |
| <i>Excl. never exposed</i> | | <0.01 | |

OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

E4.7 Analyses in men with alternative JEM without any expert-assigned exposure probabilities

| Cumulative EC exposure | All studies | | |
|---------------------------------------|----------------|-------|-----------|
| $\mu\text{g}/\text{m}^3\text{-years}$ | Cases/controls | OR | 95%CI |
| Unexposed | 5560/8270 | 1.0 | Referent |
| | 1735/2002 | 1.08 | 1.00–1.18 |
| 49–143 | 1982/2035 | 1.17 | 1.08–1.27 |
| 144–338 | 2093/2070 | 1.21 | 1.11–1.31 |
| >338 | 2235/2074 | 1.42 | 1.31–1.53 |
| <i>Test for trend, p-value§</i> | | <0.01 | |
| <i>Excl. never exposed</i> | | <0.01 | |

OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

E4.8 Analyses in men with alternative JEM restricted to jobs where expert-assigned exposure probabilities=1

| Cumulative EC exposure | All studies | | |
|---------------------------------------|----------------|-------|-----------|
| $\mu\text{g}/\text{m}^3\text{-years}$ | Cases/controls | OR | 95%CI |
| Unexposed | 9020/12051 | 1.0 | Referent |
| >0–25 | 900/1068 | 0.96 | 0.86–1.06 |
| 26–72 | 1186/1096 | 1.12 | 1.02–1.24 |
| 73–209 | 1223/1115 | 1.20 | 1.08–1.32 |
| >209 | 1276/1121 | 1.27 | 1.16–1.40 |
| <i>Test for trend, p-value§</i> | | <0.01 | |
| <i>Excl. never exposed</i> | | 0.02 | |

OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

E4.9 Analyses in women with subtypes other than adenocarcinoma

| Cumulative EC exposure | Female subjects with cancer subtypes other than adenocarcinoma | | |
|---------------------------------------|--|------|-----------|
| $\mu\text{g}/\text{m}^3\text{-years}$ | Cases/controls | OR | 95%CI |
| Unexposed | 1624/4002 | 1.0 | Referent |
| >0–22 | 110/179 | 1.18 | 0.87–1.59 |
| 23–70 | 74/162 | 1.18 | 0.84–1.65 |
| 71–178 | 38/99 | 1.06 | 0.67–1.63 |
| >178 | 23/72 | 1.18 | 0.67–2.02 |
| <i>Test for trend, p-value§</i> | | 0.33 | |
| <i>Excl. never exposed</i> | | 0.74 | |

OR is adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

Table E5: Lung cancer odds ratios (OR) in both sexes associated with time since last occupational elemental carbon (EC) exposure

| Occupational EC exposure | Exposure category | Cases (%) | Controls (%) | OR* | 95% CI |
|--|--|-------------|--------------|------|-----------|
| Men | | | | | |
| Time since last exposure (years) † | Never | 5560 (40.9) | 8270 (50.3) | 1.0 | Referent |
| | 10–19 | 5007 (37.3) | 4992 (30.3) | 1.04 | 0.93–1.15 |
| | 20–29 | 1280 (9.4) | 1367 (8.3) | 1.04 | 0.94–1.16 |
| | 30–39 | 979 (7.2) | 1005 (6.1) | 1.17 | 1.04–1.31 |
| | >39 | 709 (5.2) | 817 (5.0) | 1.00 | 0.88–1.13 |
| | <i>Test for trend, p-value (excl. never exposed)</i> | | | | 0.71 |
| Women | | | | | |
| Time since last exposure (years) † | Never | 2910 (88.3) | 4002 (88.7) | 1.0 | Referent |
| | 10–19 | 144 (4.4) | 210 (4.7) | 0.81 | 0.56–1.17 |
| | 20–29 | 66 (2.0) | 91 (2.0) | 0.82 | 0.54–2.22 |
| | 30–39 | 81 (2.5) | 78 (1.7) | 1.44 | 0.99–1.08 |
| | >39 | 95 (2.9) | 133 (2.9) | 0.92 | 0.49–1.27 |
| | <i>Test for trend, p-value (excl. never exposed)</i> | | | | 0.04 |

*OR adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs
†OR in “time since last exposure” is additionally adjusted for duration (continuous) of silica exposure.
Trend test limited to exposed subjects.

Table E6* – Occupational elemental carbon (EC) exposure measurements used in the diesel engine exhaust job-exposure matrix (DEE-JEM)

| <u>Description</u> | <u>Agent</u> [†] | <u>Duration</u> | <u>N</u> | <u>AM (SD)</u> | <u>Location</u> | <u>Year</u> | <u>Source</u> |
|---|---------------------------|-----------------|----------|----------------|-----------------|-------------|-----------------------|
| <u>Drivers</u> | | | | | | | |
| Drivers - bus | ECI | >4 | 4 | 2>LOD:11-20 | US | 1998 | Pronk et al (2009) |
| Drivers - bus | ECR | >4 | 5 | 10 | Estonia | 2002 | Pronk et al (2009) |
| Drivers - bus | ECR | >4 | 39 | 2 (1.3) | US | 2002 | Pronk et al (2009) |
| Drivers - bus and truck | | >4 | 20 | 11 | | 2002- | |
| | ECI | | | | Sweden | 2004 | Pronk et al (2009) |
| Drivers - local truck | ECNI | >4 | 4 | 5 (0.1) | US | 1985 | Pronk et al (2009) |
| Drivers - local truck | ECR | >4 | 5 | 7 | US | 1999 | Pronk et al (2009) |
| Drivers - local truck | ECS | >4 | 56 | 5 (0.9) | US | 1980s | Pronk et al (2009) |
| Drivers - local truck | | >4 | 576 | 2 (2.3) | | 2001- | |
| | ECS | | | | US | 2005 | Pronk et al (2009) |
| Drivers - locomotive | | >4 | 76 | 5 (1.1-15.8) | | 1999- | |
| | ECNI | | | | Canada | 2000 | Pronk et al (2009) |
| Driver - locomotive | | >4 | 156 | 2.8 | | 1996- | Hewett and Bullock |
| | ECR | | | | US | 2007 | (2014) |
| Drivers - locomotive | ECNI | >1 | 8 | 11.4 (5.5) | UK | 1996 | NEDB |
| Drivers - locomotive in tunnel construction | ECR | >4 | 2 | 24 (12) | UK | 2014 | Galea et al. (2015) |
| Drivers - locomotive in tunnel construction | ECR | >4 | 2 | 21 (4) | UK | 2014 | Galea et al. (2015) |
| Drivers - locomotive shunter | ECR | >4 | 19 | 20 (18.7) | Russia | 2002 | Pronk et al (2009) |
| Drivers - long haul truck | ECS | >4 | 21 | 1.55 (0.42) | US | 2006? | Sheesley et al (2008) |
| Drivers - long haul truck | ECNI | >4 | 4 | 22 (13.2) | US | 1985 | Pronk et al (2009) |
| Drivers - long haul truck | ECR | >4 | 5 | 5 | US | 1999 | Pronk et al (2009) |
| Drivers - long haul truck | ECS | >4 | 72 | 5 (0.4) | US | 1980s | Pronk et al (2009) |
| Drivers - long haul truck | | >4 | 349 | 1 (0.8) | | 2001- | |
| | ECS | | | | US | 2005 | Pronk et al (2009) |
| Drivers - taxi | | >4 | 8 | 8 | | 2002- | |
| | ECI | | | | Sweden | 2004 | Pronk et al (2009) |
| Drivers - truck | ECS | >4 | 18 | 2.71 (1.37) | US | 2006? | Sheesley et al (2008) |
| Drivers - truck | ECI | 1->4 | 3 | 10 (6) | US | 1992 | Pronk et al (2009) |

Mechanics

| | | | | | | | |
|-----------------------------------|------|----|-----|--------------|---------|-----------|-----------------------|
| Mechanics - ambulance | ECR | >4 | 3 | 31 | UK | 2000 | Pronk et al (2009) |
| Mechanics - bus | ECI | >4 | 4 | ND | US | 1998 | Pronk et al (2009) |
| Mechanics - bus | ECR | >4 | 53 | 39 | UK | 2000 | Pronk et al (2009) |
| Mechanics - bus | ECR | >4 | 15 | 39 | Estonia | 2002 | Pronk et al (2009) |
| Mechanics - diesel engine testing | ECR | >4 | 54 | 48.5 (22.1) | US | 2012-2013 | Lan et al. (2015) |
| Mechanics - locomotive | ECNI | >1 | 22 | 31.4 (40.7) | UK | 1994-2006 | NEDB |
| Mechanics - motor vehicle | ECNI | >1 | 20 | 39.1 (45.1) | UK | 1994-2006 | NEDB |
| Mechanics - truck | ECS | >4 | 7 | 2.04 (1.02) | US | 2006? | Sheesley et al (2008) |
| Mechanics - truck | ECR | >4 | 10 | 4 | US | 1999 | Pronk et al (2009) |
| Mechanics - truck | ECS | >4 | 80 | 27 (4.1) | US | 1980s | Pronk et al (2009) |
| Mechanics - truck and bus | ECI | >4 | 40 | 21 | Sweden | 2002-2004 | Pronk et al (2009) |
| Mechanics - tunnel construction | ECR | >4 | 29 | 48.39 | Norway | 2010-2011 | Bakke et al. (2014) |
| <u>Firefighters</u> | | | | | | | |
| Firefighters | ECI | >4 | 18 | 40 (20.3) | US | 1995 | Pronk et al (2009) |
| Firefighters | ECI | >4 | 12 | 10 (max) | US | 1997 | Pronk et al (2009) |
| Firefighters | ECI | <1 | 8 | ND | US | 1998 | Pronk et al (2009) |
| Firefighters | ECI | >4 | 27 | 24 (max) | US | 2002 | Pronk et al (2009) |
| Firefighters | ECR | 10 | 21 | 2 | AUS | 2010 | Bott et al (2010) |
| Firefighters | ECR | >7 | 28 | 1.34 (0.56) | US | 2016 | Couch et al (2016) |
| <u>Dockworkers</u> | | | | | | | |
| Dockworker | ECS | >4 | ≥5 | | US | 1990 | Pronk et al (2009) |
| Dockworker | ECS | >4 | 54 | 24 (0.4-2.5) | US | 1991 | Pronk et al (2009) |
| Dockworker | ECI | >4 | 5 | 4 (1.8) | US | 1992 | Pronk et al (2009) |
| Dockworker | ECR | >4 | 12 | 9 | US | 1999 | Pronk et al (2009) |
| Dockworker | ECR | >4 | 27 | 122 | UK | 2000 | Pronk et al (2009) |
| Dockworker | ECS | >4 | 14 | 1.12 (0.41) | US | 2006? | Sheesley et al (2008) |
| Dockworkers - ship loading | ECR | >4 | 20 | 49 | UK | 2000 | Pronk et al (2009) |
| Dockworkers - ship loading | ECI | >4 | 168 | 6 (0.9-9.0) | US | 2003-2005 | Pronk et al (2009) |

Miners

| | | | | | | | |
|---------------------------|------|------|-----|--------------|---------|-----------|--------------------|
| Surface production | ECS | >4 | 23 | 23 (15-54) | US | 1997 | Pronk et al (2009) |
| Surface production | ECR | >4 | 164 | 13 (2-89) | US | 2002 | Pronk et al (2009) |
| Underground maintenance | ECS | >4 | 8 | 53 (46) | US | 1997 | Pronk et al (2009) |
| Underground maintenance | ECR | >4 | 269 | 144 (17-462) | US | 2002 | Pronk et al (2009) |
| Underground not specified | ECR | NI | 7 | 66 (28) | UK | 2004 | Pronk et al (2009) |
| Underground not specified | ECNI | NI | 27 | 27 | Sweden | 2006 | Pronk et al (2009) |
| Underground production | ECR | >4 | 4 | 241 | Estonia | 2002 | Pronk et al (2009) |
| Underground production | ECR | >4 | 15 | 637 (75-508) | US | 1999 | Pronk et al (2009) |
| Underground production | ECI | <1-4 | 12 | 538 (512) | US | 2007 | Pronk et al (2009) |
| Underground production | ECS | >4 | 38 | 219 (65-193) | US | 1997 | Pronk et al (2009) |
| Underground production | ECR | >4 | 343 | 202 (32-144) | US | 2002 | Pronk et al (2009) |
| Underground production | ECR | NI | 6 | 148 (136) | UK | 2004 | Pronk et al (2009) |
| Underground production | ECR | 1->4 | 13 | 163 (141) | US | 2001-2002 | Pronk et al (2009) |

Others

| | | | | | | | |
|-------------------------------|------|----|----|-------------|--------|-----------|---------------------|
| Asphalt road pavers | ECR | >4 | 3 | 3 (0.2) | Sweden | 2005-2006 | Elihn et al (2008) |
| Baggage handling | ECI | >4 | 72 | 11 (5.4) | US | 2004 | Pronk et al (2009) |
| Bus service workers | ECI | >4 | 4 | 2>LOD:15-30 | US | 1998 | Pronk et al (2009) |
| Cleaners - general | ECNI | >1 | 4 | 22.4 (9.4) | UK | 1994-2001 | NEDB |
| Cleaners - locomotive | ECNI | >1 | 5 | 39.0 (9.4) | UK | 1996-2006 | NEDB |
| Concrete ring builders | ECR | >4 | 3 | 20 (8) | UK | 2014 | Galea et al. (2015) |
| Concrete ring segment lifters | ECR | >4 | 8 | 17 (8) | UK | 2014 | Galea et al. (2015) |
| Concrete sprayers | ECR | >4 | 7 | 57.41 | Norway | 2010-2011 | Bakke et al. (2014) |
| Conductors - locomotive | ECNI | >1 | 14 | 21.9 (36.8) | UK | 1994-2001 | NEDB |
| Construction engineers | ECR | >4 | 6 | 20 (7) | UK | 2014 | Galea et al. (2015) |
| Construction workers | ECI | >4 | 22 | 13 | Sweden | 2002-2004 | Pronk et al (2009) |
| Conveyor extension workers | ECR | >4 | 2 | 30 (3) | UK | 2014 | Galea et al. (2015) |

| | | | | | | | |
|---|------|------|-----|--------------|----------|-----------|-----------------------|
| Curbside waste collectors | ECR | >4 | 72 | 5.53 | S. Korea | 2014 | Lee et al. (2015) |
| Customer service workers - bus station | ECNI | >1 | 1 | 28.4 | UK | 2006 | NEDB |
| Customer service workers - locomotive platform | ECNI | >1 | 14 | 13.2 (6.9) | UK | 1996-2001 | NEDB |
| Drill and blast workers | ECR | >4 | 51 | 47.2 | Norway | 2010-2011 | Bakke et al. (2014) |
| Electric utility installers | ECI | >4 | 120 | 4 | US | 1996-1997 | Pronk et al (2009) |
| Electricians - railway station | ECNI | >1 | 7 | 39.5 (25.4) | UK | 1994-2006 | NEDB |
| Engineers - locomotive | ECI | 1->4 | 49 | 6 | US | 1996-1998 | Pronk et al (2009) |
| Forklift operators | ECR | >4 | 39 | 36 | UK | 2004 | Pronk et al (2009) |
| Forklift operators - warehouse | ECNI | >1 | 25 | 82.2 (130.8) | UK | 1994-2006 | NEDB |
| Gate controllers in booth | ECR | >4 | 29 | 1.8 | Canada | 2013 | Debia et al. (2016) |
| Grout pump operators | ECR | >4 | 1 | 110 | UK | 2014 | Galea et al. (2015) |
| Grout pump operators | ECR | >4 | 5 | 19 (6) | UK | 2014 | Galea et al. (2015) |
| Heavy/highway construction workers | ECR | >4 | 261 | 13 | US | 1994-1999 | Pronk et al (2009) |
| Highway toll booth workers | ECR | >4 | 63 | 6.1 (4) | China | 2002 | Shih et al (2008) |
| Hostlers - locomotive | ECNI | >4 | 5 | 4 (1.3) | Canada | 1999-2000 | Pronk et al (2009) |
| Hostlers - tractor | ECS | >4 | 4 | 1.3 (1) | US | 2006? | Sheesley et al (2008) |
| Labourers - various industries | ECNI | >1 | 20 | 60.9 (63.7) | UK | 1994-2006 | NEDB |
| Lead miners | ECR | >4 | 1 | 12 | UK | 2014 | Galea et al. (2015) |
| Loading and unloading workers - passenger ferries | ECNI | >1 | 10 | 46.2 (28.2) | UK | 1994-2006 | NEDB |
| Locomotive rail extension workers | ECR | >4 | 2 | 26 (6) | UK | 2014 | Galea et al. (2015) |
| Maintenance workers - locomotive | ECR | >4 | 64 | 39 | UK | 2000 | Pronk et al (2009) |
| Maintenance workers - locomotive | ECNI | >4 | 48 | 5 (4.9-8.8) | Canada | 1999-2000 | Pronk et al (2009) |
| Material loaders | ECR | >4 | 18 | 38.43 | Norway | 2010-2011 | Bakke et al. (2014) |
| Non-operating crew in trailing locomotive | ECI | >4 | 47 | 10 (12) | Canada | 2003 | Pronk et al (2009) |

| | | | | | | | |
|---|------|----|----|-------------|--------|-----------|---------------------------|
| Parking booth attendants | ECR | >4 | 34 | 1.1 (0.6) | US | 2002 | Pronk et al (2009) |
| Pipe/walkway extension workers | ECR | >4 | 2 | 18 (2) | UK | 2014 | Galea et al. (2015) |
| Porters - warehouse | ECNI | >1 | 3 | 30.4 (35.1) | UK | 1994-2006 | NEDB |
| Security guards | ECNI | >1 | 2 | 60.9 (2.1) | UK | 1994 | NEDB |
| Support workers | ECR | >4 | 31 | 76.14 | Norway | 2010-2011 | Bakke et al. (2014) |
| Toll attendants/cashiers | ECNI | >1 | 22 | 30.5 (22.3) | UK | 1994-2006 | NEDB |
| Tunnel boring machine operators | ECR | >4 | 5 | 17 (5) | UK | 2014 | Galea et al. (2015) |
| Tunnel construction workers | ECI | >4 | 10 | 314 | Norway | 1996-1999 | Pronk et al (2009) |
| Tunnel construction workers | ECI | >4 | 12 | 132 | Sweden | 2002-2004 | Pronk et al (2009) |
| Unloading equipment operator - shipyard | ECNI | >1 | 10 | 37.6 (24.9) | UK | 2006 | NEDB |
| Vehicle inspectors | ECNI | >1 | 2 | 21.8 (5.1) | UK | 1999 | NEDB |
| Vehicle testing workers | ECR | >4 | 11 | 11 | UK | 2000 | Pronk et al (2009) |
| Waterproofing workers | ECR | >4 | 13 | 64.82 | Norway | 2010-2011 | Bakke et al. (2014) |
| Workers in trailing locomotive | ECR | >4 | 22 | 11.1 | US | 1996-2007 | Hewett and Bullock (2014) |

*Table partially adapted from Tables 1-4 in review by Pronk and colleagues ².

†ECR: respirable elemental carbon; ECS: submicron elemental carbon; ECI: inhalable elemental carbon; ECNI: elemental carbon size fraction not indicated.

Table E7: Job codes and descriptions for List A jobs included in study population

| ISCO-68* | Job description |
|-----------------|---|
| 03810 | mining technicians (general) |
| 55130 | janitor |
| 55220 | charworker |
| 55290 | other charworkers, cleaners and related workers |
| 58110 | fire fighter (general) |
| 58190 | other fire-fighters |
| 62330 | vineyard worker |
| 70000 | production supervisors and general foremen |
| 70010 | production supervisors and general foremen (general) |
| 70020 | supervisors and general foreman, mining, quarrying and well drilling |
| 70030 | supervisors and general foreman, metal processing |
| 70050 | supervisor and general foreman, manufacturing of machinery and metal products |
| 70055 | supervisor and general foreman, manufacturing and installation of electrical and electronic equipment |
| 70075 | supervisor and general foreman, construction work |
| 70080 | supervisor and general foreman, production and distribution of electricity, gas and water |
| 70090 | other production supervisors and general foremen |
| 71100 | miners and quarrymen |
| 71105 | miner (general) |
| 71110 | quarryman (general) |
| 71120 | cutting-machine operator (mine) |
| 71130 | drilling-machine operator (mine and quarry) |
| 71150 | shot-firer (mine and quarry) |

| | |
|-------|---|
| 71160 | underground timberman |
| 71170 | sampler (mine) |
| 71190 | other miners and quarrymen |
| 71250 | jig tender |
| 71290 | other mineral and stone treaters |
| 72000 | metal processers |
| 72100 | metal smelting, converting and refining furnacemen |
| 72120 | blast furnaceman (ore smelting) |
| 72130 | open-hearth furnacemen (steel) |
| 72170 | furnaceman (non-ferrous metal converting and refining) |
| 72190 | other metal smelting, converting and refining furnacemen |
| 72220 | hot-roller (steel) |
| 72230 | continuous-mill-roller (steel) |
| 72250 | roller (non-ferrous metals) |
| 72260 | seamless pipe and tube roller |
| 72290 | other metal rolling-mill workers |
| 72320 | furnaceman (metal melting, except cupola) |
| 72330 | cupola furnaceman |
| 72340 | furnaceman (metal reheating) |
| 72390 | other metal melters and reheaters |
| 72400 | metal casters |
| 72420 | metal pourer |
| 72440 | die-casting-machine operator |
| 72450 | continuous rod-casting-machine operator (non-ferrous metal) |
| 72490 | other metal casters |

| | |
|-------|---|
| 72500 | metal moulders and coremakers |
| 72520 | bench moulder (metal) |
| 72530 | floor and pit moulder |
| 72540 | moulder (machine) |
| 72550 | coremaker (hand) |
| 72560 | coremaker (machine) |
| 72590 | other metal moulders and coremakers |
| 72620 | annealer |
| 72630 | hardener |
| 72700 | metal drawers and extruders |
| 72730 | wire drawer (machine) |
| 72740 | seamless pipe and tube drawer |
| 72750 | extruder operator (metal) |
| 72800 | metal platers and coaters |
| 72820 | electroplater |
| 72830 | hot-dip plater |
| 72840 | wire-coating-machine operator |
| 72890 | other metal platers and coaters |
| 72900 | metal processors not elsewhere classified |
| 72920 | metal bluer |
| 72930 | casting finisher |
| 72940 | metal cleaner |
| 72990 | other metal processors |
| 73210 | sawmill sawyer (general) |
| 74140 | mixing-and blending-machine operator (chemical and related processes) |

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| 74230 | roaster (chemical and related processes) |
| 74290 | other cookers, roasters and related heat-treaters |
| 74390 | other filter and separator operators |
| 74920 | coke burner |
| 74925 | coal-glass maker |
| 74990 | other chemical processors and related workers |
| 75290 | other spinners and winders |
| 79630 | vehicle upholsterer |
| 79690 | other upholsterers and related workers |
| 81120 | cabinetmaker |
| 81230 | wood turner |
| 81920 | coach-body builder |
| 81925 | cartwright |
| 81935 | wooden pattern maker |
| 81955 | wooden furniture finisher |
| 81960 | smoking-pipe maker |
| 83000 | blacksmiths, toolmakers and machine-tool operators |
| 83100 | blacksmiths, hammersmiths and forging-press operators |
| 83110 | blacksmith (general) |
| 83120 | hammersmith |
| 83130 | drop-hammer operator |
| 83140 | forging-press operator |
| 83190 | other blacksmiths, hammersmiths and forging-press operators |
| 83220 | tool and die maker |
| 83240 | metal pattern maker (foundry) |

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| 83250 | metal marker |
| 83290 | other toolmakers, metal pattern makers and metal markers |
| 83305 | metalworking-machine setter (general) |
| 83310 | metalworking-machine setter-operator (general) |
| 83320 | lathe setter-operator |
| 83330 | milling-machine setter-operator |
| 83350 | boring-machine setter-operator |
| 83370 | precision-grinding-machine setter-operator |
| 83390 | other machine-tool setter-operators |
| 83410 | machine-tool operator (general) |
| 83420 | lathe operator |
| 83430 | milling-machine-operator |
| 83440 | planing-machine-operator |
| 83450 | boring-machine-operator |
| 83460 | drilling-machine-operator |
| 83465 | precision-grinding-machine-operator |
| 83490 | other machine-tool operators |
| 83520 | buffing- and polishing machine operator |
| 83530 | tool grinder, machine tools |
| 83590 | other metal grinders, polishers and tool sharpeners |
| 83930 | locksmith |
| 83940 | metal spinner |
| 83950 | metal former (hand) |
| 83960 | metal-press operator |
| 83980 | power-shear operator |

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| 83990 | other blacksmiths, toolmakers and machine-tool operators |
| 84100 | machinery fitters and machine assemblers |
| 84105 | machinery fitter (general) |
| 84110 | machinery fitter-assembler (general) |
| 84115 | internal combustion engine fitter-assembler (except aircraft and marine engines) |
| 84125 | marine engine machinery fitter-assembler |
| 84130 | turbine fitter-assembler (except aircraft and marine engines) |
| 84135 | metalworking machine-tool fitter-assembler |
| 84175 | machinery erector and installer |
| 84180 | refrigeration and air-conditioning plan installer and mechanic |
| 84190 | other machinery fitters and machine assemblers |
| 84230 | precision -instrument maker and repairer |
| 84320 | automobile mechanic |
| 84330 | motor-truck mechanic |
| 84390 | other motor-vehicle mechanics |
| 84410 | aircraft engine mechanic (general) |
| 84490 | other aircraft engine mechanics |
| 84900 | machinery fitters, machine assemblers and precision instrument makers (except electrical) not elsewhere classified |
| 84910 | machinery mechanic (general) |
| 84915 | reciprocating steam-engine mechanic |
| 84920 | diesel engine mechanic (except motor vehicle) |
| 84930 | metalworking machine-tool mechanic |
| 84970 | plant maintenance mechanic |
| 84980 | oiler and greaser (except ships' engines) |

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| 84985 | mechanical products inspector and tester |
| 84990 | other machinery fitters, machine assemblers and precision instrument makers (except electrical) |
| 85110 | electrical fitter (general) |
| 85120 | electrical motor and generator fitter |
| 85130 | electrical transformer fitter |
| 85140 | electrical switchgear and control apparatus fitter |
| 85150 | electrical instrument fitter |
| 85190 | other electrical fitters |
| 85210 | electronics fitter (general) |
| 85250 | electronics fitter (industrial equipment) |
| 85260 | electronic signalling systems fitter |
| 85320 | electrical equipment assembler |
| 85340 | coil winder (machine) |
| 85420 | radio and television mechanic |
| 85510 | electrician (general) |
| 85520 | building electrician |
| 85530 | aircraft electrician |
| 85535 | ship's electrician |
| 85540 | vehicle electrician |
| 85560 | maintenance electrician |
| 85570 | electrical repairman |
| 85630 | telephone and telegraph mechanic |
| 85740 | telephone and telegraph lineman |
| 85920 | electrical and electronic products inspector and tester |
| 87000 | plumbers, welders, sheet metal and structural metal preparers and erectors |

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| 87105 | plumber (general) |
| 87110 | pipe fitter (general) |
| 87130 | marine pipe fitter |
| 87190 | other plumbers and pipe fitters |
| 87200 | welders and flame-cutters |
| 87210 | gas and electric welder (general) |
| 87215 | gas welder |
| 87220 | electric arc welder (hand) |
| 87225 | electric arc welder (machine) |
| 87235 | resistance welder |
| 87245 | brazier |
| 87250 | flame-cutter (hand) |
| 87255 | flame-cutter (machine) |
| 87290 | other welders and flame-cutters |
| 87300 | sheet-metal workers |
| 87310 | sheet-metal worker (general) |
| 87320 | sheet-metal marker |
| 87330 | coppersmith |
| 87340 | tinsmith |
| 87350 | boilersmith |
| 87370 | vehicle sheet-metal worker |
| 87390 | other sheet-metal workers |
| 87420 | structural metal maker |
| 87430 | structural steel worker (workshop) |
| 87440 | constructional steel erector |

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| 87450 | metal shipwright |
| 87455 | ship plater |
| 87460 | hand riveter |
| 87470 | pneumatic riveter |
| 87490 | other structural metal preparers and erectors |
| 90180 | plastics products fabricator |
| 90190 | other rubber and plastic product makers (except tire makers and tire vulcanisers) |
| 92200 | printing pressmen |
| 92700 | photographic darkroom workers |
| 93100 | painters, construction |
| 93120 | building painter |
| 93130 | structural steel and ship painter |
| 93190 | other painters, construction |
| 93900 | painters not elsewhere classified |
| 93920 | brush painter (except construction) |
| 93930 | spray painter (except construction) |
| 93940 | hand dipper |
| 93950 | sign painter |
| 93960 | automobile painter |
| 93990 | other painters |
| 94980 | quality inspector |
| 94990 | other production and related workers nec |
| 95120 | bricklayer (construction) |
| 95130 | firebrick layer |
| 95320 | slate and tile roofer |

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| 95330 | composition roofer |
| 95340 | asphalt roofer |
| 95390 | other roofers |
| 95400 | carpenters, joiners and parquetry workers |
| 95410 | carpenter (general) |
| 95415 | construction carpenter |
| 95420 | construction joiner |
| 95440 | wood shipwright |
| 95445 | ship joiner |
| 95450 | wooden boatbuilder |
| 95455 | ship's carpenter |
| 95470 | bench carpenter |
| 95475 | parquetry worker |
| 95490 | other carpenters, joiners and parquetry workers |
| 95620 | building insulator (hand) |
| 95650 | boiler and pipe insulator |
| 95790 | other glaziers |
| 95900 | construction workers not elsewhere classified |
| 95910 | housebuilder (general) |
| 95940 | scaffolder |
| 95975 | building exterior cleaner |
| 95990 | other construction workers |
| 96190 | other power-generating machinery operators |
| 96910 | stationary engine operator |
| 96930 | boiler fireman |

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| 96940 | pumping-station operator |
| 96980 | heating and ventilation equipment operator |
| 97100 | dockers and freight handlers |
| 97130 | railway and road vehicle loader |
| 97145 | warehouse porter |
| 97155 | machine packer |
| 97205 | hoisting equipment rigger (general) |
| 97230 | ship rigger |
| 97300 | crane and hoist operators |
| 97320 | bridge- or gantry-crane operator |
| 97327 | tower-crane operator |
| 97330 | mobile-crane operator |
| 97335 | hoist operator (construction) |
| 97345 | mine cageman |
| 97350 | winch operator |
| 97390 | other crane and hoist operators |
| 97445 | road-grader and scraper operator |
| 97450 | road-roller operator |
| 97460 | tar-spreading machine operator |
| 97920 | lifting-truck operator |
| 97990 | other material handling equipment operators |
| 98140 | ordinary seaman |
| 98190 | other ships' deck ratings, barge crews and boatman |
| 98290 | other ships' engine-room ratings |
| 98320 | railway engine driver |

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| 98330 | railway steam-engine fireman |
| 98420 | railway brakeman (freight train) |
| 98550 | lorry and van driver (local transport) |
| 98560 | lorry and van driver (long-distance transport) |
| 98590 | other motor-vehicle drivers |
| 99910 | labourer |

*ISCO-68: five-digit International Standard Classification of Occupations (version 1968); dashes and dots omitted.