Pleural mesothelioma risk in the construction industry: a case–control study in Italy, 2000–2018

Simona Stella [1], Dario Consonni [1], Enrica Migliore [2], Antonella Stura,[2] Domenica Cavone [3], Luigi Vimercati [3], Lucia Miligi [4], Sara Piro [4], Maria Teresa Landi,[5] Neil E Caporaso [5], Stefania Curti [6], Stefano Mattioli [7], Giovanni Brandi [6,8] Carmela Gioscia,[9] Silvia Eccher,[10] Stefano Murano,[11] Veronica Casotto,[12] Vera Comiati,[12] Corrado Negro [13], Flavia D'Agostin,[13] Carlo Genova [14,15] Lucia Benfatto,[16] Antonio Romanelli [17], Iolanda Grappasonni [18], Gabriella Madeo,[19] Ilaria Cozzi [20], Elisa Romeo,[20] Staniscia Tommaso [21], Francesco Carrozza,[22] Michele Labianca,[23] Federico Tallarigo [24], Giuseppe Cascone,[25] Massimo Melis,[26] Alessandro Marinaccio [27], Alessandra Binazzi [27], Carolina Mensi [1], ReNaM Working Group members

For numbered affiliations see end of article.

Correspondence to
Dario Consonni;
dario.consonni@unimi.it

ABSTRACT

Objectives Workers in the construction industry have been exposed to asbestos in various occupations. In Italy, a National Mesothelioma Registry has been implemented more than 20 years ago. Using cases selected from this registry and exploiting existing control data sets, we estimated relative risks for pleural mesothelioma (PM) among construction workers.

Design Case–control study.

Setting Cases from the National Mesothelioma Registry (2000–2018), controls from three previous case–control studies.

Methods We selected male PM incident cases diagnosed in 2000–2018. Population controls were taken from three studies performed in six Italian regions within two periods (2002–2004 and 2012–2016). Age-adjusted and period-adjusted unconditional logistic regression models were fitted to estimate odds ratios (OR) for occupations in the construction industry. We followed two approaches, one (primary) excluding and the other (secondary) including subjects employed in other non-construction blue collar occupations for >5 years. For both approaches, we performed an overall analysis including all cases and, given the incomplete temporal and geographic overlap of cases and controls, three time or/and space restricted sensitivity analyses.

Results The whole data set included 15 592 cases and 2210 controls. With the primary approach (4797 cases and 1085 controls), OR was 3.64 (2181 cases) for subjects ever employed in construction. We found elevated risks for blue-collar occupations (1993 cases, OR 4.52), including bricklayers (988 cases, OR 7.05), general construction workers (320 cases, OR 4.66), plumbers and pipe fitters (305 cases, OR 9.13), painters (104 cases, OR 2.17) and several others. Sensitivity analyses yielded very similar findings. Using the secondary approach, we observed similar patterns, but ORs were remarkably lower.

STRENGTH AND LIMITATIONS OF THIS STUDY

⇒ The current study benefited from the use of high-quality data covering the period from 2000 to 2018 from the National Mesothelioma Registry, an epidemiological surveillance programme organised as a network of regional operating centres which perform active search of mesothelioma cases.

⇒ Using a control-initiated case–control approach, we exploited three existing control data sets, mostly population-based, covering different periods and regions.

⇒ To minimise confounding, in a primary approach, we excluded subjects ever employed in non-construction blue-collar occupations for >5 years.

⇒ The main limitation was the incomplete spatial and temporal overlap between pleural mesothelioma cases and controls.

⇒ However, various sensitivity analyses with temporal or/and spatial restrictions confirmed the validity of using all cases occurred in the whole period in the whole Italian territory.

Conclusions We found markedly increased PM risks for most occupations in the construction industry. These findings are relevant for compensation of subjects affected with mesothelioma in the construction industry.

INTRODUCTION

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series. These include the serpentine mineral chrysotile ('white asbestos'), and the five amphibole minerals actinolite,

BMJ

amosite ('brown asbestos'), anthophyllite, crocidolite ('blue asbestos') and tremolite. All forms of asbestos are carcinogenic, causing mesothelioma (any site) and cancer of the lung, larynx and ovary.[1] Malignant meso-thelioma (MM) is a rare and aggressive neoplasm arising from pleura (>90%), peritoneum (<10%), pericardium (<1%) and tunica vaginalis testis (<1%). Notwithstanding the asbestos ban in about 70 countries, due to the long latency between exposure and MM occurrence, the number of MM deaths caused by asbestos in recent years is in the order of 25 000–38 000 per year.[2–4]

Italy produced and consumed large quantities of asbestos until the ban in 1992. For this reason, it is among the countries with the highest MM death rates[5 6] and with a high burden of asbestos-related diseases in general.[7] Pleural mesothelioma (PM) incidence and mortality are expected to remain high in the next decades.[8 9] In Italy (decree 308/2002) a national MM registry (Registro Nazionale Mesoteliomi, National Mesothelioma Registry, ReNaM) has been formally established (although some regions had already started registration in the 1990s). ReNaM recorded more than 30 000 MM cases in the period 1993–2018.[10] Construction is among the indus-tries with the largest asbestos use in the past and is paying the largest toll: of 17 191 cases with occupational expo-sure, 3574 MM cases (20.8%), almost all men, had been exposed in the construction industry.[10]

Recently, a case–control study in Italy showed elevated PM risks for workers of various industries with a large use of asbestos. For male workers ever employed in the construction industry, an odds ratio (OR) of 1.94 was found (119 cases and 77 controls), to which several blue-collar occupations contributed.[11]

In this work, we performed a 'control-initiated case–control study'[12] to examine more in depth the PM rela-tive risks in male construction workers. A control-initiated study is an efficient way to use existing control series to perform a case–control study. Controls could be drawn from a population survey or from the control groups of earlier case–control studies. In this study, we took PM cases from the national MM registry and exploited three existing data sets of controls: (1) controls from the Envi-ronment And Genetics in Lung cancer Etiology (EAGLE) study,[13] a large population-based case–control study performed in the Lombardy region in the period 2002–2005 (controls enrolled in 2002–2004), used for PM cases diagnosed in 2000–2009; (2) controls from the 'Multi-centre Italian Study on the Aetiology of Mesothelioma' MISEM study (quoted in the previous paragraph),[11] a population-based case–control study performed in five Italian regions in the period 2012–2014, used for PM cases diagnosed in 2010–2018; (3) controls from the 'Chol-angiocarcinoma Aetiology: Role of Asbestos' (CARA) study (unpublished), a hospital-based case–control study performed in the Emilia-Romagna region in the period 2014–2016, used for PM cases diagnosed in 2010–2018.

We analysed PM risk for various occupations in the construction sector. We followed and compared two kinds of approaches: (1) primary approach, in which subjects ever employed in non-construction blue-collar occupations for more than 5 years were excluded from both 'exposed' (ever employed in construction occu-pations) and 'reference' (never employed in construc-tion occupations) groups, thus overcoming potential confounding from asbestos exposure in other occupa-tions; (2) secondary approach, in which all subjects (also those employed >5 years in non-construction blue-collar occupations) were included.

For both approaches, we performed four analyses. In the overall analysis, we exploited all PM cases recorded in the whole country (60 million people) by the national registry in the period 2000–2018. In this way, we could strengthen and possibly expand MISEM results by covering the whole nation and a wider study period with a larger sample size. Ideally, as in any case–control study, including control-initiated studies, cases and controls should come from the same study base. In this study, cases came from the whole country and the whole period, while controls were collected only in some areas in restricted periods. Therefore, in order to verify the validity of results, we performed three sensitivity analyses by applying time, space and time–space restrictions to PM cases in order to match more closely the study base of which controls are a sample. We previously used a similar approach in two case–control studies on mesothelioma of the peritoneum[14] and of the pericardium and tunica vaginalis testis,[15] in which findings using all cases were remarkably similar to those obtained by applying time or/and space restrictions.

METHODS
The National Mesothelioma Registry (ReNaM)
The ReNaM is an epidemiological surveillance programme organised as a network of regional oper-ating centres (Centri Operativi Regionali, COR). It was formally established by law 277/1991 in 2002 (although some Italian regions had started in the early 1990s). Report of MM cases to CORs is compulsory (law 277/1991 and 81/2008). However, since reporting is incomplete, CORs actively search newly diagnosed cases by exploiting several information sources, including databases of hospital admissions and mortality, archives of pathology reports and reports of occupational diseases. Based on the clinical information, confirmed cases are classified as 'definite' (histological diagnosis, usually with immunohis-tochemical confirmation), 'probable' (usually, cytolog-ical diagnosis and confirmation by positive imaging) or 'possible' (positive imaging).

MM patients or their next-of-kin are then interviewed (mostly face-to-face) by qualified personnel using a stan-dardised ReNaM questionnaire that investigates lifetime job history: in particular, information about industry, occupation, tasks and the working environment are collected for each job. Industries and occupations are coded, respectively, using the Italian classifications of

industries (ATECO, 1991) and of occupations (CIP, 1991). The questionnaire also collects lifetime residential histories and occupational histories of family members.

According to ReNaM guidelines, lifetime asbestos exposure is evaluated by experts and classified as occupational (definite, probable and possible) and (only for non-occupationally exposed cases), extra-occupational. Subjects with no evidence of asbestos exposure at interview are considered as non-exposed. This information was not exploited in this paper because the focus is on occupations (independently from asbestos exposure collected at interview).

Controls

We used three sets of controls enrolled in different geographical areas and periods.

The first set of controls was taken from the EAGLE study.[13] Controls had been randomly sampled in 2002–2004 among 1.6 million residents aged 35–79 years in 216 out of 725 municipalities in five Lombardy (Northern Italy) provinces (Milan, Monza, Brescia, Pavia and Varese, 3.5 million residents). Subjects underwent a computer-assisted personal interview using a questionnaire (available on website https://eagle.cancer.gov/questionaires.html), which collected information on lifetime occupational history (industry, occupation and years of start/stop) for each job carried out for more than 6 months.

The second set of controls came from the MISEM study, conducted in five regions (Lombardy, Piedmont and Veneto in Northern Italy, Tuscany in Central Italy and Apulia in Southern Italy).[11] In Piedmont, the population was limited to residents of the province of Turin and the local health district of Casale Monferrato. In Veneto, the population from the provinces of Padua and Venice was included. Controls were randomly sampled from residents aged 31–92 years in 2012–2014. Subjects were face-to-face interviewed with the ReNaM questionnaire.

The third set of controls was taken from the CARA study performed in Emilia-Romagna (Northern Italy) in the period 2014–2016. Hospital controls aged 22–92 years were interviewed face-to-face with a detailed questionnaire, including occupational sections taken from the ReNaM questionnaire.

Since CARA controls were few and were enrolled in a period overlapping with MISEM, in statistical analyses CARA and MISEM controls were pooled together.

Cases

From the ReNaM database, we extracted all PM cases diagnosed in the period 2000–2018 with any level of diagnostic certainty (certain, probable and possible). We divided cases into two main periods of incidence (2000–2009 and 2010–2018). We subsequently performed three sensitivity analyses by applying time, space and time–space restrictions to cases in order to match more closely the study base of controls (see below).

Coding of industries and occupations

The information used for this work consisted simply of industries and occupations and was collected in a similar way across cases/controls series. Although different persons performed coding, there was some overlap: for cases and MISEM/CARA controls, the coders were the same within participating regions; in Lombardy, EAGLE controls and MISEM cases and controls were coded by the same person.

With regard to controls in all three studies, industries and occupations had been coded following the International Standard Industrial Classification of All Economic Activities (ISIC, 1971) and the International Standard Classification of Occupations (ISCO, 1968),[16] respectively. Work histories of controls in the MISEM study had been coded using both Italian and International classifications of industries (ATECO-91 and ISIC-71) and occupations (CIP-91 and ISCO-68).

For cases in the ReNaM database, we exploited a recently developed crosswalk to translate Italian CIP-91 codes of occupations into ISCO-68 codes.[17] To improve comparability of cases and controls, we applied the crosswalk also to MISEM controls.

The construction industry was identified with the ISIC-71 code 5000 or the corresponding ATECO-91 code 45. The groups of occupations considered within the construction industry were the ISCO-68 minor group 95 (bricklayers, carpenters and other construction workers), and the following three-digit unit groups: bricklayers, stonemasons and tile setters (951); reinforced-concreters, cement and terrazzo workers (952); roofers (953); carpenters, joiners and parquetry workers (954); plasterers (955); insulators (956); glaziers (957) and construction workers not elsewhere classified (959). We also separately analysed bricklayers (95120). In addition, we evaluated PM risk for the following other three-digit unit groups: electrical wiremen (855); electrical linemen and cable jointers (857); plumbers and pipe fitters (871); welders and flame-cutters (872); sheet-metal workers (873); structural metal preparers and erectors (874); painters, construction (931); crane and hoist operators (973); earth-moving and related machinery operators (974); motor-vehicle drivers (985) and labourers not elsewhere classified (999).

Statistical analysis

We assessed the relative risks of PM associated with ever employment in construction industry. The majority of construction workers were men, so women were excluded from analyses. We performed analyses for selected groups of occupations, with subjects who were ever employed in multiple occupations included in each analysis.

Unconditional logistic regression models adjusted for age (<50, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85+) and period (two periods: 2000–2009 and 2010–2018) were fitted to calculate ORs. We calculated 90% CI in order to avoid a reductive interpretation of CIs

as significance tests.[18] The reference group was made up of subjects never employed in the construction industry.

We followed two kinds of approaches:

1. Primary approach, in which subjects ever employed in non-construction blue-collar occupations for >5 years were excluded from both 'exposed' (ever employed in construction occupations) and 'reference' (never employed in construction occupations) categories. A similar approach has been used previously,[19] and has the advantage to minimise potential confounding from asbestos exposure in other (mainly blue-collar) occupations.

2. Secondary approach, theoretically less preferable, in which all subjects (also those employed >5 years in non-construction blue-collar occupations) were included.

Blue-collar occupations were identified using the following ISCO-68 codes: 55 (building caretakers, charworkers, cleaners and related workers); 56 (launderers, dry-cleaners and pressers); 581 (firefighters); 628 (farm machinery operators); 631 (loggers) and all the three major groups 7/8/9 (production and related workers, transport equipment operators and labourers).[20]

For both primary and secondary approaches we performed the following four analyses:

1. Analysis 1 (A1). Overall analysis in which we included all cases recorded by ReNaM in 2000–2009 (exploiting EAGLE controls) and 2010–2018 (exploiting MISEM and CARA controls pooled together).

2. Analysis 2 (A2). Temporally restricted analyses in which we included only cases first diagnosed in the same years of enrolment of EAGLE (2002–2004) or MISEM/CARA (2012–2016) controls.

3. Analysis 3 (A3). Spatially restricted analysis, in which we included only cases living in the same Lombardy Provinces of EAGLE (2000–2009) and in the same six regions of MISEM/CARA (2010–2018) controls.

4. Analysis 4 (A4). Temporally and spatially restricted analysis, in which we applied both restrictions of analyses A2 and A3, that is, cases 2002–2004 living in the same Lombardy Provinces of EAGLE controls and cases 2012–2016 living in the same regions of MISEM/CARA controls. This analysis is theoretically preferable (although based on a smaller sample size) because cases match more closely the study base (the population-time source of controls).

With the primary approach, we performed an overall analysis A1 by length of employment for occupation with at least 10 exposed controls.

Figure 1 shows numbers of cases and controls included in the overall analysis (time and space unrestricted analysis A1) under primary and secondary approach. Online supplemental figures 1–3 show numbers of cases and controls included in time or/and space restricted analysis A2–A4 under primary and secondary approach).

All analyses were performed using Stata V.17 (Stata Corp. 2021, College Station, TX, USA).

Patients and public involvement

We used existing data sets of cases and control. Therefore, subjects could not be involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

For the period 2000–2018, 15 592 records for men with PM were extracted from the ReNaM database, 7985 (51.2%) in the period 2000–2009 and 7607 in 2010–2018 (figure 1). Controls were 2210 in total, 1617 from EAGLE study (2002–2004) and 593 from MISEM/CARA studies (2012–2016, 490 from MISEM and 103 from CARA).

During the whole study period, there were 4729 (30.3%) out of 15 592 PM cases ever employed in the construction industry, while controls were 402 (18.2%) among 2210 (table 1). The proportions of ever employed in construction were remarkably similar in the two periods: among cases, 2372 (29.7%) out of 7985 in 2000–2009 and 2357 (31.0%) out of 7607 in 2010–2018; among EAGLE controls, 299 (18.5%) out of 1617 in 2002–2004 and 103 (17.4%) out of 593 MISEM/CARA controls in 2012–2016.

In both periods, the distribution of cases by age was fairly similar to that of controls. The majority of cases (9195, 59.0%) completed a personal interview with the ReNaM questionnaire. A definite diagnosis was available for 13 368 cases (85.7%). Most cases (9499, 60.9%) were of epithelioid histology.

Primary approach

Using the primary approach (subjects employed for >5 years in non-construction blue-collar occupations excluded), in the overall analysis A1 (time and space unrestricted), an OR of 3.64 was calculated for subjects ever employed in construction (2181 cases) (table 2). This increase was driven by numerous blue-collar occupations (OR 4.52), especially the large category of bricklayers, carpenters and other construction workers (OR 5.83). Within this category (95), high relative risks were found for bricklayers (OR 7.05) and construction workers not elsewhere classified (OR 4.66), and also for other less represented occupations, although with fewer controls. Elevated risks were also for several other occupations, especially plumbers and pipe-fitters (OR 9.13) and painters (OR 2.17). ORs could not be calculated for occupations 952, 955, 957, 872, 873 and 973.

The pattern of analysis A1 was largely confirmed in primary time or/and space restricted analyses A2–A4 (figures 2–3).

The analysis by length of employment (in which we excluded a few subjects who lacked years of start/stop work) shows that PM risk was increased also for those who worked for less than 20 years (there were no positive trends when we excluded the reference category, except for the minor group 95) (online supplemental table 1).

Period	Year	N. cases Primary/ secondary approach	Case source	Control source
2000–2018	2000	227/682	**NATIONAL MESOTHELIOMA REGISTRY** Living in any Region ReNaM questionnaire **Primary/secondary approach:** N. 4797/15 592	**EAGLE** Living in 216 municipalities in five Lombardy Provinces (Milan, Monza, Brescia, Pavia, Varese) EAGLE questionnaire **Primary/secondary approach:** N. 778/1617
	2001	207/734		
	2002	214/760		
	2003	238/758		
	2004	246/768		
	2005	259/861		
	2006	242/782		
	2007	248/882		
	2008	240/857		
	2009	285/901		
	2010	271/851		
	2011	254/886		
	2012	288/886		**MISEM** Living in five Regions (Apulia, Lombardy, Piedmont, Tuscany, Veneto) ReNaM questionnaire **Primary/secondary approach:** N. 250/490 **CARA** Living in one Region (Emilia-Romagna) ReNaM questionnaire **Primary/secondary approach:** N. 57/103
	2013	304/979		
	2014	289/928		
	2015	283/921		
	2016	294/910		
	2017	287/841		
	2018	121/405		

Figure 1 Diagram showing numbers of male pleural mesothelioma cases and controls across the years and their main characteristics, Italy, 2000–2018. Cases from all years and areas (analysis A1). In the primary approach, subjects ever employed in non-construction blue-collar occupations for >5 years were excluded; in the secondary approach, all subjects (also those ever employed in non-construction blue-collar occupation for >5 years) were included. CARA, Cholangiocarcinoma Aetiology: Role of Asbestos; EAGLE, Environment And Genetics in Lung cancer Aetiology; MISEM, Multicentre Italian Study on the Aetiology of Mesothelioma; ReNaM, Registro Nazionale Mesoteliomi.

Secondary approach

With the secondary approach (all subjects included, also those employed for >5 years in non-construction blue-collar occupations), in the overall analysis A1 (time and space unrestricted), we observed a pattern similar to that obtained with the primary approach, but ORs were substantially lower (online supplemental table 2). In addition, the time or/and space restricted analyses A2–A4 yielded results which were in general quite similar to those of the overall analysis A1 (online supplemental figures 4 and 5).

DISCUSSION

In this nationwide Italian study covering nearly two decades (2000–2018), we found markedly elevated risks of PM among males for most blue-collar occupations in the construction industry, in particular (in order of number of cases): bricklayers; general construction workers (ie, construction workers not elsewhere classified); plumbers and pipe fitters; painters; electrical wiremen; carpenters, joiners and parquetry workers; insulators; earth-moving and related machinery operators; electrical linemen and cable jointers; structural metal preparers and erectors; labourers; roofers. Findings of this primary approach were in general highly consistent across various supplementary analyses with different study base samples (ie, with space/time restriction inclusion of cases).

These results may not be fully generalised to countries with different patterns of asbestos use, including: differential quantity of asbestos-containing products employed;

Table 1 Characteristics of pleural mesothelioma cases and controls in men ever/never employed in the construction industry (ISIC-71 code 5000), Italy, 2000–2018

	Ever construction				Never construction			
	Cases		Controls		Cases		Controls	
Variable	N	%	N	%	N	%	N	%
Total	4729	100	402	100	10 863	100	1808	100
Period								
2000–2009	2372	50.2	299	74.4	5613	51.7	1318	72.9
2010–2018	2357	49.8	103	25.6	5250	48.3	490	27.1
Age (years)								
<50	112	2.4	17	4.2	272	2.5	90	5.0
50–54	171	3.6	25	6.2	359	3.3	98	5.4
55–59	360	7.6	48	11.9	767	7.1	223	12.3
60–64	553	11.7	66	16.4	1344	12.4	304	16.8
65–69	858	18.1	98	24.4	1825	16.8	435	24.1
70–74	966	20.4	91	22.6	2192	20.2	371	20.5
75–79	926	19.6	45	11.2	2107	19.4	234	12.9
80–84	538	11.4	10	2.5	1282	11.8	36	2.0
85+	245	5.2	2	0.5	715	6.6	17	0.9
Mean (SD)	70.4	(9.5)	66.2	(8.7)	70.7	(9.8)	66.1	(9.1)
Interview								
Direct	2933	62.0	402	100	6262	57.7	1808	100
Next-of-kin	1709	36.1			4242	39.0		
None	78	1.7			278	2.6		
Other	9	0.2			81	0.7		
Diagnosis								
Definite	4117	87.1			9251	85.2		
Probable	347	7.3			802	7.4		
Possible	265	5.6			810	7.5		
Morphology*								
Mesothelioma, NOS (90503)	450	9.5			1081	9.9		
Fibrous (90513)	479	10.1			1007	9.3		
Epithelioid (90523)	2897	61.3			6602	60.8		
Biphasic (90533)	583	12.3			1237	11.4		
Not available	320	6.8			936	8.6		

Percentages may not add to 100 due to rounding.
*Codes of the International Classification of Diseases for Oncology, Third Edition in parentheses.
ISIC, International Standard Industry Classification (1971); NOS, not otherwise specified.

work practices; organisation of the construction industry; differences in work tasks by occupation; and relative quantities of different fibre types used in the Italian construction industry. Unlike other countries (eg, France where almost all the asbestos used was imported and chrysotile was the most commonly used type),[21] chrysotile and amphiboles were produced and used to manufacture asbestos-cement products for the construction industry in Italy.[22] Moreover, the Italian construction industry is organised into many small and medium enterprises, so that workers in various occupations (including the large

group of bricklayers) may perform a variety of tasks and/or work in close contact with workers performing tasks entailing asbestos exposure.[23] In addition, although there are real differences in working practices in the construction sector across countries, we cannot exclude that the large number of bricklayers among cases in our study may be due to coding procedures, for example, use of ISCO-68 code 95 120 instead of less specific codes 95 910 (housebuilders) or 95 990 (other construction workers), as already noted in a large pooled analysis of case–control study on lung cancer.[24] These factors might explain the

Table 2 Pleural mesothelioma ORs and 90% CIs for selected occupations in men in the construction industry (ISIC-71 code 5000), Italy, 2000–2018. Results of the primary approach (subjects ever employed in non-construction blue-collar occupations for >5 years excluded), analysis A1

Occupation (ISCO-68 code)	Cases	Controls	OR*	90% CI
Total	4797	1085		
Never employed in construction	2616	878	1.00	Reference
Ever employed in construction	2181	207	3.64	3.17 to 4.19
Blue-collar occupations (55, 56, 581, 628, 631, 7–9)	1993	151	4.52	3.87 to 5.29
Bricklayers, carpenters and other construction workers (95)	1367	79	5.83	4.75 to 7.15
Bricklayers, stonemasons and tile setters (951)	1054	50	7.17	5.58 to 9.21
Bricklayers (95 120)	988	47	7.05	5.45 to 9.12
Reinforced concreters, cement finishers and terrazzo workers (952)	12	0	NC	
Roofers (953)	27	1	12.3	2.28 to 66.1
Carpenters, joiners and parquetry workers (954)	73	4	6.88	2.92 to 16.2
Plasterers (955)	14	0	NC	
Insulators (956)	57	4	6.27	2.64 to 14.8
Glaziers (957)	0	4	NC	
Construction worker, not elsewhere classified (959)	320	22	4.66	3.21 to 6.77
Other blue-collar occupations				
Electrical wiremen (855)	97	16	2.34	1.48 to 3.69
Electrical linemen and cable jointers (857)	41	4	3.79	1.58 to 9.13
Plumbers and pipe fitters (871)	305	12	9.13	5.58 to 14.9
Welders and flame-cutters (872)	3	0	NC	
Sheet-metal workers (873)	16	0	NC	
Structural metal preparers and erectors (874)	34	1	13.1	2.51 to 71.6
Painters, construction (931)	104	18	2.17	1.41 to 3.36
Crane and hoist operators (973)	17	0	NC	
Earth-moving and related machinery operators (974)	48	7	2.39	1.20 to 4.75
Motor-vehicle drivers (985)	14	4	1.05	0.39 to 2.81
Labourers, not elsewhere classified (999)	31	3	3.43	1.24 to 9.48

*OR calculated with unconditional logistic regression models adjusted for age (categorical) and period.
ISCO, International Standard Classification of Occupations (1968); ISIC, International Standard Industry Classification (1971); NC, not calculable.

large number of bricklayers among cases in our study and the magnitude of elevated risks we found for most occupations in the construction sector.

Our findings are, however, largely in agreement with many studies published in various countries. To name a few, studies that showed increased mesothelioma risks in the construction sector and associated occupations were performed in Canada,[25] France,[26] Italy,[11] Spain,[27] Nordic countries,[28–31] UK[19 32 33] and USA.[34 35] Asbestos (all forms) has been widely used worldwide in the construction industry due to its physical properties (flame-retardant, sound-absorbing, electrical and heat resistance) in insulation works (eg, pipes and chimneys) and to build roofs with corrugated asbestos-cement sheets. In Europe, estimates of the number of workers exposed to asbestos have been developed by CAREX (CARcinogen EXposure). Based on data collected during 1990–1993, it has

been estimated that, out of a total of 1.2 million workers exposed to asbestos, those employed in the construction industry were 574 000[1] and that 5.2% of male workers in construction industry were exposed to asbestos.[36] Some occupational groups used asbestos directly (eg, insulators and roofers, plumbers and pipe fitters), while others were likely were additionally exposed indirectly, or as bystanders, because they worked in areas where other workers handled asbestos.[37] Finally, many workers have been exposed due to removal of asbestos-containing materials. Most importantly, in this (as in other) industrial settings, the awareness of workers of health risks of asbestos exposure in the periods when these subjects were exposed was limited. Little attempt was made to inform workers and protect them from asbestos exposure. Even now, preventive measures (technical, organisational and personal) may be difficult to implement in this complex
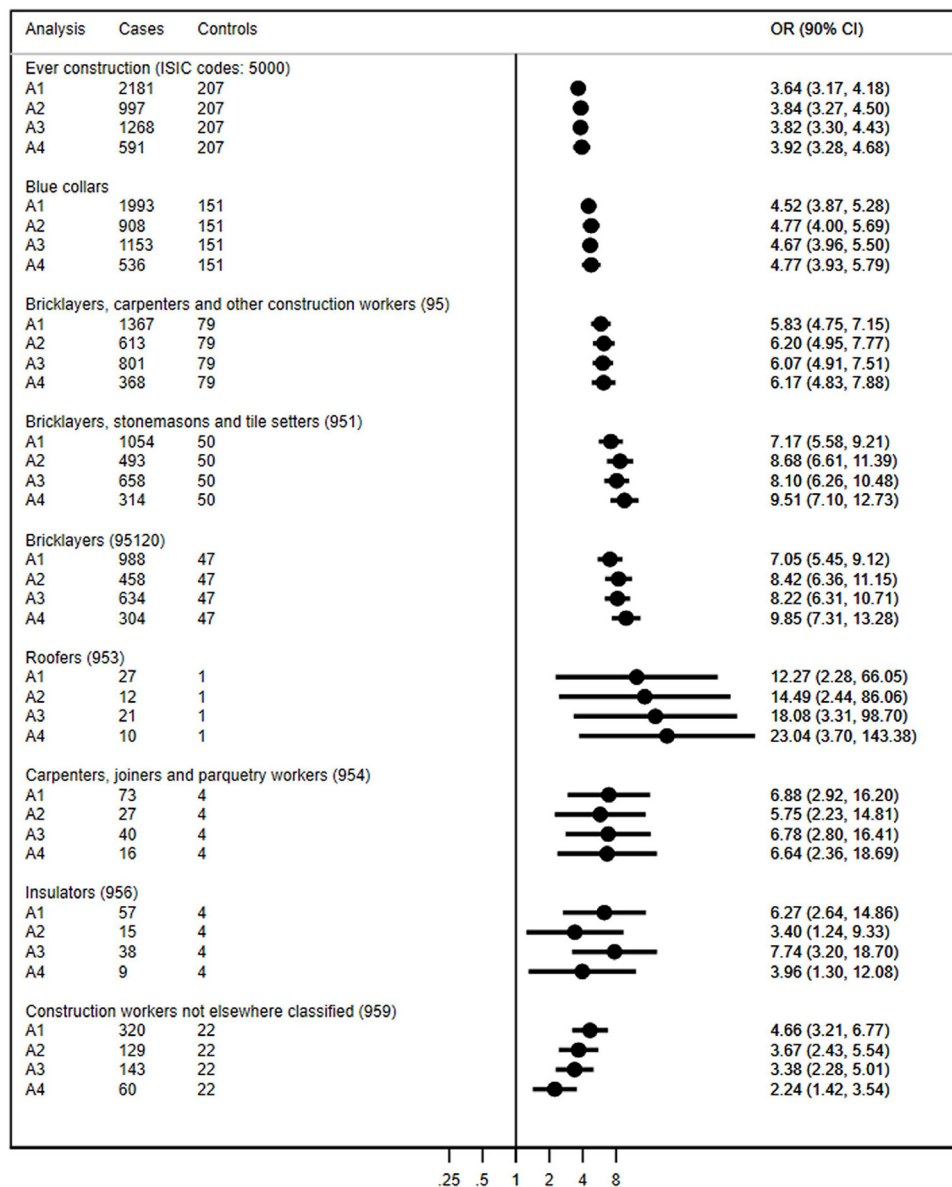
Figure 2 Pleural mesothelioma ORs and 90% CIs for selected occupations in men in the construction industry (ISIC-71 code 5000) in four analyses, Italy, 2000–2018. Results of the primary approach (subjects ever employed in non-construction blue-collar occupations for >5 years excluded): ever employed in construction, blue collars and three-digits ISCO-68 unit groups within minor group 95 'bricklayers, carpenters and other construction workers'. A1, overall analysis using all Italian cases, 2000–2018; A2, analysis with cases selected from the same periods of controls; A3, analysis with cases selected from the same areas of controls; A4, analysis with cases selected from the same periods and areas of controls. In parentheses, the International Standard Classification of Occupations (ISCO, 1968) codes. ISIC, International Standard Industrial Classification.

sector in which several tasks are performed by different workers within shared and always changing environments, especially in small or medium size companies.

Therefore, due to the large number of workers and the failure to implement preventive measures, the construction industry suffers the largest mesothelioma burden in many countries. For instance, a study in UK estimated that asbestos was responsible for more than half of the cancer registrations in construction and 70% of cancer deaths (2568 deaths, including 1249 lung cancers and 1292 mesotheliomas).[38] In Italy, in the period 1993–2018, the construction industry ranked first in the number of mesothelioma cases (3574, 16.2%) reported to ReNaM,

including 1332 bricklayers, 383 general construction workers, 232 plumbers and pipe fitters, 140 stonemasons, 117 electricians and 114 insulators.[39] Moreover, the proportion of mesothelioma cases among construction workers showed an increasing trend from 15.8% in the 1993–1998 period to 23.9% in 2014–2018.[10]

Asbestos exposure after the asbestos ban (1992)

Findings in this study mostly concern exposure occurred before the asbestos ban in 1992. However, it has been estimated that more than 30 million tons of asbestos-containing material was installed in the Italian territory in 1992 and that about 23 million tons are yet to be
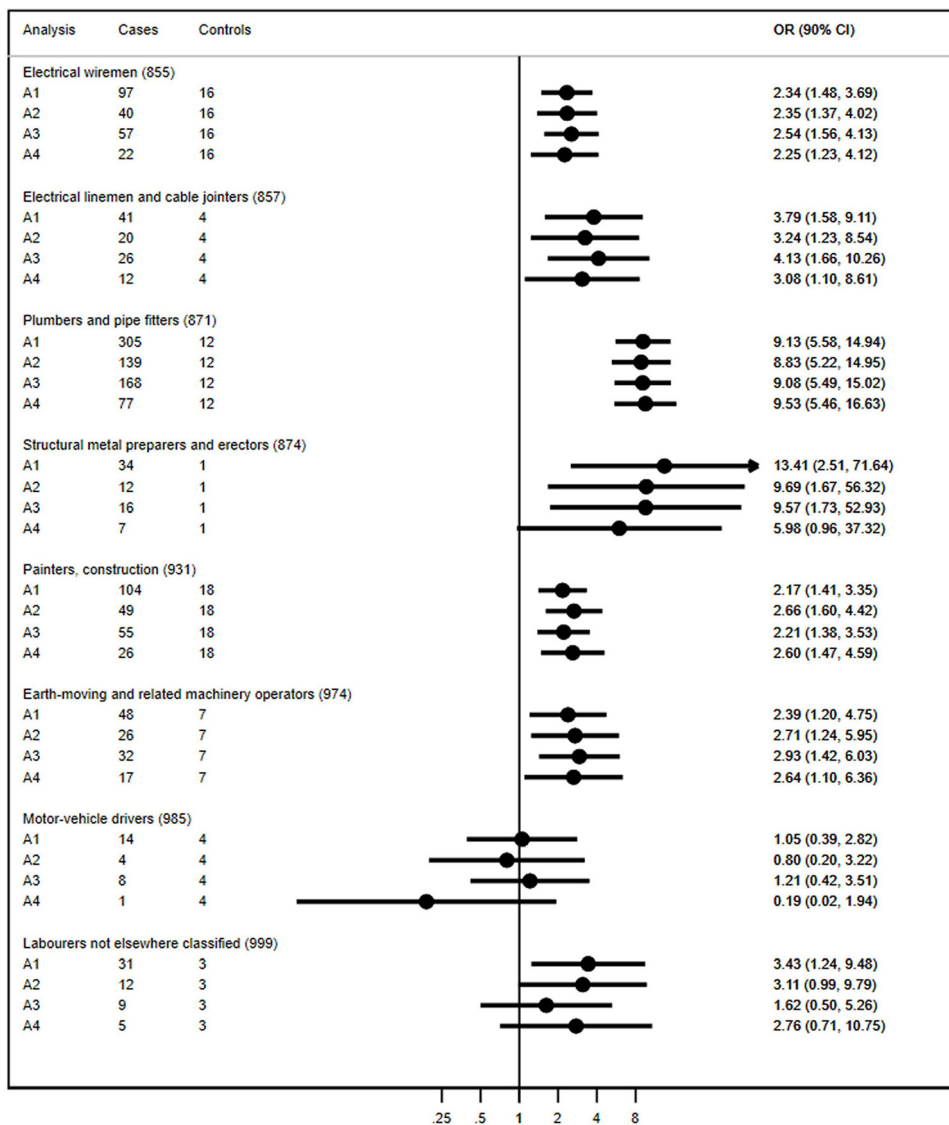
Figure 3 Pleural mesothelioma ORs and 90% CIs for selected occupations in men in the construction industry (ISIC-71 code 5000) in four analyses, Italy, 2000–2018. Results of the primary approach (subjects ever employed in non-construction blue-collar occupations for >5 years excluded): other three-digit ISCO-68 unit groups. A1, overall analysis using all Italian cases, 2000–2018; A2, analysis with cases selected from the same periods of controls; A3, analysis with cases selected from the same areas of controls; A4, analysis with cases selected from the same periods and areas of controls. In parentheses, the International Standard Classification of Occupations (ISCO, 1968) codes. ISIC, International Standard Industrial Classification.

reclaimed.[40] In an update of CAREX for Italy (2000–2003), it was estimated that 70 000 workers were still exposed to asbestos.[41] Hence, asbestos exposure continued to occur after the ban and may do so in future years or decades unless adequate preventive measures are used during asbestos removal. A recent study in Italy covering the period 1996–2013 showed that workers employed in the removal and disposal of asbestos-containing materials may be exposed to asbestos levels above the national action limit (0.01 fibres/cc) and occasionally also the European action limit at 0.1 fibres/cc.[42]

Strengths and limitations

The study has several strengths. First, the PM case series was extracted from the database of a national registry (ReNaM) in which active search for MM cases is performed according to common procedures: in particular, standardised criteria are used for MM diagnosis classification and collection and evaluation of lifetime job histories collected by a structured questionnaire.[10] Second, our study included MM cases from the whole country and covered a large time window (2000–2018). This was possible thanks to a recently developed crosswalk which allowed translation of thousands of Italian codes of occupations into international (ISCO-68) codes.[17] Third, we used three control series for the large majority (95.3% of 2210) randomly sampled from the general population (EAGLE and MISEM studies). Fourth, analogous to other studies,[19] we could perform analyses in which we excluded subjects employed in non-construction blue-collar occupations for more than 5 years: this approach

9

reduced potential confounding from asbestos exposure in non-construction occupations and yielded relative risk estimates markedly higher than the other approach (in which all subjects were included).[11 26]

The study has some limitations. First, although the three control series covered about 30 million people (half of the Italian population) over 8 years, the overlap of cases with controls was only partial. However, the various time and space restricted supplementary analyses produced quite consistent results, with few exceptions, showing that theoretically less preferable samples of the study base performed quite well in practice. This is in agreement with previous studies on peritoneal mesothelioma in Lombardy[14] and on mesothelioma of pericardium and tunica vaginalis testis in Italy.[15] A similar approach, though criticised, proved to be valid also in case–control studies on PM in France.[43–45] A second limitation pertains to information quality, since in the various studies, different persons performed data collection. However, the personnel were adequately trained, and we used only simple information on industries and occupations: hence, we do not expect substantially different accuracy across studies and case–control status. Conversely, errors and heterogeneity in coding occupations are likely, because the international codes of industries and occupations were assigned by different persons or were derived from Italian codes by applying a crosswalk, which probably caused some degree of misclassification of occupations.

CONCLUSIONS

The existence of a national epidemiological surveillance system of mesothelioma covering the whole Italian territory for more than 20 years enabled this nationwide case–control study with almost all controls sampled from the general population. We found clearly increased PM risk for most occupations in the construction industry. This is due to the past widespread use of asbestos in this economic sector and is consistent with findings in international literature. Our results are relevant for compensation of workers affected with mesothelioma in the construction industry.

Given that huge amounts of asbestos-containing materials are still present in the environment, the potential for asbestos exposure still exists if adequate technical, organisational and personal preventive measures are not taken during asbestos manipulation. In the future, special attention to surveillance of mesothelioma (and other asbestos-related diseases like lung cancer) must be given for workers employed in asbestos removal after the asbestos ban in 1992.

Author affiliations
[1]Occupational Health Unit, Regional Operating Center of Lombardy (COR Lombardia), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[2]COR Piemonte, Cancer Epidemiology Unit, CPO and University of Turin, Turin, Italy
[3]COR Puglia, Section of Occupational Medicine 'B Ramazzini', Department of Interdisciplinary Medicine, University of Bari Aldo Moro, Bari, Italy
[4]COR Toscana, Unit of Environmental and Occupational Epidemiology, Institute for Cancer Research, Prevention and Clinical Network, Florence, Italy
[5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland, USA
[6]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[7]Department of Environmental and Prevention Sciences, University of Ferrara, Ferrara, Italy
[8]Oncology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[9]COR Valle d'Aosta, Valle d'Aosta Health Local Unit, Aosta, Italy
[10]COR Province of Trento, Provincial Unit of Health, Hygiene and Occupational Medicine, Trento, Italy
[11]COR Province of Bolzano, Alto Adige Health Local Unit, Bolzano, Italy
[12]COR Veneto, Epidemiological Department, Azienda Zero, Padova, Italy
[13]COR Friuli-Venezia Giulia, Clinical Unit of Occupational Medicine, University of Trieste—Trieste General Hospitals, Trieste, Italy
[14]UO Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy
[15]Dipartimento di Medicina Interna e Specialità Mediche, Università degli Studi di Genova, Genova, Italy
[16]COR Liguria, UO Epidemiologia Clinica, IRCCS Ospedale Policlinico San Martino, Genova, Liguria, Italy
[17]COR Emilia-Romagna, Public Health Department, Health Local Unit, Reggio Emilia, Italy
[18]COR Marche, School of Medicinal and Health Products Sciences, University of Camerino, Camerino, Italy
[19]COR Umbria, Servizio Prevenzione, Sanità Veterinaria e Sicurezza Alimentare, Regione Umbria, Perugia, Umbria, Italy
[20]COR Lazio, Department of Epidemiology, Lazio Regional Health Service, ASL Roma 1, Rome, Lazio, Italy
[21]COR Abruzzo, Abruzzo Regional Health Agency (ASR), Pescara, Italy
[22]COR Molise, Registri Tumori Regione Molise, Campobasso, Italy
[23]COR Basilicata, Epidemiologic Regional Center, Potenza, Italy
[24]COR Calabria, Public Health Unit, Crotone, Italy
[25]COR Sicilia, Cancer Registry ASP Ragusa and Sicily Regional Epidemiological Observatory, Ragusa, Italy
[26]COR Sardegna, Regional Epidemiological Center, Cagliari, Italy
[27]Occupational and Environmental Medicine, Epidemiology and Hygiene Department, Italian Workers' Compensation Authority (INAIL), Rome, Italy

LV: data collection (MISEM study); MTL and NEC: principal investigators (EAGLE study); SC, SMa and GB: principal investigators, data collection (CARA study); AS, LM, SP, CGi, SE, SMu, VCa, VCo, CN, FDA, CGe, LB, AR, IG, GM, IC, ER, TS, FC, ML, FT, GC and MM: data collection (Regional Operating Centres); AM: director (ReNaM), study conceptualisation; AB: data management (ReNaM) and CM: study design, data collection and manuscript drafting. All authors contributed to interpretation of findings and discussion. All authors revised and approved the manuscript for intellectual content.

Competing interests DCo, SMa and CM served as consultants in trials concerning asbestos-related diseases.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The EAGLE, MISEM and CARA studies were approved by the following institutional review boards (IRBs): National Cancer Institute Special Studies IRB: 01-C-N211, National Cancer Institute, Bethesda, Maryland, USA (EAGLE); Comitato Etico Interaziendale, AOU San Giovanni Battista di Torino and AO CTO/Maria Adelaide di Torino, Turin, Italy: CEI-589 (MISEM); Comitato Etico del Policlinico di Sant'Orsola, Bologna, Italy: 111/2013/U/OssN (CARA).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Simona Stella http://orcid.org/0000-0003-4276-2583
Dario Consonni http://orcid.org/0000-0002-8935-3843
Enrica Migliore http://orcid.org/0000-0003-0121-6295
Domenica Cavone http://orcid.org/0000-0002-2009-1806
Luigi Vimercati http://orcid.org/0000-0002-4072-2871
Lucia Miligi http://orcid.org/0000-0002-8223-485X
Sara Piro http://orcid.org/0000-0003-4198-7035
Neil E Caporaso http://orcid.org/0000-0001-7562-4609
Stefania Curti http://orcid.org/0000-0003-4343-8873
Stefano Mattioli http://orcid.org/0000-0002-9639-7430
Giovanni Brandi http://orcid.org/0000-0003-0013-2858
Corrado Negro http://orcid.org/0000-0002-2007-3608
Carlo Genova http://orcid.org/0000-0003-3690-8582
Antonio Romanelli http://orcid.org/0000-0003-4899-1889
Iolanda Grappasonni http://orcid.org/0000-0003-1131-4286
Ilaria Cozzi http://orcid.org/0000-0003-0313-9799
Staniscia Tommaso http://orcid.org/0000-0002-5077-515X
Federico Tallarigo http://orcid.org/0000-0002-4131-9531
Alessandro Marinaccio http://orcid.org/0000-0001-9068-2137
Alessandra Binazzi http://orcid.org/0000-0002-0435-600X
Carolina Mensi http://orcid.org/0000-0002-9075-3684

REFERENCES
1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. *Arsenic, Metals, Fibres, and Dusts*. Lyon, France: International Agency for Research on Cancer, 2012.
2 GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2018;392:1923–94.
3 GBD 2016 Occupational Carcinogens Collaborators. 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;77:151–9.
4 Odgerel C-O, Takahashi K, Sorahan T, *et al*. Estimation of the global burden of mesothelioma deaths from incomplete national mortality data. *Occup Environ Med* 2017;74:851–8.
5 Park E-K, Takahashi K, Hoshuyama T, *et al*. Global magnitude of reported and unreported mesothelioma. *Environ Health Perspect* 2011;119:514–8.
6 Rath EM, Yuen ML, Odgerel C-O, *et al*. The ecological association between asbestos consumption and asbestos-related diseases 15 years later. *Environ Health Perspect* 2022;130:57703.
7 Fazzo L, Binazzi A, Ferrante D, *et al*. Burden of mortality from asbestos-related diseases in Italy. *Int J Environ Res Public Health* 2021;18:10012.
8 Oddone E, Bollon J, Nava CR, *et al*. Predictions of mortality from pleural mesothelioma in Italy after the ban of asbestos use. *Int J Environ Res Public Health* 2020;17:607.
9 Oddone E, Bollon J, Nava CR, *et al*. Effect of asbestos consumption on malignant pleural mesothelioma in Italy: forecasts of mortality up to 2040. *Cancers (Basel)* 2021;13:3338.
10 Binazzi A, Di Marzio D, Verardo M, *et al*. Asbestos exposure and malignant mesothelioma in construction workers-Epidemiological remarks by the Italian National Mesothelioma Registry (ReNaM). *Int J Environ Res Public Health* 2021;19:235.
11 Migliore E, Consonni D, Peters S, *et al*. Pleural mesothelioma risk by industry and occupation: results from the Multicentre Italian Study on the Etiology of Mesothelioma (MISEM). *Environ Health* 2022;21:60.
12 Greenland S. Control-initiated case-control studies. *Int J Epidemiol* 1985;14:130–4.
13 Landi MT, Consonni D, Rotunno M, *et al*. Environment And Genetics in Lung cancer Etiology (EAGLE) study: an integrative population-based case-control study of lung cancer. *BMC Public Health* 2008;8:203.
14 Consonni D, Calvi C, De Matteis S, *et al*. Peritoneal mesothelioma and asbestos exposure: a population-based case-control study in Lombardy, Italy. *Occup Environ Med* 2019;76:545–53.
15 Marinaccio A, Consonni D, Mensi C, *et al*. Association between asbestos exposure and pericardial and tunica vaginalis testis malignant mesothelioma: a case-control study and epidemiological remarks. *Scand J Work Environ Health* 2020;46:609–17.
16 Consonni D, De Matteis S, Lubin JH, *et al*. Occupational risks for lung cancer in a population-based case-control study. *Am J Epidemiol* 2010;171:323–33.
17 Spinazzè A, Consonni D, Borghi F, *et al*. Development of a crosswalk to translate Italian occupation codes to ISCO-68 codes. *Ann Work Expo Health* 2022;66:815–21.
18 Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests *BMJ* 2001;322:226–31.
19 Rake C, Gilham C, Hatch J, *et al*. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. *Br J Cancer* 2009;100:1175–83.
20 Ahrens W, Merletti F. A standard tool for the analysis of occupational lung cancer in epidemiologic studies. *Int J Occup Environ Health* 1998;4:236–40.
21 Lacourt A, Gramond C, Rolland P, *et al*. Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural Mesothelioma. *Thorax* 2014;69:532–9.
22 Mensi C, Riboldi L, De Matteis S, *et al*. Impact of an asbestos cement factory on mesothelioma incidence: global assessment of effects of occupational, familial, and environmental exposure. *Environ Int* 2015;74:191–9.
23 Vimercati L, Cavone D, De Maria L, *et al*. Mesothelioma risk among construction workers according to job title: data from the Italian Mesothelioma Register. *Med Lav* 2023;114:e2023025.
24 Consonni D, De Matteis S, Pesatori AC, *et al*. Lung cancer risk among bricklayers in a pooled analysis of case-control studies. *Int J Cancer* 2015;136:360–71.
25 DeBono NL, Warden H, Logar-Henderson C, *et al*. Incidence of mesothelioma and asbestosis by occupation in a diverse workforce. *Am J Ind Med* 2021;64:476–87.
26 Rolland P, Gramond C, Lacourt A, *et al*. Occupations and industries in France at high risk for pleural mesothelioma: A population-based case-control study (1998-2002). *Am J Ind Med* 2010;53:1207–19.

27 Agudo A, González CA, Bleda MJ, *et al*. Occupation and risk of malignant pleural mesothelioma: A case-control study in Spain. *Am J Ind Med* 2000;37:159–68.

28 Plato N, Martinsen JI, Sparén P, *et al*. Occupation and mesothelioma in Sweden: updated incidence in men and women in the 27 years after the asbestos ban. *Epidemiol Health* 2016;38:e2016039.

29 Pukkala E, Martinsen JI, Lynge E, *et al*. Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol* 2009;48:646–790.

30 Järvholm B, Englund A. The impact of asbestos exposure in Swedish construction workers. *Am J Ind Med* 2014;57:49–55.

31 Engholm G, Englund A. Asbestos hazard in the Swedish construction industry--recent trends in mesothelioma incidence. *Scand J Work Environ Health* 2005;31 Suppl 2:27–30.

32 Coggon D, Inskip H, Winter P, *et al*. Differences in occupational mortality from pleural cancer, peritoneal cancer, and Asbestosis. *Occup Environ Med* 1995;52:775–7.

33 Frost G, Harding A-H, Darnton A, *et al*. Occupational exposure to asbestos and mortality among asbestos removal workers: a Poisson regression analysis. *Br J Cancer* 2008;99:822–9.

34 Tomasallo CD, Christensen KY, Raymond M, *et al*. An occupational legacy: malignant mesothelioma incidence and mortality in Wisconsin. *J Occup Environ Med* 2018;60:1143–9.

35 Ringen K, Dement J, Hines S, *et al*. Mortality of older construction and craft workers employed at department of energy nuclear sites: follow-up through 2016. *Am J Ind Med* 2019;62:742–54.

36 Driscoll T, Nelson DI, Steenland K, *et al*. The global burden of disease due to occupational carcinogens. *Am J Ind Med* 2005;48:419–31.

37 Järvholm B. Carcinogens in the construction industry. *Ann N Y Acad Sci* 2006;1076:421–8.

38 Hutchings SJ, Rushton L, British Occupational Cancer Burden Study Group. Occupational cancer in Britain. industry sector results. *Br J Cancer* 2012;107:S92–103.

39 Marinaccio A, Binazzi A, DiD. *Il Registro Nazionale dei Mesoteliomi. Settimo Rapporto:1-258 (Italian)*. Rome: INAIL, 2021.

40 Angelini A, Silvestri S. Asbestos removal acceleration for new jobs and fossil fuel use reduction for public health and climate readiness: A contribution to the revival of the Italian economy post-COVID-19. *New Solut* 2022;31:434–40.

41 Mirabelli D, Kauppinen T. Occupational exposures to carcinogens in Italy: an update of CAREX database. *Int J Occup Environ Health* 2005;11:53–63.

42 Scarselli A, Corfiati M, Di Marzio D. Occupational exposure in the removal and disposal of asbestos-containing materials in Italy. *Int Arch Occup Environ Health* 2016;89:857–65.

43 Lacourt A, Lévque E, Guichard E, *et al*. Dose-time-response association between occupational asbestos exposure and pleural mesothelioma. *Occup Environ Med* 2017;74:691–7.

44 Lacourt A, Leveque E, Goldberg M, *et al*. Dose-time response association between occupational asbestos exposure and pleural Mesothelioma: authors' response. *Occup Environ Med* 2018;75:161–2.

45 Boffetta P, Pira E, Romano C, *et al*. "Response to: 'dose-time-response association between occupational asbestos exposure and pleural mesothelioma' by Lacourt et al" *Occup Environ Med* 2018;75:160.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open

Supplementary Figure 1 Diagram showing numbers of male pleural mesothelioma cases and controls across the years and their main characteristics, Italy, 2002-2004 and 2012-2016. Cases selected from the **same periods** of controls **(analysis A2)**. In the primary approach subjects ever employed in non-construction blue collar occupations for >5 years were excluded; in the secondary approach all subjects (also those ever employed in non-construction blue collar occupations for >5 years) were included.

Period	Year	N. cases Primary/ secondary approach	Case source	Control source
2002-2004 and 2012-2016	2002	214/760	**NATIONAL MESOTHELIOMA REGISTRY** Living in any Region ReNaM questionnaire **Primary/secondary approach: N. 2156/6910**	**EAGLE** Living in 216 municipalities in five Lombardy Provinces (Milan, Monza, Brescia, Pavia, Varese) EAGLE questionnaire **Primary/secondary approach: N. 778/1617**
	2003	238/758		
	2004	246/768		
	2012	288/886		**MISEM** Living in five Regions (Apulia, Lombardy, Piedmont, Tuscany, Veneto) ReNaM questionnaire **Primary/secondary approach: N. 250/490** **CARA** Living in one Region (Emilia-Romagna) ReNaM questionnaire **Primary/secondary approach: N. 57/103**
	2013	304/979		
	2014	289/928		
	2015	283/921		
	2016	294/910		

CARA, Cholangiocarcinoma Aetiology: Role of Asbestos; EAGLE, Environment And Genetics in Lung cancer Etiology; MISEM, Multicentre Italian Study on the Etiology of Mesothelioma; ReNaM, Registro Nazionale Mesoteliomi

1

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open

Supplementary Figure 2 Diagram showing numbers of male pleural mesothelioma cases and controls across the years and their main characteristics, Italy, 2000–2018. Cases selected from the **same areas** of controls **(analysis A3)**. In the primary approach subjects ever employed in non-construction blue collar occupations for >5 years were excluded; in the secondary approach all subjects (also those ever employed in non-construction blue collar occupations for >5 years) were included.

Period	Year	N. cases Primary/ secondary approach	Case source	Control source
2000-2018	2000	134/389	**LOMBARDY MESOTHELIOMA REGISTRY** Living in six Regions (Lombardy, Piedmont, Veneto, Tuscany, Apulia, Emilia-Romagna) ReNaM questionnaire **Primary/secondary approach: N. 2690/8933**	
	2001	117/399		
	2002	114/405		**EAGLE** Living in 216 municipalities in five Lombardy Provinces (Milan, Monza, Brescia, Pavia, Varese) EAGLE questionnaire **Primary/secondary approach: N. 778/1617**
	2003	142/444		
	2004	134/443		
	2005	135/481		
	2006	125/419		
	2007	121/471		
	2008	129/469		
	2009	156/507		
	2010	142/482		
	2011	156/540		
	2012	176/532		**MISEM** Living in five Regions (Apulia, Lombardy, Piedmont, Tuscany, Veneto) ReNaM questionnaire **Primary/secondary approach: N. 250/490** **CARA** Living in one Region (Emilia-Romagna) ReNaM questionnaire **Primary/secondary approach: N. 57/103**
	2013	176/604		
	2014	146/505		
	2015	161/526		
	2016	188/592		
	2017	179/536		
	2018	59/189		

CARA, Cholangiocarcinoma Aetiology: Role of Asbestos; EAGLE, Environment And Genetics in Lung cancer Etiology; MISEM, Multicentre Italian Study on the Etiology of Mesothelioma; ReNaM, Registro Nazionale Mesoteliomi

2

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance
placed on this supplemental material which has been supplied by the author(s)

BMJ Open

Supplementary Figure 3 Diagram showing numbers of male pleural mesothelioma cases and controls across the years and their main characteristics, Italy, 2002-2004 and 2012-2016. Cases selected from the **same periods and areas** of controls **(analysis A4)**. In the primary approach subjects ever employed in non-construction blue collar occupations for >5 years were excluded; in the secondary approach all subjects (also those ever employed in non-construction blue collar occupations for >5 years) were included.

Period	Year	N. cases Primary/ secondary approach	Case source	Control source
2002-2004 and 2012-2016	2002	114/405	**NATIONAL MESOTHELIOMA REGISTRY** Living in six Regions (Lombardy, Piedmont, Veneto, Tuscany, Apulia, Emilia-Romagna) ReNaM questionnaire **Primary/secondary approach: N. 1237/4051**	**EAGLE** Living in 216 municipalities in five Lombardy Provinces (Milan, Monza, Brescia, Pavia, Varese) EAGLE questionnaire **Primary/secondary approach: N. 778/1617**
	2003	142/444		
	2004	134/443		
	2012	176/532		**MISEM** Living in five Regions (Apulia, Lombardy, Piedmont, Tuscany, Veneto) ReNaM questionnaire **Primary/secondary approach: N. 250/490**
	2013	176/605		
	2014	146/504		
	2015	161/526		**CARA** Living in one Region (Emilia-Romagna) ReNaM questionnaire **Primary/secondary approach: N. 57/103**
	2016	188/592		

CARA, Cholangiocarcinoma Aetiology: Role of Asbestos; EAGLE, Environment And Genetics in Lung cancer Etiology; MISEM, Multicentre Italian Study on the Etiology of Mesothelioma; ReNaM, Registro Nazionale Mesoteliomi

Supplementary Table 1 Pleural mesothelioma odds ratios (OR) and 90% confidence intervals (CI) by **length of employment** for selected occupations in men in the construction industry (ISIC-71 code 5000), Italy, 2000–2018. Results of the **primary approach** (subjects ever employed in non-construction blue collar occupations for >5 years excluded), **analysis A1**

Occupation (ISCO-68 code)	Cases	Controls	OR[a]	90% CI
Never employed in construction	2616	878	1.00	Reference
Length of employment (years)				
Bricklayers, stonemasons and other construction workers (95)				
0.5-19	370	33	3.98	2.92-5.43
20+	971	45	7.11	5.47-9.24
P-value for trend			<0.001	
P-value for trend, reference category excluded			0.02	
Bricklayers, stonemasons and tile setters (951)				
0.5-19	246	14	6.72	4.24-10.7
20+	788	34	7.61	5.64-10.3
P-value for trend			<0.001	
P-value for trend, reference category excluded			0.79	
Bricklayers (95120)				
0.5-19	233	14	6.27	3.95-9.96
20+	735	29	8.25	5.98-11.4
P-value for trend			<0.001	
P-value for trend, reference category excluded			0.44	
Construction workers not elsewhere classified (959)				
0.5-19	224	16	4.48	2.90-6.93
20+	90	6	4.78	2.36-9.68
P-value for trend			<0.001	
P-value for trend, reference category excluded			0.59	
Electrical wiremen (855)				
0.5-19	42	7	2.39	1.20-4.75
20+	55	9	2.30	1.25-4.21
P-value for trend			0.004	
P-value for trend, reference category excluded			0.61	
Plumbers and pipe fitters (871)				
0.5-19	90	6	5.48	2.71-11.1
20+	213	6	12.56	6.31-25.0
P-value for trend			<0.001	
P-value for trend, reference category excluded			0.20	
Painters (931)				
0.5-19	37	7	2.33	1.16-4.67
20+	64	10	2.11	1.18-3.76
P-value for trend			0.007	
P-value for trend, reference category excluded			0.65	

ISCO, International Standard Classification of Occupations (1968); ISIC, International Standard Industry Classification (1971)
[a]OR calculated with unconditional logistic regression models adjusted for age (categorical) and period

Supplementary Table 2 Pleural mesothelioma odds ratios (OR) and 90% confidence intervals (CI) for selected occupations in men in the construction industry (ISIC-71 code 5000), Italy, 2000–2018. Results of the **secondary approach** (all subjects included, also those ever employed in non-construction blue collar occupations for >5 years), **analysis A1**

Occupation (ISCO-68 code)	Cases	Controls	OR*	90% CI
Total	15 592	2210		
Never employed in construction	10 863	1808	1.00	Reference
Ever employed in construction	4729	402	2.00	1.82-2.21
Blue collars (55, 56, 581, 628, 631, 7-9)	4506	342	2.24	2.02-2.48
Bricklayers, carpenters, and other construction workers (95)	2877	183	2.60	2.28-2.98
Bricklayers, stonemasons and tile setters (951)	1921	127	2.48	2.12-2.91
Bricklayers (95120)	1778	118	2.44	2.07-2.87
Reinforced concreters, cement finishers and terrazzo workers (952)	35	0	NC	
Roofers (953)	66	3	4.55	1.71-12.1
Carpenters, joiners and parquetry workers (954)	161	9	3.19	1.80-5.65
Plasterers (955)	20	2	1.66	0.48-5.81
Insulators (956)	122	4	6.16	2.66-14.3
Glaziers (957)	1	12	NC	
Construction workers NEC (959)	873	39	3.49	2.65-4.60
Other blue collar occupations				
Electrical wiremen (855)	298	40	1.38	1.03-1.83
Electrical linemen and cable jointers (857)	119	8	2.64	1.44-4.85
Plumbers and pipe fitters (871)	608	31	3.54	2.60-4.82
Welders and flame-cutters (872)	18	0	NC	
Sheet-metal workers (873)	33	1	7.06	1.32-37.8
Structural metal preparers and erectors (874)	121	3	7.37	2.81-19.4
Painters, construction (931)	241	33	1.25	0.91-1.71
Crane and hoist operators (973)	49	4	2.39	1.01-5.67
Earth-moving and related machinery operators (974)	100	23	0.69	0.47-1.03
Motor-vehicle drivers (985)	70	11	1.08	0.63-1.88
Labourers NEC (999)	101	5	3.21	1.50-6.88

ISCO, International Standard Classification of Occupations (1968); ISIC, International Standard Industry Classification (1971); NC, not calculable; NEC, not elsewhere classified.

*OR calculated with unconditional logistic regression models adjusted for age (categorical) and period.

Supplementary Figure 4 Pleural mesothelioma odds ratios (OR) and 90% confidence intervals (CI) for selected occupations in men in the construction industry (ISIC-71 code 5000) in four analyses, Italy, 2000–2018. Results of the **secondary approach** (all subjects included, also those ever employed in non-construction blue collar occupations for >5 years): ever employed in construction, blue collars, and three-digits ISCO-68 unit groups within minor group 95 "Bricklayers, carpenters and other construction workers". A1: overall analysis using all Italian cases, 2000-2018; A2: analysis with cases selected from the same periods of controls; A3: analysis with cases selected from the same areas of controls; A4: analysis with cases selected from the same periods and areas of controls. In parentheses the International Standard Classification of Occupations (ISCO, 1968) codes.

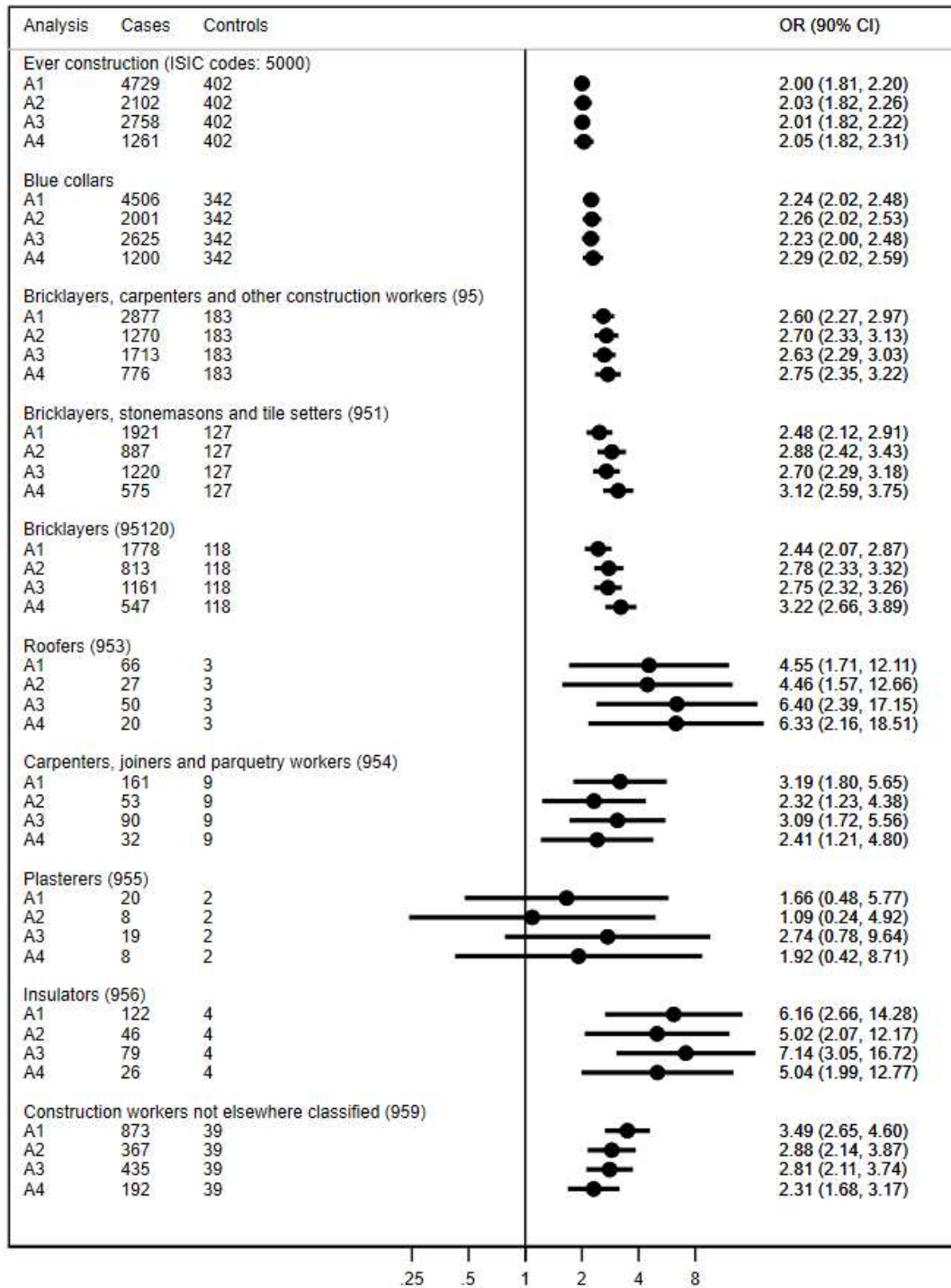| Analysis	Cases	Controls	OR (90% CI)
Ever construction (ISIC codes: 5000)			
A1	4729	402	2.00 (1.81, 2.20)
A2	2102	402	2.03 (1.82, 2.26)
A3	2758	402	2.01 (1.82, 2.22)
A4	1261	402	2.05 (1.82, 2.31)
Blue collars			
A1	4506	342	2.24 (2.02, 2.48)
A2	2001	342	2.26 (2.02, 2.53)
A3	2625	342	2.23 (2.00, 2.48)
A4	1200	342	2.29 (2.02, 2.59)
Bricklayers, carpenters and other construction workers (95)			
A1	2877	183	2.60 (2.27, 2.97)
A2	1270	183	2.70 (2.33, 3.13)
A3	1713	183	2.63 (2.29, 3.03)
A4	776	183	2.75 (2.35, 3.22)
Bricklayers, stonemasons and tile setters (951)			
A1	1921	127	2.48 (2.12, 2.91)
A2	887	127	2.88 (2.42, 3.43)
A3	1220	127	2.70 (2.29, 3.18)
A4	575	127	3.12 (2.59, 3.75)
Bricklayers (95120)			
A1	1778	118	2.44 (2.07, 2.87)
A2	813	118	2.78 (2.33, 3.32)
A3	1161	118	2.75 (2.32, 3.26)
A4	547	118	3.22 (2.66, 3.89)
Roofers (953)			
A1	66	3	4.55 (1.71, 12.11)
A2	27	3	4.46 (1.57, 12.66)
A3	50	3	6.40 (2.39, 17.15)
A4	20	3	6.33 (2.16, 18.51)
Carpenters, joiners and parquetry workers (954)			
A1	161	9	3.19 (1.80, 5.65)
A2	53	9	2.32 (1.23, 4.38)
A3	90	9	3.09 (1.72, 5.56)
A4	32	9	2.41 (1.21, 4.80)
Plasterers (955)			
A1	20	2	1.66 (0.48, 5.77)
A2	8	2	1.09 (0.24, 4.92)
A3	19	2	2.74 (0.78, 9.64)
A4	8	2	1.92 (0.42, 8.71)
Insulators (956)			
A1	122	4	6.16 (2.66, 14.28)
A2	46	4	5.02 (2.07, 12.17)
A3	79	4	7.14 (3.05, 16.72)
A4	26	4	5.04 (1.99, 12.77)
Construction workers not elsewhere classified (959)			
A1	873	39	3.49 (2.65, 4.60)
A2	367	39	2.88 (2.14, 3.87)
A3	435	39	2.81 (2.11, 3.74)
A4	192	39	2.31 (1.68, 3.17)

6

Supplementary Figure 5 Pleural mesothelioma odds ratios (OR) and 90% confidence intervals (CI) for selected occupations in men in the construction industry (ISIC-71 code 5000) in four analyses, Italy, 2000–2018. Results of the **secondary approach** (all subjects included, also those ever employed in non-construction blue collar occupations for >5 years): other three-digit ISCO-68 unit groups. A1: overall analysis using all Italian cases, 2000-2018; A2: analysis with cases selected from the same periods of controls; A3: analysis with cases selected from the same areas of controls; A4: analysis with cases selected from the same periods and areas of controls. In parentheses the International Standard Classification of Occupations (ISCO, 1968) codes.

Analysis	Cases	Controls	OR (90% CI)
Electrical wiremen (855)			
A1	298	40	1.38 (1.04, 1.84)
A2	123	40	1.21 (0.87, 1.68)
A3	193	40	1.57 (1.17, 2.11)
A4	82	40	1.39 (0.97, 1.99)
Electrical linemen and cable jointers (857)			
A1	119	8	2.64 (1.44, 4.84)
A2	57	8	2.59 (1.35, 4.96)
A3	63	8	2.42 (1.29, 4.54)
A4	31	8	2.42 (1.20, 4.87)
Plumbers and pipe fitters (871)			
A1	608	31	3.54 (2.60, 4.82)
A2	285	31	3.43 (2.47, 4.77)
A3	335	31	3.44 (2.50, 4.73)
A4	159	31	3.35 (2.36, 4.76)
Sheet-metal workers (873)			
A1	33	1	7.06 (1.32, 37.76)
A2	17	1	10.34 (1.85, 57.79)
A3	16	1	5.23 (0.94, 29.09)
A4	7	1	6.16 (0.97, 39.12)
Structural metal preparers and erectors (874)			
A1	121	3	7.37 (2.81, 19.36)
A2	43	3	6.05 (2.20, 16.63)
A3	54	3	4.90 (1.82, 13.16)
A4	16	3	2.82 (0.95, 8.40)
Painters, construction (931)			
A1	241	33	1.25 (0.91, 1.71)
A2	114	33	1.40 (0.98, 1.99)
A3	147	33	1.29 (0.93, 1.79)
A4	68	33	1.43 (0.97, 2.11)
Crane and hoist operators (973)			
A1	49	4	2.39 (1.01, 5.66)
A2	22	4	3.01 (1.19, 7.61)
A3	25	4	2.18 (0.89, 5.36)
A4	11	4	2.55 (0.93, 7.00)
Earth-moving and related machinery operators (974)			
A1	100	23	0.69 (0.47, 1.02)
A2	52	23	0.74 (0.47, 1.17)
A3	65	23	0.77 (0.50, 1.18)
A4	32	23	0.70 (0.41, 1.19)
Motor-vehicle drivers (985)			
A1	70	11	1.08 (0.63, 1.87)
A2	33	11	1.41 (0.75, 2.64)
A3	42	11	1.18 (0.66, 2.11)
A4	21	11	1.63 (0.82, 3.23)
Labourers not elsewhere classified (999)			
A1	101	5	3.21 (1.50, 6.87)
A2	44	5	3.44 (1.52, 7.79)
A3	26	5	1.41 (0.61, 3.26)
A4	19	5	3.16 (1.29, 7.72)

.25 .5 1 2 4 8

7