

## Application of two job indices for general occupational demands in a pooled analysis of case-control studies on lung cancer

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**Running Head (max 60 characters)**

Lung cancer and general occupational demands

**Summary: what is new in the paper (ca. 60 words)**

For the first time, two indices for general physical and psychosocial job demands were applied to lung cancer data. Higher job demands were associated with increasing lung cancer risks. The associations were stronger for physical job demands and weaker for psychosocial job demands. Psychosocial job demands did not contribute to explain the association between occupational social prestige and lung cancer.

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### **Competing interests**

The authors do not declare any conflict of interest.

JH, SC, BP, TBr, and TB as staff of the Institute for Prevention and Occupational Medicine (IPA), are employed at the “Berufsgenossenschaft Rohstoffe und chemische Industrie” (BG RCI), a public body, which is a member of the study’s main sponsor, the German Social Accident Insurance. IPA is an independent research institute of the Ruhr University Bochum. The authors are independent from the German Social Accident Insurance in study design, access to the collected data, responsibility for data analysis and interpretation, and the right to publish. The views expressed in this paper are those of the authors and not necessarily those of the sponsor.

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.

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### **Contributorship**

JH, SC, DC, JS, KHJ, TBr, BP, and TBe interpreted the data and supported drafting of the manuscript. JH and SC were responsible for the statistical analysis. TBr, KS, HK,

RV, and AO conceived the design of the pooled analysis. KS, HK, and TBr are the main coordinators of this international consortium. All other authors were responsible for conception, design and data acquisition of the studies in their respective country. All authors contributed to the revision of the manuscript and approved the final version.

## **Abstract**

*Objectives:* We investigated general job demands as a risk factor for lung cancer as well as their role in the association between occupational prestige and lung cancer.

*Methods:* In 13 case-control studies on lung cancer of the international SYNERGY project, we applied indices for physical (PHI) and psychosocial (PSI) job demands – each with four categories (high to low). We estimated odds ratios (OR) and 95% confidence intervals (CI) for lung cancer by unconditional logistic regression, separately for men and women and adjusted for study centre, age, smoking behaviour, and former employment in occupations with potential exposure to carcinogens. Further, we investigated, whether higher risks among men with low occupational prestige (SIOPS - Treiman's Standard International Occupational Prestige Scale) were affected by adjustment for the job indices.

*Results:* In 30,355 men and 7,371 women, we found increased risks for lung cancer with high relative to low job demands in both men (OR (95%CI) PHI 1.74 (1.56-1.93), PSI 1.33 (1.17-1.51)) and women (PHI 1.62 (1.24-2.11), PSI 1.31 (1.09-1.56)). ORs for lung cancer in men with low occupational prestige were slightly reduced when adjusting for PHI (low vs. high prestige OR (95%CI) from 1.44 (1.32-1.58) to 1.30 (1.17-1.45)), but not PSI.

*Conclusions:* Higher physical job demands were associated with increased risks of lung cancer, while associations for higher psychosocial demands were less strong. In contrast to physical demands, psychosocial demands did not contribute to clarify the association of occupational prestige and lung cancer.



**Keywords:**

Social prestige; psychosocial; smoking; tumour subtype

## **Introduction**

Lung cancer risks are largely attributed to tobacco smoking, and occupational exposures to lung carcinogens (1, 2). Occupational social prestige and socioeconomic status are also identified as important risk factors, but apart from supposed residual effects of smoking and exposure to occupational carcinogens, the pathways from occupational social determinants to lung cancer remain uncertain (3–6). Occupational conditions including psychosocial strain have been associated with elevated lung cancer risk (7) and may help to understand increased risks for occupations with a lower societal standing. Occupational prestige assigns a position in a perceived, hierarchical order of occupations that particularly captures work- and rank-related psychosocial demands. In addition, as an occupational indicator, it reflects material aspects of subject's socioeconomic position (via income) and is directly linked with health outcomes by physical occupational hazards (8).

We extended analyses of the association between occupational prestige and lung cancer previously identified in the international SYNERGY project (3), to investigate the role of further occupational exposures in this association: To cover a broad range of exposures and with regard to available job histories in SYNERGY, we applied two job-title based indices for general occupational demands (9) that have not yet been applied in the context of lung cancer: an index for environmental/physical demands, potentially also indicating effects of occupational carcinogens, and an index for psychosocial occupational demands. To our knowledge, psychosocial demands have not been analysed yet together with occupational prestige and lung cancer.

Before extending analysis of occupational prestige, we examined if the two occupational indices themselves were associated with lung cancer and thus appropriate for further analysis. This could additionally show if the job-title based

indices are suitable for facilitated assessment of work environment risks when detailed occupational exposure information is not available.

Thus, in the first step we analysed the association of the two indices for general job demands and lung cancer, and in the second step the role of these demands in the association of occupational prestige and lung cancer.

## **Methods**

The detailed methodology employed in SYNERGY has been published elsewhere (10). For this analysis of lung cancer and job indices we included 13 European and Canadian case-control studies with 19 study centres of the SYNERGY dataset. Details and distribution of cases and controls are included in supplementary table S1. After exclusion of subjects with largely (>50%) missing or invalid occupational histories (n=1236) and missing smoking information (n=25), the dataset included 37,726 men and women (16,909 cases, 20,817 controls). To extend the previous social prestige analysis (3), we adapted inclusion criteria accordingly: prestige analyses were restricted to 12 studies (18 study centres) and to men (11,420 cases, 14,130 controls).

Job demands were assigned by two indices for general job demands (9). These indices were constructed and validated using German survey data for men and women and contain two/three dimensions of occupational demands: i) a physical index (PHI) for ergonomic demands and environmental exposures (including acid, dust, fumes, climatic conditions, radiation, environmental tobacco smoke (ETS), dirt, noise, vibrations, low/glaring light, or need for protective clothing) and ii) a psychosocial index (PSI) for mental (e.g. overload, disruptions, low error tolerance), social (e.g. lacking work control, conflicts, lacking support), and temporal (e.g. on-call service, excessive working hours, shift work) demands. Originally, both indices may be summarised to an

overall index, which we did not apply due to its high correlation with the PHI (Spearman correlation coefficient 0.95). We assigned both indices (range of 1-10 from low to high demands) to the subjects' entire occupational histories and calculated time-weighted average (TWA) scores. TWA-scores were categorised into four categories (low (1-2), lower middle (3-5), upper middle (6-8), and high demands (9-10) (9)). In sensitivity analyses, we recalculated scores disregarding the last 10 years before diagnosis/interview to consider cancer latency. In the opposite direction, we used the last job to rather consider job demand effects on tumour promotion or progression.

To estimate lung cancer risks for job-demand indices (PHI, PSI), we calculated odds ratios (OR) with 95% confidence intervals (CI) by unconditional multiple logistic regression in a pooled analysis of all studies. We first adjusted for age ( $\ln(\text{age})$ ) and study centre, then added smoking habits (smoking status (never (<1 pack-year in lifetime), former, current (including quitting smoking before <2 years), and other type of tobacco, including subdivision of former smokers by time since quitting smoking (2-7, 8-15, 16-25, >25 years)) and cigarette pack-years ( $\ln(\text{pack-years} + 1)$ ), and finally added ever employment in occupations and industries known to be associated with lung cancer with potential exposure to carcinogens ('list A' occupations) (12, 13) (final model). ORs were estimated separately for main histological lung cancer subtypes (squamous cell carcinoma (SQCC), small cell lung cancer (SCLC), adenocarcinoma (ADC)). In addition, job-demand indices were included as continuous variables to test for linear trends. To consider effects of individual studies, we compared results from the pooled analyses with meta-analyses (random-effects model) using the Paule–Mandel heterogeneity variance estimator (14) and displayed heterogeneity by  $I^2$ .

For the prestige analysis, we adopted TWA prestige scores of Treiman's Standard International Occupational Prestige Scale (SIOPS) (15), based on subject's

occupational history, and categorised it into low, medium, and high TWA prestige (3). We repeated models according to the original publication, adjusting for factors mentioned above (final model), education (<6 years, 6–9 years, 10–13 years, >13 years), and additionally the respective job index.

All calculations were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC).

## **Results**

Descriptive information on the study population is shown in table 1. Both indices revealed higher job demands for cases than controls, with less pronounced differences for women and for psychosocial exposures. TWA prestige was lower among cases.

In regression analysis (table 2), we found a gradient of lung cancer risks for increasing PHI in men (high vs. low OR (95%CI) 1.74 (1.56-1.93)) and women (1.62 (1.24-2.11)) in the final models. Estimates for highest vs. lowest PSI were lower than for PHI in men (OR (95%CI) 1.33 (1.17-1.51)) and women (1.31 (1.09-1.56)). Despite consistently significant tests for trend, risks were elevated just for the highest psychosocial demands in women. Only in men, risks decreased particularly after adjustment for smoking, and less after adjustment for 'list A' industries/occupations. Increased risks for higher job demands were detected for SQCC and SCLC, but not for ADC. Estimates of the random-effects model were slightly reduced compared to those of the one-stage regression (high vs. low OR (95% CI) PHI: men 1.61 (1.30-1.99), women 1.53 (1.14-2.06) PSI: men 1.29 (1.11-1.50), women 1.23 (0.89-1.69)). Statistically significant heterogeneity between the studies was only found for PHI in men ( $I^2=60\%$ ,  $p<0.001$ ). Both sensitivity analyses, assuming 10-year lag time and restriction to the last job, showed slightly reduced estimates for men and women, except slightly elevated ORs for PHI for the last job in women (supplementary table S2).

In the analysis of occupational prestige in men, lung cancer risks for low and medium vs. high prestige (OR (95%CI) 1.44 (1.32-1.58), 1.23 (1.13-1.34), respectively) were reduced by additional adjustment for PHI (low prestige 1.30 (1.17-1.45), medium prestige 1.14 (1.04-1.26)), but not for PSI (low prestige 1.46 (1.33-1.61), medium prestige 1.24 (1.14-1.35)).

## **Discussion**

In our analysis of lung cancer and job-demand indices in men and women, we found elevated lung cancer risks in particular for high physical job demands, and less strong associations for psychosocial job demands. Adjustment for PHI reduced lung cancer risks of men with low occupational prestige, but adjustment for PSI did not influence results.

We made use of the large SYNERGY database with its detailed smoking information and occupational histories. Previous SYNERGY analyses have identified possible residual effects of smoking due to potential information bias, lacking data on ETS, and possibly the inclusion of occasional smokers among non-smokers (defined by <1 cigarette pack-year) (3, 4). Similarly, we confirmed higher risks for higher job demands in the subtypes of lung cancer that are particularly related to smoking (SQCC, SCLC) and decreased risks for ADC (3, 4, 16). A potential limitation lies in the German data base of the job indices, which we applied to international data. However, these data were all from (post-)industrial countries (Europe and Canada), and results of the random-effects model, considering study-specific variances, were similar to pooled estimates.

The applied job indices were constructed to allow assignment of general occupational demands on the basis of occupational job codes in the absence of more detailed

information (9), which are included in SYNERGY for selected occupational carcinogens. We considered occupational lung carcinogens in general by ever exposure in 'list A' industries and occupations, a simplified exposure assessment. Occupational carcinogens therefore may also mainly account for the elevated risks for higher physical job index, i.e. manual jobs, which may also include exposure to occupational fumes, dusts, and ETS. The reduction of risks of lower prestige occupations by adjustment for PHI might account for these previously uncaptured exposures to occupational carcinogens. Therefore, the physical index appears as crude but easily applicable proxy for occupational lung cancer hazards when only job titles were solicited.

Associations with lung cancer were lower for psychosocial job demands compared to physical demands. However, the PSI includes indicators for potential (lung) cancer risk factors, in particular chronic stress. Our results were similar to one study on lung cancer and work-related stress in men (7), while other studies did not find significantly increased risks (17, 18). We found an overall pattern of higher lung cancer risks for men, increasing with job demands, but no increase of risks for women with moderate psychosocial demands. The reasons for this finding remain unclear, also because the job indices were constructed for men and women.

Generally, methodological issues in the assignment of job demands are critical in occupational cancer risk estimation as shown for two analyses of oesophageal cancer and psychosocial exposures (19, 20): one of which used personal questionnaires on job strain exposure and did not find an association for higher job strain (19), whereas in contrast, increased risks were detected when deducing job strain from job titles (20). However, in comparison to physical demands, derivation of psychosocial dimensions by objective job titles may be limited and dependent more on individual characteristics

(9). This could explain why the observed associations were lower compared to the physical demands. This limitation has to be considered particularly for our analysis of occupational prestige and lung cancer, i.e., we could have missed possible effects by adjusting for psychosocial job demands due to insufficient capture of these demands by job titles.

## **Conclusion**

The job-title based indices suggested a role of occupational demands for lung cancer, beyond exposure to known occupational carcinogens, and their application in understanding work environment risks in the absence of detailed quantitative occupational exposure information. Lung cancer risks were particularly increased for higher physical job demands, likely due to capturing undetermined effects of occupational lung carcinogens. The index for psychosocial demands was less clearly associated with lung cancer, and – in contrast to physical demands – did not contribute to clarify the association of occupational prestige and lung cancer.



## References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68(6):394–424.
2. GBD 2016 Occupational Carcinogens Collaborators. Global and regional burden of cancer in 2016 arising from occupational exposure to selected carcinogens: a systematic analysis for the Global Burden of Disease Study 2016. *Occup Environ Med* 2020; 77(3):151–9.
3. Behrens T, Gross I, Siemiatycki J, Conway DI, Olsson A, Stucker I et al. Occupational prestige, social mobility and the association with lung cancer in men. *BMC Cancer* 2016; 16:395.
4. Hovanec J, Siemiatycki J, Conway DI, Olsson A, Stücker I, Guida F et al. Lung cancer and socioeconomic status in a pooled analysis of case-control studies. *PLoS ONE* 2018; 13(2):e0192999.
5. Menvielle G, Franck J, Radoï L, Sanchez M, Févotte J, Guizard A-V et al. Quantifying the mediating effects of smoking and occupational exposures in the relation between education and lung cancer: the ICARE study. *Eur J Epidemiol* 2016:1–9.
6. Menvielle G, Dugas J, Franck J, Carton M, Trétarre B, Stücker I, et al. Occupational prestige trajectory and the risk of lung and head and neck cancer among men and women in France. *Int J Public Health* 2018;63:833–45.
7. Blanc-Lapierre A, Rousseau M-C, Weiss D, El-Zein M, Siemiatycki J, Parent M-É. Lifetime report of perceived stress at work and cancer among men: A case-control study in Montreal, Canada. *Prev Med* 2017; 96:28–35.
8. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health* 2006;60:7–12.
9. Kroll LE. Konstruktion und Validierung eines allgemeinen Index für die Arbeitsbelastung in beruflichen Tätigkeiten anhand von ISCO-88 und KldB-92. *Methoden – Daten – Analysen* 2011; 5(1):63–90.
10. Olsson AC, Gustavsson P, Kromhout H, Peters S, Vermeulen R, Brüske I et al. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from

- case-control studies in Europe and Canada. *Am J Respir Crit Care Med* 2011; 183(7):941–8.
11. Santi I, Kroll LE, Dietz A, Becher H, Ramroth H. Occupation and educational inequalities in laryngeal cancer: The use of a job index. *BMC Public Health* 2013; 13:1080.
  12. Ahrens W, Merletti F. A standard tool for the analysis of occupational lung cancer in epidemiologic studies. *Int J Occup Environ Health* 1998; 4(4):236–40.
  13. Mirabelli D, Chiusolo M, Calisti R, Massacesi S, Richiardi L, Nesti M et al. Database of occupations and industrial activities that involve the risk of pulmonary tumors. *Epidemiol Prev* 2001; 25(4-5):215–21.
  14. Paule RC, Mandel J. Consensus Values and Weighting Factors. *J Res Natl Bur Stand* 1982; 87:377–85.
  15. Treiman DJ. *Occupational Prestige in Comparative Perspective*. Burlington: Elsevier Science; 1977. Available from:  
URL:<http://gbv.ebib.com/patron/FullRecord.aspx?p=1875253>.
  16. Pesch B, Kendzia B, Gustavsson P, Jöckel K-H, Johnen G, Pohlmann H et al. Cigarette smoking and lung cancer—relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer* 2012; 131(5):1210–9.
  17. Heikkilä K, Nyberg ST, Theorell T, Fransson EI, Alfredsson L, Bjorner JB et al. Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116,000 European men and women. *BMJ (Clinical research ed.)* 2013; 346:f165.
  18. Vesterlund GK, Høeg BL, Johansen C, Heitmann BL, E Bidstrup P. Prolonged job strain and subsequent risk of cancer in women - a longitudinal study, based on the Danish Nurse Cohort. *Acta oncologica (Stockholm, Sweden)* 2017; 56(2):301–6.
  19. Jansson C, Johansson ALV, Jeding K, Dickman PW, Nyrén O, Lagergren J. Psychosocial working conditions and the risk of esophageal and gastric cardia cancers. *Eur J Epidemiol* 2004; 19(7):631–41.
  20. Jansson C, Jeding K, Lagergren J. Job strain and risk of esophageal and cardia cancers. *Cancer Epidemiol* 2009; 33(6):473–5.

## Tables

**Table 1. Study population**

	Men				Women			
	Cases (n=13,791)		Controls (n=16,564)		Cases (n=3118)		Controls (n=4253)	
	Median		Median		Median		Median	
	n (%)	(IQR)	n (%)	(IQR)	n (%)	(IQR)	n (%)	(IQR)
Age (years)		63 (56-69)		63 (56-69)		61 (53-69)		61 (52-69)
Smoking status								
Non-smoker	393 (2.9)		4489 (27.1)		877 (28.1)		2689 (63.2)	
Former smoker	4829 (35.0)		7052 (42.6)		591 (19.0)		737 (17.3)	
Current smoker	8423 (61.1)		4680 (28.3)		1650 (52.9)		826 (19.4)	
Other types of tobacco only	146 (1.1)		343 (2.1)		0 (0)		1 (0)	
Cigarette pack-years in former and current smokers		39 (27-54)		25 (12-40)		31 (20-45)		17 (8-30)
Subtype of lung cancer								
Squamous cell carcinoma	5904 (42.8)				627 (20.1)			
Small cell	2226 (16.1)				502 (16.1)			
Adenocarcinoma	3391 (24.6)				1354 (43.4)			
Other/mixed	1401 (15.9)				622 (20.0)			
Missing	80 (0.6)				13 (0.4)			
Ever worked in list A occupations/industries <sup>a</sup>								
Yes	2038 (14.8)		1559 (9.4)		80 (2.6)		53 (1.3)	
	11753		15005					
No	(85.2)		(90.6)		3038 (97.4)		4200 (98.8)	

Physical job exposure				
Low	854 (6.2)	1743 (10.5)	212 (6.8)	332 (7.8)
Lower middle	2727 (19.8)	4906 (29.6)	1214 (38.9)	1963 (46.2)
Upper middle	4739 (34.4)	5187 (31.3)	1358 (43.6)	1611 (37.9)
High	5471 (39.7)	4728 (28.5)	334 (10.7)	347 (8.2)
Psychosocial job exposure				
Low	740 (5.4)	1398 (8.4)	483 (15.5)	695 (16.3)
Lower middle	4356 (31.6)	5695 (34.4)	691 (22.2)	1020 (24.0)
Upper middle	6934 (50.3)	7528 (45.5)	1220 (39.1)	1797 (42.3)
High	1761 (12.8)	1943 (11.7)	724 (23.2)	741 (17.4)
Occupational prestige <sup>b</sup>				
High	2209 (19.3)	4586 (32.5)		
Medium	3975 (34.8)	4847 (34.3)		
Low	5236 (45.9)	4697 (33.2)		

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IQR – interquartile range

<sup>a</sup> Occupations and industries known to be associated with lung cancer

<sup>b</sup> Analysis restricted to men and with reduced data set (11,420 cases and 14,130 controls)

**Table 2. Associations between lung cancer and job-exposure indices**

Lung cancer type	Men					Women					
	Job index	Cases	Controls	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>b</sup>	OR (95% CI) <sup>c</sup>	Cases	Controls	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>b</sup>	OR (95% CI) <sup>c</sup>
<b>All lung cancers</b>											
<b>PHI</b>											
Low	854	1743	1.00	1.00	1.00	212	332	1.00	1.00	1.00	
Lower middle	2727	4906	1.08 (0.98-1.19)	1.06 (0.95-1.18)	1.05 (0.95-1.17)	1214	1963	0.99 (0.81-1.19)	1.07 (0.86-1.33)	1.07 (0.86-1.33)	
Upper middle	4739	5187	1.82 (1.66-1.99)	1.47 (1.32-1.63)	1.43 (1.29-1.59)	1358	1611	1.30 (1.08-1.58)	1.34 (1.08-1.66)	1.32 (1.06-1.64)	
High	5471	4728	2.27 (2.07-2.49)	1.82 (1.64-2.02)	1.74 (1.56-1.93)	334	347	1.44 (1.14-1.82)	1.66 (1.27-2.16)	1.62 (1.24-2.11)	
<b>PSI</b>											
Low	740	1398	1.00	1.00	1.00	483	695	1.00	1.00*	1.00*	
Lower middle	4356	5695	1.47 (1.33-1.62)	1.29 (1.15-1.44)	1.25 (1.12-1.40)	691	1020	0.98 (0.84-1.15)	1.01 (0.85-1.20)	1.00 (0.84-1.19)	
Upper middle	6934	7528	1.75 (1.59-1.93)	1.41 (1.26-1.57)	1.35 (1.21-1.51)	1220	1797	0.98 (0.86-1.13)	0.97 (0.83-1.14)	0.96 (0.82-1.12)	
High	1761	1943	1.75 (1.56-1.95)	1.37 (1.21-1.56)	1.33 (1.17-1.51)	724	741	1.46 (1.24-1.71)	1.32 (1.10-1.58)	1.31 (1.09-1.56)	
<b>SQCC</b>											
<b>PHI</b>											
Low	283	1743	1.00	1.00	1.00	26	332	1.00	1.00	1.00	
Lower middle	1061	4906	1.21 (1.05-1.40)	1.18 (1.01-1.38)	1.18 (1.01-1.38)	227	1963	1.43 (0.93-2.20)	1.50 (0.93-2.40)	1.50 (0.93-2.40)	

Lung cancer type	Men					Women					
	Job index	Cases	Controls	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>b</sup>	OR (95% CI) <sup>c</sup>	Cases	Controls	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>b</sup>	OR (95% CI) <sup>c</sup>
Upper middle	2063	5187	2.27 (1.98-2.61)	1.84 (1.58-2.13)	1.81 (1.55-2.10)	306	1611	2.08 (1.36-3.20)	2.26 (1.41-3.62)	2.26 (1.41-3.62)	
High	2497	4728	2.99 (2.60-3.42)	2.38 (2.05-2.76)	2.31 (1.99-2.68)	68	347	1.93 (1.18-3.16)	2.47 (1.44-4.25)	2.47 (1.43-4.25)	
<b>PSI</b>											
Low	295	1398	1.00	1.00	1.00	81	695	1.00	1.00	1.00	
Lower middle	1813	5695	1.54 (1.34-1.77)	1.34 (1.15-1.56)	1.30 (1.12-1.52)	117	1020	0.91 (0.67-1.24)	1.03 (0.73-1.46)	1.03 (0.73-1.45)	
Upper middle	3043	7528	1.89 (1.65-2.16)	1.50 (1.30-1.74)	1.45 (1.25-1.68)	272	1797	1.21 (0.92-1.58)	1.35 (0.99-1.83)	1.34 (0.99-1.82)	
High	753	1943	1.85 (1.59-2.16)	1.41 (1.19-1.68)	1.38 (1.16-1.64)	157	741	1.64 (1.22-2.21)	1.59 (1.14-2.23)	1.59 (1.14-2.22)	
<b>SCLC</b>											
<b>PHI</b>											
Low	131	1743	1.00	1.00*	1.00	39	332	1.00	1.00	1.00	
Lower middle	406	4906	1.05 (0.85-1.29)	1.01 (0.81-1.26)	1.00 (0.81-1.25)	161	1963	0.76 (0.52-1.11)	0.77 (0.49-1.19)	0.76 (0.49-1.18)	
Upper middle	791	5187	1.99 (1.64-2.42)	1.52 (1.23-1.87)	1.49 (1.21-1.83)	238	1611	1.29 (0.89-1.88)	1.31 (0.85-2.01)	1.29 (0.84-1.98)	
High	898	4728	2.47 (2.04-3.00)	1.90 (1.55-2.34)	1.83 (1.48-2.25)	64	347	1.70 (1.09-2.65)	2.05 (1.21-3.48)	1.97 (1.16-3.34)	
<b>PSI</b>											
Low	95	1398	1.00	1.00	1.00*	65	695	1.00	1.00	1.00	

Lung cancer type <i>Job index</i>	Men					Women				
	Cases	Controls	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>b</sup>	OR (95% CI) <sup>c</sup>	Cases	Controls	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>b</sup>	OR (95% CI) <sup>c</sup>
Lower middle	720	5695	1.81 (1.45-2.26)	1.56 (1.23-1.98)	1.51 (1.19-1.92)	109	1020	1.15 (0.83-1.60)	1.19 (0.82-1.74)	1.18 (0.81-1.72)
Upper middle	1126	7528	2.17 (1.74-2.70)	1.66 (1.31-2.09)	1.59 (1.26-2.01)	197	1797	1.18 (0.87-1.59)	1.27 (0.90-1.80)	1.24 (0.88-1.76)
High	285	1943	2.21 (1.73-2.82)	1.65 (1.27-2.15)	1.61 (1.24-2.1)	131	741	2.10 (1.52-2.90)	1.98 (1.36-2.88)	1.93 (1.32-2.82)
<b>ADC</b>										
<b><i>PHI</i></b>										
Low	259	1743	1.00	1.00	1.00	86	332	1.00*	1.00*	1.00*
Lower middle	841	4906	1.11 (0.96-1.30)	1.11 (0.95-1.31)	1.10 (0.94-1.30)	575	1963	1.06 (0.81-1.37)	1.10 (0.84-1.45)	1.10 (0.83-1.45)
Upper middle	1095	5187	1.41 (1.22-1.64)	1.17 (1.00-1.38)	1.14 (0.97-1.33)	551	1611	1.24 (0.95-1.61)	1.25 (0.95-1.65)	1.24 (0.94-1.64)
High	1196	4728	1.65 (1.42-1.91)	1.37 (1.17-1.60)	1.28 (1.09-1.51)	142	347	1.45 (1.05-1.99)	1.60 (1.15-2.24)	1.57 (1.12-2.20)
<b><i>PSI</i></b>										
Low	232	1398	1.00	1.00 <sup>†</sup>	1.00 <sup>†</sup>	239	695	1.00 <sup>†</sup>	1.00 <sup>†</sup>	1.00 <sup>†</sup>
Lower middle	1105	5695	1.21 (1.03-1.41)	1.07 (0.91-1.27)	1.04 (0.88-1.23)	306	1020	0.92 (0.75-1.12)	0.92 (0.74-1.13)	0.91 (0.74-1.12)
Upper middle	1625	7528	1.34 (1.15-1.57)	1.11 (0.94-1.30)	1.06 (0.90-1.25)	523	1797	0.87 (0.73-1.04)	0.87 (0.72-1.05)	0.86 (0.71-1.04)
High	429	1943	1.35 (1.13-1.61)	1.10 (0.91-1.32)	1.07 (0.88-1.29)	286	741	1.17 (0.95-1.44)	1.09 (0.87-1.35)	1.08 (0.87-1.34)

ADC – adeno carcinoma, PHI – physical index, PSI – psychosocial index, SCLC – small cell lung cancer, SQCC- squamous cell carcinoma

All tests for linear trend with  $p < 0.001$ , except for \*  $p < 0.05$  and †  $p > 0.05$

<sup>a</sup> Odds ratio with 95% confidence interval adjusted for  $\ln(\text{age})$  and study centre.

<sup>b</sup> Odds ratio with 95% confidence interval adjusted for  $\ln(\text{age})$ , study centre, smoking status including time since quitting (non-smoker, quitted 2-7, 8-15, 16-25, >26 years before interview/diagnosis, current smoker, other types of tobacco only) and cigarette pack-years ( $\ln(\text{pack-years}+1)$ ).

<sup>c</sup> Odds ratio with 95% confidence interval adjusted for  $\ln(\text{age})$ , study centre, smoking status including time since quitting (non-smoker, quitted 2-7, 8-15, 16-25, >26 years before interview/diagnosis, current smoker, other types of tobacco only) and cigarette pack-years ( $\ln(\text{pack-years}+1)$ ) and ever employment in occupations and industries with potential exposure to carcinogens.



## Supplementary tables

**Table S1. Description of selected case-control studies of the SYNERGY data base**

Study	Country	Recruitment period	Cases <sup>a</sup>				Controls				Type of control recruitment <sup>c</sup>	Type of interview
			Resp <sup>b</sup>	Men	Women	n	Resp <sup>b</sup>	Men	Women	n		
AUT	Germany	1990–1995	77%	2656	499	3155	41%	2699	524	3223	P	Face-to-face
CAPUA	Spain	2000–2009	91%	640	51	691	96%	587	62	649	H	Face-to-face
EAGLE	Italy	2002–2005	87%	1525	358	1883	72%	1600	456	2056	P	Face-to-face
HdA	Germany	1988–1993	69%	838	161	999	68%	835	158	993	P	Face-to-face
ICARE	France	2001–2006	80%	2209	572	2781	76%	2742	713	3455	P	Face-to-face <sup>d</sup>
INCO	Czech. Rep.	1999–2002	94%	235	67	302	80%	292	158	450	H	Face-to-face
INCO	Hungary	1998–2001	90%	308	78	386	100%	243	56	299	H	Face-to-face
INCO	Poland	1998–2002	88%	547	237	784	88%	567	259	826	H/P	Face-to-face
INCO	Romania	1998–2002	90%	140	37	177	99%	149	68	217	H	Face-to-face
INCO	Russia	1998–2001	96%	519	79	598	90%	503	77	580	H	Face-to-face
INCO	Slovakia	1998–2002	90%	285	57	342	84%	236	48	284	H	Face-to-face
INCO	UK	1998–2005	78%	281	150	431	84%	572	327	899	P	Face-to-face
LUCA	France	1989–1992	98%	296	0	296	98%	293	0	293	H	Face-to-face
LUCAS	Sweden	1985–1990	87%	1009	0	1009	85%	2285	0	2285	P	Mail, telephone <sup>d</sup>
MONTREAL	Canada	1996–2002	85%	710	403	1113	69%	891	541	1432	P	Face-to-face <sup>d</sup>

PARIS	France	1988–1992	95%	161	8	169	95%	215	11	226	H	Face-to-face
ROME	Italy	1993–1996	74%	291	35	326	63%	261	61	322	H	Face-to-face
TORONTO	Canada	1997–2002	62%	192	184	376	71%	355	484	839	H/P	Face-to-face
TURIN/VENETO	Italy	1990–1994	79%	949	142	1091	80%	1239	250	1489	P	Face-to-face
Total		1985–2009		13,791	3118	16,909		16,564	4253	20,817		

<sup>a</sup> Histologically confirmed lung cancer cases

<sup>b</sup> Response rate

<sup>c</sup> H – hospital, P - population

<sup>d</sup> Including next-of-kin interviews

**Table S2. Sensitivity analyses for associations between lung cancer and job-exposure indices: disregarding last 10 years of job history (lag time), restriction to last job**

Job index	Ten years lag time		Last job	
	Men	Women	Men	Women
	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>a</sup>
<b><i>PHI</i></b>				
Low	1.00	1.00	1.00	1.00
Lower middle	1.02 (0.91-1.14)	0.99 (0.79-1.24)	1.02 (0.94-1.12)	1.30 (1.09-1.57)
Upper middle	1.41 (1.27-1.57)	1.23 (0.98-1.54)	1.34 (1.23-1.46)	1.57 (1.31-1.89)
High	1.66 (1.49-1.85)	1.48 (1.13-1.93)	1.62 (1.49-1.76)	1.75 (1.39-2.21)
<b><i>PSI</i></b>				
Low	1.00	1.00	1.00	1.00
Lower middle	1.23 (1.10-1.38)	0.95 (0.80-1.13)	1.26 (1.15-1.38)	1.05 (0.89-1.25)
Upper middle	1.32 (1.19-1.48)	0.99 (0.85-1.16)	1.30 (1.19-1.42)	0.92 (0.79-1.06)
High	1.32 (1.16-1.50)	1.25 (1.05-1.49)	1.28 (1.16-1.41)	1.29 (1.11-1.50)

PHI – physical index, PSI – psychosocial index

<sup>a</sup>Odds ratio with 95% confidence interval adjusted for ln(age), study centre, smoking status including time since quitting (non-smoker, quit 2-7, 8-15, 16-25, >26 years before interview/diagnosis, current smoker, other types of tobacco only) and cigarette pack-years (ln(pack-years+1)) and ever employment in occupations and industries with potential exposure to carcinogens.