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Systematic Reviews and Meta- and Pooled Analyses

Welding and Lung Cancer in a Pooled Analysis of Case-Control Studies

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Several epidemiologic studies have indicated an increased risk of lung cancer among welders. We used the SYNERGY project database to assess welding as a risk factor for developing lung cancer. The database includes data on 15,483 male lung cancer cases and 18,388 male controls from 16 studies in Europe, Canada, China, and New Zealand conducted between 1985 and 2010. Odds ratios and 95% confidence intervals between regular or occasional welding and lung cancer were estimated, with adjustment for smoking, age, study center, and employment in other occupations associated with lung cancer risk. Overall, 568 cases and 427 controls had ever worked as welders and had an odds ratio of developing lung cancer of 1.44 (95% confidence interval: 1.25, 1.67) with the odds ratio increasing for longer duration of welding. In never and light smokers, the odds ratio was 1.96 (95% confidence interval: 1.37, 2.79). The odds ratios were somewhat higher for squamous and small cell lung cancers than for adenocarcinoma. Another 1,994 cases and 1,930 controls had ever worked in occupations with occasional welding. Work in any of these occupations was associated with some elevation of risk, though not as much as observed in regular welders. Our findings lend further support to the hypothesis that welding is associated with an increased risk of lung cancer.

case-control studies; lung cancer; occupational exposure; welding

Abbreviations: CI, confidence interval; ISCO-68, *International Standard Classification of Occupations, Revised Edition 1968* ; OR, odds ratio; SCLC, small cell lung cancer; SqCC, squamous cell carcinoma of the lung.

Worldwide, several million workers are exposed to welding fumes while working as welders or in occupations or workplaces in which the joining of metal parts is commonly performed. In 1990, the International Agency for Research on Cancer (Lyon, France) classified welding fumes as a possible human carcinogen (group 2B) (1). New evidence for excess lung cancer risk in welders has been found in several studies, including a recent meta-analysis and a large record-linkage study (2, 3). Research gaps and recommendations have been discussed by Ward et al. (4).

Welding fumes comprise complex mixtures of particles containing metals and gases that are formed during the burning of electrodes and heating of the base metal. Welding of mild steel and stainless steel generates distinct welding environments. Shipbuilding is a prominent example of an industry that involves welding of large parts of mild steel. This setting is

associated with high levels of exposure to respirable particles but with relatively lower concentrations of chromium and nickel compared with welding environments that use stainless steel with low-emission techniques (5, 6).

There is reasonably consistent evidence that stainless-steel welding increases the risk of lung cancer, but there is less indication of risk associated with mild-steel welding. However, a recent meta-analysis found similar excess risks of lung cancer among mild-steel welders and stainless-steel welders (2). There remain outstanding questions regarding whether welding-related risks differ between histological types of lung cancer and how welding interacts with smoking in lung cancer development.

We used a large collection of data from lung cancer cases and controls with occupational and smoking histories from the SYNERGY project (a pooled analysis of case-control studies on the joint effects of occupational carcinogens in the development of lung cancer) to explore welding as a risk factor for developing lung cancer. More information about the SYNERGY project and the component studies is available at http://synergy.iarc.fr.

MATERIALS AND METHODS

Study population

The collection of cases and controls for the SYNERGY project has been previously described (7). The SYNERGY project brings together original data from 16 studies conducted in Europe, Canada, China, and New Zealand between 1985 and 2010. Web Table 1, available at http://aje.oxfordjournals.org/, provides a brief description of the component studies. Most were population-based case-control studies that included both women and men. Cases were recruited from hospitals or cancer registries and had a diagnosis of lung cancer that was confirmed by histology or cytology. In aggregate, 82% of controls were recruited from the general population. The overall response rate was 85% among cases and 77% among controls. All studies collected job history information, at least at the level of occupation and industry titles, detailed smoking information, and information on other covariates. Occupational and smoking histories were assessed primarily in face-to-face interviews (81%). The majority of subjects were still alive at the time of interview (93% of controls and 94% of cases with known vital status). Although the entire data set included both women and men, only 32 women worked as welders. Consequently, the present study was restricted to the pooled data set of 15,483 male cases and 18,388 male controls. The ethics committees of the individual studies approved this study, as did the institutional review board of the International Agency for Research on Cancer.

Assessment of welding activities

All occupations in all subjects' histories were coded according to the *International Standard Classification of Occupations, Revised Edition 1968* (ISCO-68) (8). Industries were classified according to the *International Standard Industrial Classification, Second Revision* (9). We defined exposure to welding according to the occupations held by using the 5-digit ISCO-68 codes (Web Table 2). The following subjects were considered exposed: 1) men whose job title was "welder" for at least 1 year, and 2) men whose job title was 1 of several that we considered as potentially and occasionally involving welding activities. We refer to subjects in this category as "occasional welders." This list of occupations was created by a group of occupational exposure experts on our team (B.K., B.P., H.K., R.V., and S.P.). Occasional welding occupations were predominantly plumbers, fitters, and sheet-metal workers. We further stratified both groups by industry in which welding is commonly applied (shipbuilding and repair, construction, manufacture of machines and related equipment, manufacture of motor vehicles and repair of transport equipment, and "other") (Web Table 3).

Statistical analysis

The odds ratios for working as a welder or in occasional welding and 95% confidence intervals were estimated by unconditional logistic regression. The odds ratios for model 1 were adjusted for age (log-transformed) and study center (22 centers). The odds ratios for model 2 were additionally adjusted for smoking (log(pack-years + 1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopped smoking 2–7, 8–15, 16–25, or $\geq$ 26 years before interview/diagnosis, or never smokers)). Smoking variables were omitted when analyzing never smokers. We defined light smokers as subjects who smoked for fewer than 10 pack-years. The fully adjusted odds ratio (model 3) additionally considered employment in occupations associated with risk of lung cancer, excluding welding-related occupations (referred to as "List A" jobs (10, 11)). In another analysis, we estimated the lung cancer risk in men who never worked in other occupations associated with lung cancer. Subjects who had never worked in welding-related occupations comprised the reference group. For some analyses, the reference group was restricted to "blue-collar" workers; this was done by defining "blue-collar jobs" as those with an ISCO-68 first digit of 7, 8, or 9. We analyzed the relative risk of welding in various industries that characterize specific welding environments. Tests for linear trend were performed for the odds ratio as a function of duration of employment and time since last employment as a welder. We investigated the joint effects between welding and smoking by using multiplicative and additive models. For the multiplicative model, ever welding, ever smoking, and the product of both variables were entered in a logistic regression model together with the potential confounders. For the additive model, interaction between smoking and welding was estimated with the relative excess risk due to interaction (12). We used a linear odds model to estimate these risks and calculated the confidence interval with bootstrapping (1,000 runs) (13). Sensitivity analyses were performed by type of control. Meta-regression models with random effects were applied to estimate odds ratios for the combined and individual studies, and heterogeneity between studies was assessed by I^2 statistics with Comprehensive Meta-Analysis, version 2.2.027, software, (Biostat, Inc., Englewood, New Jersey). All other analyses were performed with SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Study population

Table 1 characterizes the study groups. A total of 568 male lung cancer cases (3.7%) and 427 controls (2.3%) ever worked as welders. A large fraction (40.1%) of welders among the controls reported this occupation as the longest-held job, with a median of 27 years (interquartile range, 18–35). An additional 1,994 cases (12.9%) and 1,930 controls (10.5%) were identified as having worked in occupations with occasional welding. Among the controls, 36.1% had these occupations as the longest-held job (median, 31 years; interquartile range, 23–38) (Table 2). Welders were more likely to be smokers than were men who never worked in welding-related occupations.

Lung cancer risk among welders and occasional welders

In the following sections, we consider the fully-adjusted relative risk estimates from model 3. Figure 1 shows meta–odds ratios of 1.42 (95% confidence interval (CI): 1.23, 1.66) for ever working as a welder, with marginal heterogeneity between individual studies ($I^2 = 29.6\%$; $P = 0.10$) and 1.17 (95% CI: 1.08, 1.27) for occasional welders ($I^2 = 20.9\%$; $P = 0.19$). Table 2 presents the risk estimates from the pooled analysis. Working as a welder was associated with an increased lung cancer risk (for ever welders, odds ratio (OR) = 1.44, 95% CI: 1.25, 1.67; for longest-held job, OR = 1.50, 95% CI: 1.20, 1.88). Occasional welding was also associated with an elevated lung cancer risk (for ever welders, OR = 1.19, 95% CI: 1.10, 1.28). The risk estimates remained increased when restricted to men who never worked in a List A job or to blue-collar workers (for welder as the longest-held occupation, OR = 1.63, 95% CI: 1.26, 2.11; and OR = 1.39, 95% CI: 1.11, 1.73, respectively). Odds ratios were 1.53 (95% CI: 1.29, 1.82) in studies with population controls and 1.10 (95% CI: 0.84, 1.44) in studies with hospital controls (Web Table 4). Another 59 men ever worked as flame cutters, who had an odds ratio of 2.01 (95% CI: 1.09, 3.69) (data not shown).

Lung cancer risk for welders in different industries

Welding in the construction industry was associated with an increased lung cancer risk (for ever welders, OR = 1.47, 95% CI: 1.22, 1.78; for ever occasional welding, OR = 1.21, 95% CI: 1.09, 1.33). We estimated an elevated risk for ever working as welder in shipbuilding and repair (OR = 1.53, 95% CI: 1.06, 2.21), but not for occasional welding in the shipbuilding industry (OR = 0.90, 95% CI: 0.68, 1.20). The estimates of the lung cancer risk of those working in motor vehicle and motor bike production were not elevated, with

Table 1. Distribution of Various Characteristics of the Study Population According to Case-Control and Welding Exposure Status, SYNERGY Project, 2007–2012

Characteristic	Welders[a]				Occasional Welding Occupations[b]				Never Worked in Welding Occupations[c]			
	Controls		Cases		Controls		Cases		Controls		Cases	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of participants	427	2.3	568	3.7	1,930	10.5	1,994	12.9	16,031	87.2	12,921	83.5
Cigarette smoking												
Never	78	18.3	15	2.6	408	21.1	48	2.4	4,391	27.4	439	3.4
Former	194	45.4	185	32.6	901	46.7	704	35.3	6,995	43.6	4,533	35.1
Current	153	35.8	366	64.4	577	29.9	1,228	61.6	4,268	26.6	7,805	60.4
Other types of tobacco only	2	0.5	2	0.4	44	2.3	14	0.7	377	2.4	144	1.1
List A occupations[d]												
Never	314	73.5	394	69.4	1,630	84.5	1,599	80.2	14,765	92.1	11,324	87.6
Ever	113	26.5	174	30.6	300	15.5	395	19.8	1,266	7.9	1,597	12.4
Histological subtype												
Adenocarcinoma			132	23.2			510	25.6			3,339	25.8
Squamous cell cancer			264	46.5			812	40.7			5,294	41.0
Small cell lung cancer			92	16.2			314	15.7			2,005	15.5
Other or mixed			80	14.1			358	18.0			2,283	17.7

Abbreviation: IQR, interquartile range.

[a] For welders, the median ages were 62 (IQR, 55–68) years for controls and 61 (IQR, 55–68) years for cases. The median levels of smoking were 25 (IQR, 14–40) pack-years for controls and 39 (IQR, 28–54) pack-years for cases. The median duration of employment in welding was 10 (IQR, 3–22) years for controls and 12 (IQR, 4–26) years for cases.

[b] For those who worked in occasional welding occupations, the median age was 62 (IQR, 55–68) years for both controls and cases. The median levels of smoking were 24 (IQR, 11–38) pack-years for controls and 37 (IQR, 26–50) pack-years for cases. The median duration of employment in welding was 10 (IQR, 3–25) years for controls and 10 (IQR, 3–27) years for cases.

[c] For those who never worked in welding-related occupations, the median ages were 64 (IQR, 56–70) years for controls and 64 (IQR, 57–70) years for cases. The median levels of smoking were 24 (IQR, 11–40) pack-years for controls and 40 (IQR, 27–56) pack-years for cases.

[d] Occupations involving risk of lung cancer, excluding welding-related occupations.

Table 2. Lung Cancer Risk Among Workers in Welding-Related Occupations, SYNERGY Project, 2007–2012

Occupation	No. of Controls	No. of Cases	OR[a] (Model 1)	OR[b] (Model 2)	95% CI (Model 2)	OR[c] (Model 3)	95% CI (Model 3)
All subjects							
Reference group[d]	16,031	12,921	1.00	1.00	Referent	1.00	Referent
Welders							
Ever	427	568	1.69	1.45	1.25, 1.68	1.44	1.25, 1.67
Longest-held occupation	172	246	1.78	1.48	1.19, 1.86	1.50	1.20, 1.88
Occasional welding occupations							
Ever	1,930	1,994	1.27	1.18	1.10, 1.28	1.19	1.10, 1.28
Longest-held occupation	697	746	1.37	1.31	1.16, 1.48	1.32	1.17, 1.49
Never employed in a List A job[e]							
Never worked in welding-related occupations	14,765	11,323	1.00	1.00	Referent		
Welders							
Ever	314	394	1.70	1.46	1.23, 1.74		
Longest-held occupation	129	186	1.92	1.63	1.26, 2.11		
Occasional welding occupations							
Ever	1,630	1,599	1.28	1.18	1.09, 1.29		
Longest-held occupation	623	627	1.37	1.27	1.11, 1.45		
Ever employed in a "blue collar" job							
Never worked in welding-related occupations	10,289	9,796	1.00	1.00	Referent	1.00	Referent
Welders							
Ever	427	568	1.45	1.32	1.14, 1.53	1.33	1.15, 1.54
Longest-held occupation	172	246	1.55	1.36	1.09, 1.71	1.39	1.11, 1.73
Occasional welding occupations							
Ever	1,930	1,994	1.08	1.06	0.98, 1.15	1.07	0.99, 1.16
Longest-held occupation	697	746	1.16	1.18	1.04, 1.33	1.20	1.06, 1.36

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Odds ratios for model 1 are adjusted for log(age) and study center.
[b] Odds ratios for model 2 are additionally adjusted for log(pack-years + 1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopped smoking 2–7, 8–15, 16–25, or ≥ 26 years before interview/diagnosis, never smokers).
[c] Odds ratios for model 3 are additionally adjusted for ever working in a List A job.
[d] Subjects who had never worked in welding-related occupations.
[e] Occupations involving risk of lung cancer, excluding welding-related occupations.

an odds ratio of 0.62 (95% CI: 0.28, 1.36) for welding as the longest-held job. More results are shown in Table 3.

Lung cancer risk by duration of employment as a regular or occasional welder

Short-term exposure (<3 years of welding) was associated with relative lung cancer risks of 1.14 (95% CI: 0.80, 1.61) in regular welders and 1.13 (95% CI: 0.94, 1.34) in occasional welders (Table 4). The risks increased with longer duration of welding. Long-term exposure (>25 years of welding) was associated with odds ratios of 1.77 (95% CI: 1.31, 2.39) in welders and 1.40 (95% CI: 1.21, 1.62) in occasional welders. We did not observe a risk reduction with increasing time since last welding (data not shown).

Lung cancer risk by histological subtype

Table 5 shows the relative risk estimates of ever working as a welder separately for the major subtypes of lung cancer (for adenocarcinoma, OR = 1.23, 95% CI: 0.99, 1.53; for squamous cell carcinoma of the lung (SqCC), OR = 1.58, 95% CI: 1.32, 1.89; and for small cell lung cancer (SCLC), OR = 1.41, 95% CI: 1.09, 1.82). Among never-or light-smoking welders, the estimates of the risk for SqCC and SCLC were more strongly increased, but were based on small numbers (for never smokers with adenocarcinoma, OR = 1.89, 95% CI: 0.79, 4.52; for never smokers with SqCC, OR = 3.01, 95% CI: 1.07, 8.49; and for never smokers with SCLC, OR = 4.45, 95% CI: 1.03, 19.18). This pattern was not observed among never-smoking occasional welders.

Joint effects of welding and smoking

Estimates of the joint effects of welding and smoking are presented in Table 6. There was no significant interaction of ever welding and smoking on the multiplicative scale (P = 0.22 for regular welders, and P = 0.92 for occasional welders). Ever working as a welder was associated with a 2-fold

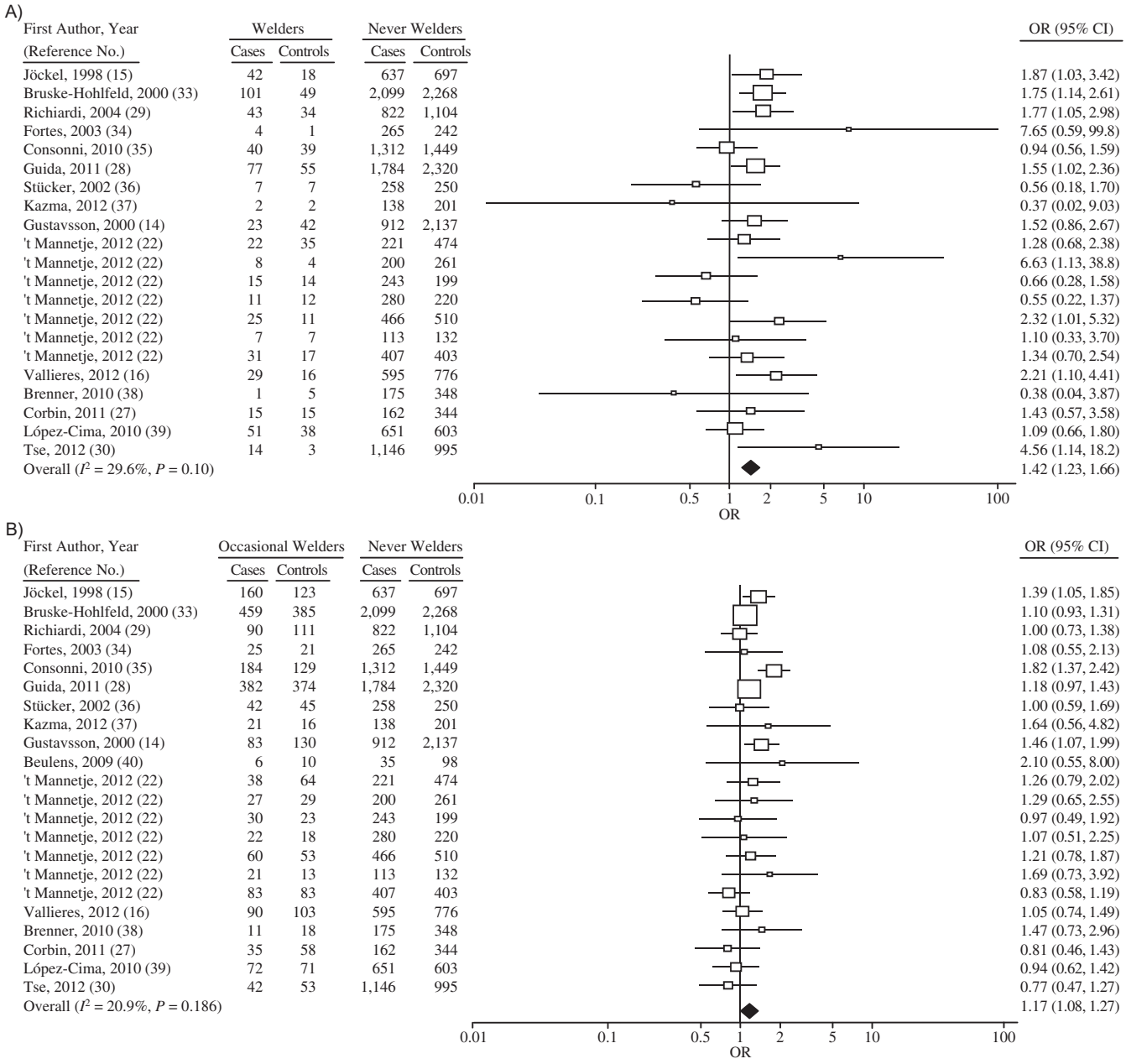

Figure 1. Study-specific odds ratios (ORs) for model 3 with 95% confidence intervals (CIs) for A) ever working as a welder or B) working in occasional welding occupations compared with men who never worked in welding-related occupations, adjusted for log(age), study center, log (pack-years + 1), time-since-quitting smoking cigarettes, and ever working in an occupation involving lung cancer risk, excluding welding-related occupations. The 7 rows for the article by 't Mannetje et al. (22) correspond to the following study locations, from top to bottom: the United Kingdom, Czech Republic, Slovakia, Hungary, Poland, Romania, and Russia.

higher odds ratio in never smokers (OR = 2.04, 95% CI: 1.16, 3.61), but lower risk in occasional welders (OR = 1.16, 95% CI: 0.84, 1.59). Among ever smokers, welders had a higher odds ratio (16.31) than did occasional welders (13.46) or unexposed smokers (11.44). When we further detailed the amount of smoking and duration of welding (Table 7), the highest estimate of relative risk was found in never smokers and light smokers who worked as welders for more than 25 years (OR = 3.72, 95% CI: 1.93, 7.19).

DISCUSSION

This analysis of a large database of occupational and smoking history data from approximately 33,900 men within the

Table 3. Lung Cancer Risk Among Workers in Welding-Related Occupations by Industry, SYNERGY Project, 2007–2012

Industry	Ever-Held Job						Longest-Held Job					
	No. of Controls	No. of Cases	OR[a] (Model 1)	OR[b] (Model 2)	OR[c] (Model 3)	95% CI (Model 3)	No. of Controls	No. of Cases	OR[a] (Model 1)	OR[b] (Model 2)	OR[c] (Model 3)	95% CI (Model 3)
Reference group[d]	16,031	12,921	1.00	1.00	1.00	Referent	16,031	12,921	1.00	1.00	1.00	Referent
Welders												
Shipbuilding and repair	59	93	1.99	1.57	1.53	1.06, 2.21	15	33	2.50	1.73	1.53	0.89, 3.41
Construction and related building services	240	336	1.78	1.50	1.47	1.22, 1.78	32	46	1.67	1.31	1.33	0.81, 2.20
Manufacture of machines, equipment, appliances	271	352	1.65	1.40	1.40	1.17, 1.68	57	104	2.38	2.08	2.11	1.45, 3.08
Manufacture of motor vehicles and motor bikes	93	102	1.56	1.33	1.30	0.94, 1.80	23	12	0.75	0.62	0.62	0.28, 1.36
Repair of transport equipment	101	136	1.70	1.51	1.51	1.12, 2.03	12	16	1.49	1.14	1.10	0.49, 2.46
Others	13	22	1.98	2.27	2.31	0.99, 5.39	33	35	1.29	1.25	1.27	0.74, 2.20
Occasional welding occupations												
Shipbuilding and repair	132	132	1.26	1.17	0.90	0.68, 1.20	47	45	1.77	1.73	1.32	0.78, 2.23
Construction and related building services	1,152	1,238	1.36	1.24	1.21	1.09, 1.33	216	244	1.53	1.44	1.43	1.21, 1.67
Manufacture of machines, equipment, appliances	739	734	1.20	1.17	1.14	1.01, 1.28	132	136	1.33	1.30	1.28	1.02, 1.60
Manufacture of motor vehicles and motor bikes	264	228	1.11	0.98	0.95	0.77, 1.16	69	60	1.28	1.04	1.03	0.71, 1.49
Repair of transport equipment	843	835	1.22	1.14	1.11	0.99, 1.24	170	206	1.23	1.20	1.18	0.98, 1.44
Others	112	101	1.05	0.89	0.91	0.67, 1.24	63	55	1.08	0.99	1.01	0.66, 1.54

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

[a] Odds ratios for model 1 are adjusted for log(age) and study center.

[b] Odds ratios for model 2 are additionally adjusted for log(pack-years + 1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopped smoking 2–7, 8–15, 16–25, or ≥ 26 years before interview/diagnosis, never smokers).

[c] Odds ratios for model 3 are additionally adjusted for ever working in a List A job (occupation involving risk of lung cancer, excluding welding-related occupations).

[d] Subjects who had never worked in welding-related occupations.

Table 4. Lung Cancer Risk of Welding-Related Occupations by Histological Subtype and Duration of Employment, SYNERGY Project, 2007–2012

Duration	No. of Controls	All Cases			Adenocarcinoma			Squamous Cell Lung Cancer			Small Cell Lung Cancer		
		No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI
Reference group[b]	16,031	12,921	1.00	Referent	3,313	1.00	Referent	5,226	1.00	Referent	1,979	1.00	Referent
Years as welder	427	568	1.44	1.25, 1.67	132	1.23	0.99, 1.53	264	1.58	1.32, 1.89	92	1.41	1.09, 1.82
1–<3	84	82	1.14	0.80, 1.61	18	0.84	0.49, 1.45	41	1.38	0.90, 2.11	14	1.25	0.67, 2.35
3–<10	124	171	1.46	1.26, 1.91	39	1.14	0.77, 1.68	77	1.62	1.16, 2.25	32	1.49	0.96, 2.32
10–≤25	129	167	1.38	1.06, 1.79	41	1.26	0.85, 1.87	76	1.34	0.97, 1.85	28	1.30	0.82, 2.07
>25	90	148	1.77	1.31, 2.39	34	1.31	0.85, 2.02	70	1.71	1.19, 2.46	18	1.20	0.69, 2.11
P value*				<0.0001			0.1041			0.0002			0.1311
Years in occasional welding occupations	1,930	1,994	1.19	1.10, 1.28	510	1.22	1.09, 1.37	812	1.14	1.03, 1.25	314	1.09	0.94, 1.25
1–<3	323	333	1.13	0.94, 1.34	93	1.26	0.98, 1.62	141	1.17	0.93, 1.48	49	0.98	0.70, 1.37
3–<10	642	638	1.11	1.00, 1.24	153	1.11	0.91, 1.35	241	0.90	0.76, 1.06	117	1.05	0.84, 1.31
10–≤25	485	487	1.16	1.00, 1.34	131	1.18	0.95, 1.46	207	1.14	0.94, 1.37	75	1.05	0.80, 1.38
>25	480	536	1.40	1.21, 1.62	133	1.28	1.03, 1.58	223	1.37	1.13, 1.65	73	1.15	0.87, 1.51
P value*				<0.0001			0.0193			0.0011			0.5687

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

[a] Odds ratios are adjusted for log(age), study center, log(pack-years + 1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopped smoking 2–7, 8–15, 16–25, or ≥ 26 years before interview/diagnosis, never smokers), and for ever working in a List A job (occupation involving risk of lung cancer, excluding welding-related occupations).

[b] Subjects who had never worked in welding-related occupations.

* *P* values for trend were computed by entering the continuous variable, duration of employment, into the model.

Table 5. Lung Cancer Risk of Welding-Related Occupations by Histological Subtype and Smoking, SYNERGY Project, 2007–2012

Occupation	No. of Controls	All Cases			Adenocarcinoma			Squamous Cell Lung Cancer			Small Cell Lung Cancer		
		No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI
Reference group[b]	16,031	12,921	1.00	Referent	3,313	1.00	Referent	5,226	1.00	Referent	1,979	1.00	Referent
Welders	427	568	1.44	1.25, 1.67	132	1.23	0.99, 1.53	264	1.58	1.32, 1.89	92	1.41	1.09, 1.82
Smoking status													
Never	78	15	2.34	1.31, 4.17	6	1.89	0.79, 4.52	4	3.01	1.07, 8.49	2	4.45	1.03, 19.2
Ever	349	553	1.33	1.14, 1.54	126	1.12	0.90, 1.41	260	1.49	1.24, 1.78	90	1.31	1.01, 1.70
Pack-years													
0–<10	146	47	1.96	1.37, 2.79	12	1.37	0.74, 2.52	18	2.25	1.30, 3.91	7	2.28	0.99, 5.29
10–35	174	189	1.19	0.95, 1.49	45	1.07	0.75, 1.52	86	1.35	1.01, 1.79	35	1.36	0.91, 2.04
≥35	107	332	1.34	1.06, 1.69	75	1.15	0.84, 1.59	160	1.50	1.16, 1.96	50	1.12	0.78, 1.62
Occasional welding occupations	1,930	1,994	1.19	1.10, 1.28	510	1.22	1.09, 1.37	812	1.14	1.03, 1.25	314	1.09	0.94, 1.25
Smoking status													
Never	408	48	1.31	0.95, 1.81	25	1.16	0.76, 1.78	8	1.13	0.54, 2.37	2	0.76	0.18, 3.19
Ever	1,522	1,946	1.15	1.07, 1.25	485	1.19	1.06, 1.34	804	1.11	1.00, 1.23	312	1.06	0.92, 1.23
Pack-years													
0–<10	784	166	1.20	0.99, 1.45	62	1.31	0.98, 1.74	53	1.02	0.74, 1.41	22	1.14	0.70, 1.85
10–35	699	767	1.20	1.07, 1.35	190	1.16	0.97, 1.39	313	1.20	1.03, 1.40	122	1.09	0.87, 1.36
≥35	447	1,061	1.09	0.96, 1.24	258	1.16	0.96, 1.39	446	1.06	0.91, 1.23	170	1.01	0.82, 1.24

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

[a] Odds ratios for model 3 are adjusted for log(age), study center, log(pack-years + 1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopped smoking 2–7, 8–15, 16–25, or ≥ 26 years before interview/diagnosis, never smokers), and for ever working in a List A job (occupation involving risk of lung cancer, excluding welding-related occupations). Smoking variables were omitted when analyzing never smokers.

[b] Subjects who had never worked in welding-related occupations.

Table 6. Interaction Between Welding-Related Occupations and Smoking by Histological Subtype of Lung Cancer, SYNERGY Project, 2007–2012

Occupation by Smoking Status	No. of Controls	All Cases		
		No.	OR[a]	95% CI
Reference group[b]				
Never smokers	4,391	439	1.00	Referent
Ever smokers	11,640	12,482	11.44	10.31, 12.68
Welders				
Never smokers	78	15	2.04	1.16, 3.61
Ever smokers	349	553	16.31	13.76, 19.33
P value*				0.222
RERI[c]			3.72	1.19, 6.25
Occasional welding occupations				
Never smokers	408	48	1.16	0.84, 1.59
Ever smokers	1,522	1,946	13.46	11.91, 15.21
P value[d]				0.922
RERI[c]			1.86	0.83, 2.89

Abbreviations: CI, confidence interval; OR, odds ratio; RERI, relative excess risk due to interaction.

[a] Odds ratios for model 3 are adjusted for log(age), study center, and for ever working in a List A job (occupation involving risk of lung cancer, excluding welding-related occupations).

[b] Subjects who had never worked in welding-related occupations.

[c] RERI from linear odds ratio model; confidence interval is based on 1,000 bootstrap samples.

[d] *P* values were computed for the product term of ever welding and ever smoking.

SYNERGY project demonstrated that being employed as a regular or occasional welder was associated with increased lung cancer risks of 1.42 and 1.17, respectively, in the meta-analysis of the individual studies. This result is in line with that of a meta-analysis of 66 epidemiologic studies, which revealed a 26% excess of lung cancer risk among welders (2). Two of these studies were part of our analysis (14, 15). Also, a large record-linkage study in the Nordic countries estimated a 33% increased lung cancer incidence in welders, although this study did not adjust for smoking (3). Finally, a study that went beyond job titles to welding exposures of individual subjects as assessed by experts found that welding exposure carried an excess risk of lung cancer (16).

Welding is a common task in many occupations in which the joining of metal parts is occasionally performed. To provide better evidence for the lung cancer risks of welding, we separately investigated welders and workers in occupations with potential welding activities. In the pooled analysis of 16 case-control studies, we observed a 44% smoking-adjusted increase in risk for those who ever worked as welders and a 19% increase for those who worked in occasional welding. The risk estimates after adjustment for smoking habits suggest that confounding by tobacco smoking may explain approximately 20% of the increase in lung cancer risk in welders.

Table 7. Lung Cancer Risk of Subjects in Welding-Related Occupations by Duration of Welding and Smoking, SYNERGY Project, 2007–2012

Duration of Welding	0–<10 Pack-Years				10–<35 Pack-Years				≥35 Pack-Years			
	No. of Controls	No. of Cases	OR[a]	95% CI	No. of Controls	No. of Cases	OR[a]	95% CI	No. of Controls	No. of Cases	OR[a]	95% CI
Reference group[b]	7,327	1,228	1.00	Referent	5,184	4,246	1.00	Referent	3,520	7,447	1.00	Referent
Years as welder												
1–<3	32	6	1.27	0.52, 3.09	37	28	0.82	0.50, 1.36	15	48	1.41	0.78, 2.55
3–<10	42	12	1.78	0.96, 3.31	48	62	1.11	0.75, 1.65	34	97	1.44	0.95, 2.20
10–≤25	47	14	1.84	0.95, 3.56	53	55	1.55	1.05, 2.30	29	98	1.21	0.81, 1.81
>25	25	15	3.72	1.93, 7.19	36	44	1.49	0.95, 2.35	29	89	1.36	0.88, 2.09
Years in occasional welding occupations												
1–<3	139	21	0.93	0.58, 1.49	112	133	1.32	1.02, 1.71	72	176	1.00	0.76, 1.33
3–<10	245	58	1.24	0.86, 1.78	240	247	1.29	1.05, 1.59	157	331	0.97	0.78, 1.22
10–≤25	182	39	1.39	1.03, 1.88	184	201	1.09	0.90, 1.31	119	254	0.89	0.73, 1.09
>25	218	48	1.31	0.94, 1.81	163	186	1.41	1.13, 1.76	99	300	1.49	1.17, 1.89

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

[a] Odds ratios for model 3 are adjusted for log(age), study center, and for ever working in a List A job (occupation involving risk of lung cancer, excluding welding-related occupations).

[b] Subjects who had never worked in welding-related occupations.

This relative risk estimate showed only minor changes when we restricted the analysis to blue-collar workers or to subjects not working in other occupations associated with lung cancer risk. The risk increased up to 77% for regular welders who worked more than 25 years. The odds ratios in SYNERGY studies with population controls were higher than those in the studies with hospital controls. Hospital controls included higher proportions of smokers and blue-collar workers than did population controls (for ever smokers, 75% (median pack-years, 29) vs. 69% (median pack-years, 23); for blue-collar workers, 74% vs. 67%). This difference may be at least partially due to the inclusion of patients with smoking-related disease and to a lower response of blue-collar workers in the general population. Numerous sources of heterogeneity among studies in this international pooled case-control study may also account for the different results between hospital-based and population-based studies. A comparison of I^2 statistics revealed values of 39% for hospital-based studies and 0% for population-based studies.

The elevated lung cancer incidence has been frequently attributed to welding fumes containing chromium and nickel. However, in a previous study, no obvious differences in excess lung cancer risks could be shown between stainless-steel and mild-steel welders (2). There are a variety of welding techniques with a wide range of emissions of particles and metals (5). Stainless steel differs from mild steel by the amount of chromium it contains. Nickel is frequently added to improve the quality of steel. Hence, welding of stainless steel is associated with higher levels of exposure to chromium and nickel than is welding of mild steel (6). By contrast, welding of mild steel is commonly performed with high-emission techniques that generate higher mass concentrations of particulate matter than does stainless-steel welding (5). Gas metal arc welding and, in particular, flux-cored arc welding are frequently used for joining large metal parts of mild steel (e.g., in shipyards). Our finding that lung cancer risk was also increased among regular welders in shipyards indicates that the excess lung cancer risk is not restricted to stainless-steel welding. However, we did not observe a significantly increased lung cancer risk among those welding in the manufacture of motor vehicles. Welding of car parts has been subject to technological improvements, leading to a reduction of exposure to welding fumes, whereas the joining of large ship parts is still performed with high-emission technologies (2).

A limitation of this study is that information on the welding process and on the specific nature of workplace exposures was not available in this job title–based analysis. Still, the job title of "welder" is one that carries a strong likelihood of exposure to some form of welding fumes. There is certainly a possibility for workers with other job titles to engage in or to be in proximity to welding operations. We attempted to identify the main occupations in our list of occupations with occasional welding activities. These workers comprise a larger group compared with subjects who worked as regular welders (17). However, some occasional welders may actually have done very little welding. On the other hand, some of the unexposed subjects may have actually performed some welding. To the extent that there was misclassification, it was likely nondifferential, which would have led to attenuation of relative risk estimates toward the null.

Exposure to asbestos can occur during welding, especially in shipyards. The US National Institute of Occupational Safety and Health (Washington, DC) concluded in 1988 that there is an elevated risk of lung cancer among welders that cannot be completely accounted for by smoking or asbestos exposure (18). Asbestos could be used as a filler of cylinders with acetylene gas or as part of certain covered rod electrodes. Asbestos fibers are not stable at high temperatures during welding (19). Asbestos-containing materials were used for heat protection, and, for example, to cover the weld in order to delay the cooling process. Exposure to asbestos is further possible when repairing metal parts with asbestos insulation or as a bystander to such activity. Elevated mesothelioma risks among welders have been reported (20). The asbestos burden in the lungs of welders with mesothelioma was lower than in cases from the asbestos manufacturing industry or insulation sector (21). We adjusted for other occupations associated with lung cancer risk except welding and considered welding as a complex exposure circumstance, in which exposure to asbestos could be an integral part. Several studies have attempted to adjust for exposure to asbestos, including 4 studies that were part of our pooled analysis (14–16, 22). Exposure to asbestos was usually assessed with categorical variables based on expert rating. In the International Cooperation (INCO-Copernicus) Study (22), the inclusion of lifetime exposure to asbestos in the model did not influence the estimate of the relative lung cancer risk among welders. Taking this together, we conclude that welding fumes may exert a lung cancer risk that cannot be sufficiently explained by asbestos.

The large SYNERGY project data set allowed assessment of the interaction of welding with smoking. The elevated odds ratios observed for regular welders who were never smokers or light smokers are in line with a previous report from a study in Montreal, Canada (16). We further observed higher odds ratios in ever smoking welders compared with smokers who never worked in welding-related occupations. The relative risk estimates did not indicate a multiplicative effect, but rather a greater than additive effect between ever smoking and welding. A more detailed stratification by level of exposure to tobacco smoke indicated a rise in relative risk estimates by duration of working as a welder in never and light smokers but no trend in heavy smokers. Notably, the prevalence of smoking in welders was higher than in the reference group. Adjustment for smoking attenuated the risk estimates, but residual confounding may still be a problem.

The elevated odds ratios observed for cases with SCLC and SqCC may support a causal effect of welding fumes. Although many questions regarding cancer development are yet unanswered, progress has been made in explaining the diverse ontogeny of lung cancer (23). Our findings of higher relative risks of SqCC and SCLC in smokers, as well as in welders, are in line with their molecular signatures and the higher potency of their possible cellular precursors to restore damage of a larger extent (24). This different association in welders was also observed in other studies (25, 26). Individual SYNERGY project studies (14–16, 22, 27–30) have reported on histological subtypes of lung cancer but were based on smaller numbers. The same pattern was reported for exposure to pulmonary carcinogens in uranium miners (31) and was even more pronounced in the association of smoking with lung cancer (32).

In summary, our findings contribute to the increasing evidence that welding is associated with an increased risk of lung cancer. The lung cancer risk of regular welders was higher than that of occasional welders. We observed a slightly stronger risk in never smokers and light smokers and a trend with duration of employment in welding-related jobs, as well as a stronger association of welding with SqCC and SCLC than with adenocarcinoma. The findings from this investigation support the need for additional research to identify the agent(s) responsible for possible lung cancer risks.

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