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

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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 a case-control design based on cases from this registry, we estimated relative risks for pleural mesothelioma (PM) among construction workers.

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- and period-adjusted unconditional logistic regression models were fitted to estimate odds ratios (ORs) and 90% confidence intervals (CIs) for occupations in the construction industry. The main analysis included all cases. Given the incomplete overlap of cases and controls, we performed three time, space, and time-space restricted sensitivity analyses.

Results We included 15,592 incident PM cases and 2,210 controls. OR for blue collar occupations was 2.24 (4,506 cases), mostly bricklayers, stonemasons, and tile setters (1,921 cases, OR 2.48). ORs>2 were found for electrical linemen and cable jointers; plumbers and pipe fitters; structural metal preparers and erectors; roofers; carpenters, joiners and parquetry workers; insulators; general construction workers; crane and hoist operators, and labourers. Moderate increased risks (<2) were estimated for electrical wiremen, painters, and plasterers. Sensitivity analyses yielded similar findings, with few exceptions.

Conclusions We found increased pleural mesothelioma risks for most occupations in the construction industry. These findings are relevant for compensation of subjects affected with mesothelioma employed as blue collars in the construction industry.

What is already known about this subject?

According to the Italian Mesothelioma Registry, the largest mesothelioma burden (16%) occurs in the construction industry. However, relative risks of mesothelioma in this sector has never been investigated at a country-wide level.

What are the new findings?

Using a case-control design with incomplete overlap of cases and controls (cases diagnosed in Italy in 2000-2018, controls enrolled in six regions in 2002-2004 and 2012-2016), we found elevated risks for most blue collar occupations in construction. Validity of this approach was verified in sensitivity analyses.

How might this impact on policy or clinical practice in the foreseeable future?

These results are relevant for compensation of mesothelioma patients employed in the construction sector, either with direct or indirect asbestos exposure.

INTRODUCTION

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibers of the serpentine and amphibole series. These include the serpentine mineral chrysotile ("white asbestos"), and the five amphibole minerals actinolite, 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 mesothelioma (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 25-38 thousands 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, 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 industries with the largest asbestos use in the past and which is paying the largest toll: out of 17,191 with occupational exposure, 3,574 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, 77 controls), to which contributed several blue collar occupations.[11]

In this work, we performed a "control-initiated case-control study"[12] to examine more in depth the PM relative risks in male construction workers by exploiting three existing datasets of controls: 1) Controls from the Environment 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 "Multicentre Italian Study on the Etiology 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 "Cholangiocarcinoma 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 analyzed PM risk for various occupations in the construction sector. In the main 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. In order to verify the reliability of results, we then performed three sensitivity analyses by applying time, space, and time-space restrictions to cases in order to more closely match the study base of which controls are a sample. We previously used a similar approach in two case-control studies on mesothelioma of peritoneum[14] and of pericardium and tunica vaginalis testis,[15] in which findings using all cases were remarkably similar to those obtained by applying time and space restrictions.

METHODS

The National Mesothelioma Registry (ReNaM)

The National Mesothelioma Registry (ReNaM) is an epidemiological surveillance programme organized as a network of regional operating centers (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 far from complete, 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 immunohistochemical confirmation), "probable" (usually, cytological 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 standardized ReNaM questionnaire which 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, 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 (Figure 1).

Figure 1 here

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 261 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 six 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 interviewed with the ReNaM questionnaire.

The third set of controls was taken from the CARA study performed in Emilia-Romagna (Northern Italy). Subjects were interviewed with a detailed questionnaire including 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, possible). We divided cases in 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 more closely match 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.

Statistical analysis

We assessed the relative risks of PM associated with ever employment in construction industry (ISIC-71 code 5000 or the corresponding ATECO-91 code 45). The majority of construction workers were men, so women were excluded from analyses. We performed analyses for selected occupations and groups of occupations, with subjects ever employed in multiple occupations included in each analysis. We considered results with at least 2 cases and 2 controls.

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% confidence intervals (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 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, i.e., 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).

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

We used existing datasets of cases and control. Therefore, subjects could not be involved in the design, or conduct, or 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, 7,985 (51.2%) in the period 2000-2009 and 7,607 in 2010-2018 (Figure 1). EAGLE controls (2002-2004) were 1,617, while MISEM/CARA controls (2012-2016) were 603 (490 from MISEM, 103 from CARA).

In the whole study period there were 4,729 (30.3%) out of 15,592 PM cases ever employed in the construction industry (ISIC code 5000), while controls were 402 (18.2%) among 2,210 (Table 1). The proportions of ever employed in construction were remarkably similar in the two periods: among cases,

2,372 (29.7%) out of 7,985 in 2000-2009 and 2,357 (31.0%) out of 7,607 in 2010-2018; among EAGLE controls, 299 (18.5%) out of 1,617 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 (9,195, 59.9%) completed a personal interview with the ReNaM questionnaire. A definite diagnosis was available for 13,368 cases (85.7%). Most cases (9,499, 60.9%) were of the epithelioid histotype.

Table 1 Characteristics of pleural mesothelioma cases and controls in men ever/never employed in the construction industry, Italy, 2000–2018.

	Ever construction				Never construction				Total			
	Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	4,729	100	402	100	10,863	100	1,808	100	15,592	100.0	2,210	100
Period												
<2010	2,372	50.2	299	74.4	5,613	51.7	1,318	72.9	7,985	51.2	1,617	73.2
2010+	2,357	49.8	103	25.6	5,250	48.3	490	27.1	7,607	48.8	593	26.8
Age (years)												
<50	112	2.4	17	4.2	272	2.5	90	5.0	384	2.5	107	4.8
50-54	171	3.6	25	6.2	359	3.3	98	5.4	530	3.4	123	5.6
55-59	360	7.6	48	11.9	767	7.1	223	12.3	1,127	7.2	271	12.3
60-64	553	11.7	66	16.4	1,344	12.4	304	16.8	1,897	12.2	370	16.7
65-69	858	18.1	98	24.4	1,825	16.8	435	24.1	2,683	17.2	533	24.1
70-74	966	20.4	91	22.6	2,192	20.2	371	20.5	3,158	20.3	462	20.9
75-79	926	19.6	45	11.2	2,107	19.4	234	12.9	3,033	19.5	279	12.6
80-84	538	11.4	10	2.5	1,282	11.8	36	2.0	1,820	11.7	46	2.1
85+	245	5.2	2	0.5	715	6.6	17	0.9	960	6.2	19	0.9
Mean (SD)	70.4	(9.5)	66.2	(8.7)	70.7	(9.8)	66.1	(9.1)	70.6	(9.7)	66.1	(9.0)
Interview												
Direct	2,933	62.0	402	100	6,262	57.7	1,808	100	9,195	59.0	2,210	100
Next-of-kin	1,709	36.1			4,242	39.1			5,951	38.2		
None	78	1.7			278	2.6			356	2.3		
Other	9	0.2			81	0.8			90	0.6		
Diagnosis												
Definite	4,117	87.1			9,251	85.2			13,368	85.7		
Probable	347	7.3			802	7.4			1,149	7.4		
Possible	265	5.6			810	7.5			1,075	6.9		
Morphology*												
Epitheliod (90253)	2,897	61.3			6,602	60.8			9,499	60.9		
Sarcomatoid (90513)	479	10.1			1,007	9.3			1,486	9.5		
Biphasic (90533)	583	12.3			1,237	11.4			1,820	11.7		
NOS (90503)	450	9.5			1,081	10.0			1,531	9.8		
Not available	320	6.8			936	8.6			1,256	8.1		

*Codes of the International Classification of Diseases for Oncology, Third Edition in parentheses; NOS, not otherwise specified

In the overall analysis (A1) which included all cases recorded in Italy in 2000-2018, an OR of 2.00 was calculated for subjects ever employed in construction (4,729 cases) (Table 2). This increase was driven by numerous blue collars occupations (OR 2.24), including: electrical linemen and cable jointers (OR 2.64); plumbers and pipe fitters (OR 3.54); structural metal preparers and erectors (OR 7.37); bricklayers, stonemasons and tile setters (OR 2.48), in particular bricklayers, by far the most represented

occupation (1,778 cases, OR 2.44); roofers (OR 4.55); carpenters, joiners and parquetry workers (OR 3.19); insulators (OR 6.16); construction workers not elsewhere classified (OR 3.49); crane and hoist operators (OR 2.39) and labourers not elsewhere classified (OR 3.21). Moderate increased risks were estimated for electrical wiremen (OR 1.38), painters (OR 1.25), and plasterers (OR 1.66).

Table 2 Pleural mesothelioma odds ratios (OR) and 90% confidence intervals (CI) for selected occupations in men in the construction industry (ISIC 5000), Italy, 2000–2018.

Occupation (ISCO code)	Cases	Controls	OR[a]	90% CI
Total	15,592	2,210		
Never employed in construction	10,863	1,808	1.00	Reference
Ever employed in construction	4,729	402	2.00	1.82-2.21
White collars	307	64	0.86	0.68-1.09
Blue collars (55, 56, 581, 628, 631, 7-9)	4,506	342	2.24	2.02-2.48
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
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
Bricklayers, stonemasons and tile setters (951)	1,921	127	2.48	2.12-2.91
Bricklayers (95120)	1,778	118	2.44	2.07-2.87
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
Construction workers not elsewhere classified (959)	873	39	3.49	2.65-4.60
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 not elsewhere classified (999)	101	5	3.21	1.50-6.88

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

Most findings were highly comparable with those estimated in time (A2) or space (A3) restricted analyses (Supplementary Figures 1-2, Supplementary Tables 1-2) and in the analysis in which both time and space restrictions were applied (A4, Supplementary Figure 3 and Supplementary Table 3). Figure 2 shows the general good agreement across the four analyses, with the exception of motor-vehicle drivers (no increase in the overall analysis A1, increased risk analysis A4).

Figure 2 here

DISCUSSION

In this nationwide Italian study we found in males an elevated risk of pleural mesothelioma for most blue collar occupations in the construction industry, in particular (in order of number of cases): bricklayers; general construction workers (i.e., construction workers not elsewhere classified); plumbers and pipe fitters; electrical wiremen; painters; carpenters; joiner and parquetry workers; insulators; structural metal preparers an erectors; electrical linemen and cable jointers; labourers; roofers; crane and hoist operators; and plasterers. Findings were in general consistent across various supplementary analyses with different study base samples except for motor-vehicle drivers, for which risk was not

elevated in the overall analysis but was increased in the in the theoretically preferable time and space restricted analysis.

Our findings are in agreement with many studies published in various countries. Just to name a few, studies that showed increased mesothelioma risks in the construction sector and in various occupations therein were performed in Canada,[19] France,[20] Italy,[11] Spain,[21] Nordic countries,[22-25] UK,[26-28] and USA.[29 30] Our results are largely plausible. 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 (e.g., pipes, 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.[31] Some occupational groups used asbestos directly (e.g., insulators and roofers, plumbers and pipe fitters), while other might have been exposed indirectly because they worked in areas where other workers handled asbestos (e.g., electricians, carpenters, painters, concrete workers, maintenance workers).[32] Finally, many workers have been exposed because involved in removal of asbestos-containing materials. It should be added that preventive measures (technical, organizational, and personal) are difficult to implement in this complex 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 difficulty of implementing 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 (2,568 deaths, including 1,249 lung cancers and 1,292 mesotheliomas).[33] In Italy, in the period 1993-2018, the construction industry ranked first in the number of mesothelioma cases (3,574, 16.2%) reported to ReNaM, including 1,332 bricklayers, 383 general construction workers, 232 plumbers and pipe fitters, 140 stonemasons, 117 electricians, and 114 insulators.[34] Moreover, the proportion of 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 reclaimed.[35] In an update of CAREX for Italy (2000-2003) it was estimated that 70,000 workers were still exposed to asbestos.[36] Hence, asbestos exposure continued to occur after the ban and may do 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 fibers/cc) and occasionally also the European action limit at 0.1 fibers/cc.[37]

Strengths and limitations

The study has several strengths. First, the pleural mesothelioma 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, standardized 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%) randomly sampled from the general population (EAGLE and MISEM studies).

The study has some limitations. First, although the three control series covered about 30 million people (half of the Italian population) over eight 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 criticized, proved to be valid also in case-control studies on pleural mesothelioma in France.[38-40] A second limitation regard information quality, since in the various studies different persons performed data collection. However, the personnel was 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 in coding occupations are a possibility because the codes were in part assigned by different persons or by a crosswalk, which likely caused some degree of misclassification of occupations.

CONCLUSIONS

This work was made possible thanks to data collected through an epidemiological surveillance system of mesothelioma covering the whole Italian territory since more than 20 years. In this nationwide case-control study with almost all controls sampled from the general population, we found increased pleural mesothelioma risk for most occupations in the construction industry. This is largely plausible given 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 blue collar 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, organizational, 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.

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Contributors SS: statistical analysis, manuscript drafting; DC, conceptualization, study design, statistical supervision, manuscript drafting; EM: manuscript drafting and statistical analysis (MISEM study); DCa, LV: data collection (MISEM study); MTL, NEC: principal investigators (EAGLE study); SC, SM, GB: principal investigators, data collection (CARA study); AS, LM, SP, CG, SE, SMu, VC, VCo, CN, FDA, CGe, LB, AR, IG, GM, IC, ER, TS, FC, ML, FT, GC, MM: data collection (Regional Operating Centers); AM: director (ReNaM), study conceptualization; AB: data management (ReNaM); CM: study design, data collection, manuscript drafting. All authors contributed to interpretation of findings and discussion. All authors revised and approved the manuscript for intellectual content.

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Competing interests DC, SM, CM served as consultants in trials concerning asbestos-related diseases.

Patient consent for publication As reporting of mesothelioma to the National Mesothelioma Registry (ReNaM) is compulsory by law (277/1991 and 81/2008), patient consent is not required for cases. In the EAGLE, MISEM, and CARA studies, enrolled subjects signed and informed consent form.

Ethical 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/MariaAdelaide di Torino, Turin, Italy: CEI-589 (MISEM); Comitato Etico del Policlinico di Sant'Orsola, Bologna, Italy: 111/2013/U/OssN (CARA).

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Figure legends

Figure 1 Diagram showing numbers of male pleural mesothelioma cases and controls across the years and their main characteristics, Italy, 2000-2018.

Figure 1 footnotes

Abbreviations: 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

Figure 2 Pleural mesothelioma odds ratios (OR) and 90% confidence intervals (CI) for selected occupations in men in the construction industry (ISIC 5000) in four analyses, Italy, 2000–2018. A1: overall analysis using all Italian cases, 2000-2018; A2: analysis with cases selected frrm 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 parenthesis the International Standard Classification of Occupations (ISCO, 1968) codes.

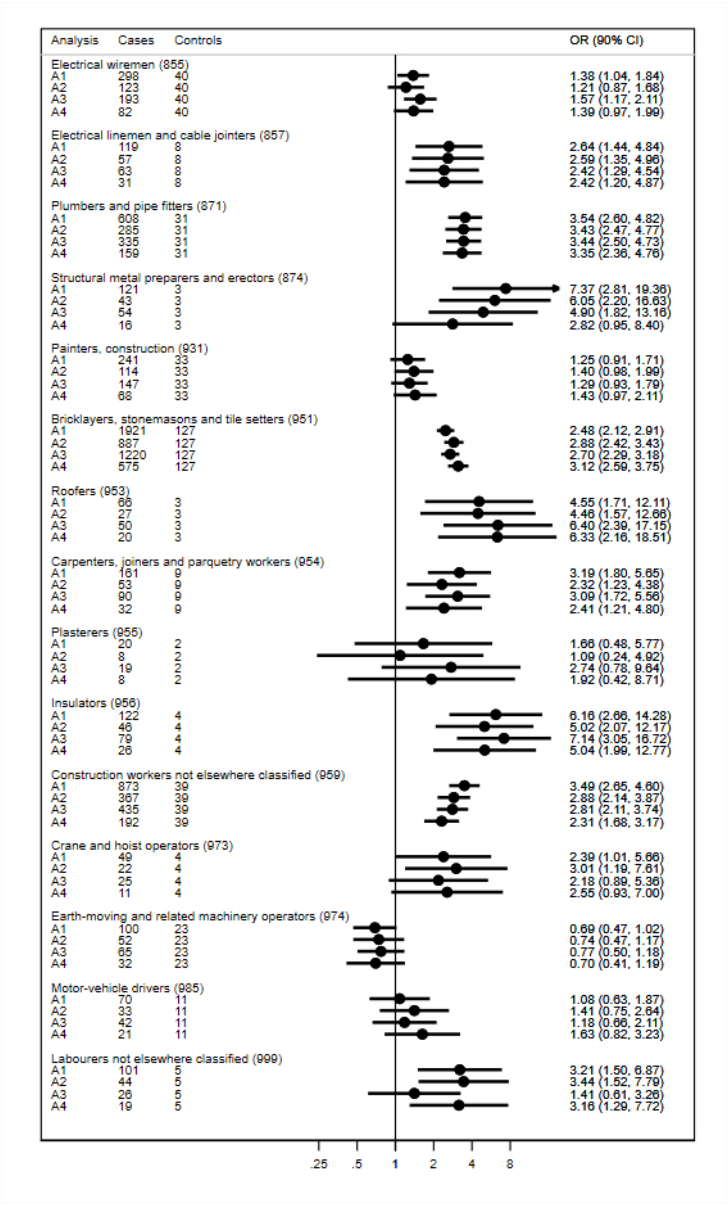
Figure 2 footnotes

*Codes of the International Classification of Diseases for Oncology, Third Edition in parentheses; NOS, not otherwise specified

Period	Year	N. cases	Case source	Control source
2000-2018	2000	682	**NATIONAL MESOTHELIOMA REGISTRY** N. 15,592, living in any Region ReNaM questionnaire	
	2001	734		
	2002	760		**EAGLE** N. 1,617, living in 216 municipalities in five Lombardy Provinces (Milan, Monza, Brescia, Pavia, Varese) EAGLE questionnaire
	2003	758		
	2004	768		
	2005	861		
	2006	782		
	2007	882		
	2008	857		
	2009	901		
	2010	851		
	2011	886		
	2012	886		**MISEM** N. 490, living in five Regions (Apulia, Lombardy, Piedmont, Tuscany, Veneto) ReNaM questionnaire **CARA** N. 103, living in one Region (Emilia-Romagna) ReNaM questionnaire
	2013	979		
	2014	928		
	2015	921		
	2016	910		
	2017	841		
	2018	405		

1

210x297mm (200 x 200 DPI)



199x329mm (72 x 72 DPI)

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.

<table>
<tr><th>Period</th><th>Year</th><th>N. cases</th><th>Case source</th><th>Control source</th></tr>
<tr><td rowspan="8">2002-2004 and 2012-2016</td><td>2002</td><td>760</td><td rowspan="8">NATIONAL MESOTHELIOMA REGISTRY
N. 6,910, living in any Region
ReNaM questionnaire</td><td rowspan="3">EAGLE N. 1,617, living in 216 municipalities in five Lombardy Provinces (Milan, Monza, Brescia, Pavia, Varese)
EAGLE questionnaire</td></tr>
<tr><td>2003</td><td>758</td></tr>
<tr><td>2004</td><td>768</td></tr>
<tr><td>2012</td><td>886</td><td rowspan="5">MISEM N. 490, living in five Regions (Apulia, Lombardy, Piedmont, Tuscany, Veneto)
ReNaM questionnaire

CARA N. 103, living in one Region (Emilia-Romagna)
ReNaM questionnaire</td></tr>
<tr><td>2013</td><td>979</td></tr>
<tr><td>2014</td><td>928</td></tr>
<tr><td>2015</td><td>921</td></tr>
<tr><td>2016</td><td>910</td></tr>
</table>

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) for selected occupations in men in the construction industry (ISIC 5000), Italy, 2002-2004 and 2012-2016. Cases selected from the **same periods** of controls.

Occupation (ISCO code)	Cases	Controls	OR[a]	90% CI
Total	6,910	2,210		
Never employed in construction	4,808	1,808	1.00	Reference
Ever employed in construction	2,102	402	2.03	1.82-2.26
White collars	150	64	0.96	0.73-1.26
Blue collars (55, 56, 581, 628, 631, 7-9)	2,001	342	2.26	2.02-2.54
Electrical wiremen (855)	123	40	1.21	0.87-1.68
Electrical linemen and cable jointers (857)	57	8	2.59	1.35-4.96
Plumbers and pipe fitters (871)	285	31	3.43	2.47-4.77
Structural metal preparers and erectors (874)	43	3	6.05	2.20-16.6
Painters, construction (931)	114	33	1.40	0.98-1.99
Bricklayers, stonemasons and tile setters (951)	887	127	2.88	2.42-3.43
Bricklayers (95120)	813	118	2.78	2.33-3.33
Roofers (953)	27	3	4.46	1.57-12.6
Carpenters, joiners and parquetry workers (954)	53	9	2.32	1.23-4.38
Plasterers (955)	8	2	1.09	0.24-4.89
Insulators (956)	46	4	5.02	2.07-12.2
Construction workers not elsewhere classified (959)	367	39	2.88	2.14-3.86
Crane and hoist operators (973)	22	4	3.01	1.19-7.60
Earth-moving and related machinery operators (974)	52	23	0.74	0.47-1.18
Motor-vehicle drivers (985)	33	11	1.41	0.75-2.63
Labourers not elsewhere classified (999)	44	5	3.44	1.52-7.80

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 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.

<table>
<tr><th>Period</th><th>Year</th><th>N cases</th><th>Case source</th><th>Control source</th></tr>
<tr><td rowspan="19">2000-2018</td><td>2000</td><td>389</td><td rowspan="19">LOMBARDY MESOTHELIOMA REGISTRY
N. 8,933, living in five Lombardy Provinces (Milan, Monza, Brescia, Pavia, Varese)
ReNaM questionnaire</td><td></td></tr>
<tr><td>2001</td><td>399</td><td></td></tr>
<tr><td>2002</td><td>405</td><td rowspan="4">EAGLE N. 1,617, living in 216 municipalities in five Lombardy Provinces (Milan, Monza, Brescia, Pavia, Varese)
EAGLE questionnaire</td></tr>
<tr><td>2003</td><td>444</td></tr>
<tr><td>2004</td><td>443</td></tr>
<tr><td>2005</td><td>481</td><td rowspan="4"></td></tr>
<tr><td>2006</td><td>419</td></tr>
<tr><td>2007</td><td>471</td></tr>
<tr><td>2008</td><td>469</td></tr>
<tr><td>2009</td><td>507</td></tr>
<tr><td>2010</td><td>482</td><td rowspan="2"></td></tr>
<tr><td>2011</td><td>540</td></tr>
<tr><td>2012</td><td>532</td><td rowspan="6">MISEM N. 490, living in five Regions (Apulia, Lombardy, Piedmont, Tuscany, Veneto)
ReNaM questionnaire

CARA N. 103, living in one Region (Emilia-Romagna)
ReNaM questionnaire</td></tr>
<tr><td>2013</td><td>604</td></tr>
<tr><td>2014</td><td>505</td></tr>
<tr><td>2015</td><td>526</td></tr>
<tr><td>2016</td><td>592</td></tr>
<tr><td>2017</td><td>536</td><td></td></tr>
<tr><td>2018</td><td>189</td><td></td></tr>
</table>

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 2 Pleural mesothelioma odds ratios (OR) and 90% confidence intervals (CI) for selected occupations in the construction industry (ISIC 5000), Italy, 2002-2004 and 2012-2016. Cases selected from the **same areas** of controls.

Occupation (ISCO code)	Cases	Controls	OR[a]	90% CI
Total	8,933	2,210		
Never employed in construction	6,175	1,808	1.00	Reference
Ever employed in construction	2,758	402	2.01	1.82-2.22
White collars	177	64	0.86	0.67-1.11
Blue collars (55, 56, 581, 628, 631, 7-9)	2,625	342	2.23	2.01-2.49
Electrical wiremen (855)	193	40	1.57	1.17-2.11
Electrical linemen and cable jointers (857)	63	8	2.42	1.29-4.54
Plumbers and pipe fitters (871)	335	31	3.44	2.50-4.72
Structural metal preparers and erectors (874)	54	3	4.90	1.82-13.1
Painters, construction (931)	147	33	1.29	0.93-1.80
Bricklayers, stonemasons and tile setters (951)	1,220	127	2.70	2.29-3.18
Bricklayers (95120)	1,161	118	2.75	2.32-3.26
Roofers (953)	50	3	6.40	2.39-17.2
Carpenters, joiners and parquetry workers (954)	90	9	3.09	1.72-5.57
Plasterers (955)	19	2	2.74	0.78-9.65
Insulators (956)	79	4	7.14	3.05-16.7
Construction workers not elsewhere classified (959)	435	39	2.81	2.11-3.73
Crane and hoist operators (973)	25	4	2.18	0.89-5.38
Earth-moving and related machinery operators (974)	65	23	0.77	0.50-1.17
Motor-vehicle drivers (985)	42	11	1.18	0.66-2.11
Labourers not elsewhere classified (999)	26	5	1.41	0.61-3.26

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 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.

Period	Year	N. cases	Case source	Control source
2002-2004 and 2012-2016	2002	405	**NATIONAL MESOTHELIOMA REGISTRY** N. 4,051, living in six Regions (Lombardy, Piedmont, Veneto, Tuscany, Apulia, Emilia-Romagna) ReNaM questionnaire	**EAGLE** N. 1,617, living in 216 municipalities in five Lombardy Provinces (Milan, Monza, Brescia, Pavia, Varese) EAGLE questionnaire
	2003	444		
	2004	443		
	2012	532		**MISEM** N. 490, living in five Regions (Apulia, Lombardy, Piedmont, Tuscany, Veneto) ReNaM questionnaire **CARA** N. 103, living in one Region (Emilia-Romagna) ReNaM questionnaire
	2013	605		
	2014	505		
	2015	526		
	2016	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 3 Pleural mesothelioma odds ratios (OR) and 90% confidence intervals (CI) for selected occupations in men in the construction sector (ISIC 5000), Italy, 2000–2018. Cases selected from the **same periods and areas** of controls.

Occupation (ISCO code)	Cases	Controls	OR[a]	90% CI
Total	4,051	2,210		
Never employed in construction	2,790	1,808	1.00	Reference
Ever employed in construction	1,261	402	2.05	1.82-2.31
White collars	89	64	0.97	0.71-1.31
Blue collars (55, 56, 581, 628, 631, 7-9)	1,200	342	2.29	2.02-2.59
Electrical wiremen (855)	82	40	1.39	0.97-1.98
Electrical linemen and cable jointers (857)	31	8	2.42	1.20-4.86
Plumbers and pipe fitters (871)	159	31	3.35	2.36-4.76
Structural metal preparers and erectors (874)	16	3	2.82	0.95-8.43
Painters, construction (931)	68	33	1.43	0.97-2.12
Bricklayers, stonemasons and tile setters (951)	575	127	3.12	2.59-3.75
Bricklayers (95120)	547	118	3.22	2.66-3.89
Roofers (953)	20	3	6.33	2.16-18.48
Carpenters, joiners and parquetry workers (954)	32	9	2.41	1.21-4.80
Plasterers (955)	8	2	1.92	0.42-8.65
Insulators (956)	26	4	5.04	1.99-12.77
Construction workers not elsewhere classified (959)	192	39	2.31	1.68-3.16
Crane and hoist operators (973)	11	4	2.55	0.93-7.01
Earth-moving and related machinery operators (974)	32	23	0.70	0.41-1.18
Motor-vehicle drivers (985)	21	11	1.63	0.82-3.22
Labourers not elsewhere classified (999)	19	5	3.16	1.29-7.70

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

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Comment
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Done
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Done
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Done
Objectives	3	State specific objectives, including any prespecified hypotheses	Done
Methods			
Study design	4	Present key elements of study design early in the paper	Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Done
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Done
		(*b*) For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Done
Bias	9	Describe any efforts to address potential sources of bias	Done
Study size	10	Explain how the study size was arrived at	Done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Done
		(*b*) Describe any methods used to examine subgroups and interactions	Done
		(*c*) Explain how missing data were addressed	Done
		(*d*) If applicable, explain how matching of cases and controls was addressed	Done
		(*e*) Describe any sensitivity analyses	Done (three sensitivity analyses)
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Done
		(b) Give reasons for non-participation at each stage	Participation had been reported in the

			original studies)
		(c) Consider use of a flow diagram	Diagram provided
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Done
		(b) Indicate number of participants with missing data for each variable of interest	Done
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Done
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Since previous studies were matched, crude analysis is not appropriate
		(*b*) Report category boundaries when continuous variables were categorized	Done
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Done
Discussion			
Key results	18	Summarise key results with reference to study objectives	Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Done

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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

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Key words: case-control study, asbestos, pleural cancer; mesothelioma, construction industry, occupations

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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 datasets, 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- and period-adjusted unconditional logistic regression models were fitted to estimate odds ratios (ORs) 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 dataset included 15 592 cases and 2210 controls. With the primary approach (4797 cases, 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.

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

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 (ReNaM), an epidemiological surveillance program organized as a network of regional operating centers which perform active search of mesothelioma cases
- Using a control-initiated case-control approach, we exploited three existing control datasets, mostly population-based, covering different periods and regions
- To minimize confounding, in a primary approach we excluded subjects ever employed in non-construction blue collar occupations for 5 years or more

- 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

INTRODUCTION

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibers of the serpentine and amphibole series. These include the serpentine mineral chrysotile ("white asbestos"), and the five amphibole minerals actinolite, 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 mesothelioma (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 25-38 thousands 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, 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 industries with the largest asbestos use in the past and which is paying the largest toll: out of 17 191 with occupational exposure, 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, 77 controls), to which contributed several blue collar occupations.[11]

In this work, we performed a "control-initiated case-control study"[12] to examine more in depth the PM relative 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 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 datasets of controls: 1) Controls from the Environment 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 "Multicentre Italian Study on the Etiology 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 "Cholangiocarcinoma 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 analyzed 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 occupations) and "reference" (never employed in construction occupations) groups, thus overcoming potential confounding from asbestos exposure in other occupations; 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, also in 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 more closely match the study base of which controls are a sample. We previously used a similar approach in two case-control studies on mesothelioma of peritoneum[14] and of 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 National Mesothelioma Registry (ReNaM) is an epidemiological surveillance program organized as a network of regional operating centers (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 far from complete, 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 immunohistochemical confirmation), "probable" (usually, cytological 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 standardized ReNaM questionnaire which 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, 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 six 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 face-to-face interviewed 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, possible). We divided cases in 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 more closely match 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 group: 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); Construction workers not elsewhere classified (959). We also separately analyzed 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); 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 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% confidence intervals (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 minimize 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, i.e., 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. Supplementary Figures 1-3 show numbers of cases and controls included in time or/and space restricted analysis A2-A4 under primary and secondary approach).

Figure 1 here.

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

Patients and public involvement

We used existing datasets of cases and control. Therefore, subjects could not be involved in the design, or conduct, or 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, 103 from CARA).

In 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 the epithelioid histotype.

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

Variable	Ever construction				Never construction			
	Cases		Controls		Cases		Controls	
	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		
Epitheliod (90523)	2897	61.3			6602	60.8		
Biphasic (90533)	583	12.3			1237	11.4		
Not available	320	6.8			936	8.6		

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

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 collars occupations (OR 4.52), especially the large category of Bricklayers, carpenters and other construction workers (OR 5.83). Within this category, high relative risks were found Bricklayers (OR 7.05) and construction workers not elsewhere classified (OR 4.66), and also for other less represented occupations, although with a low number of controls. Elevated risks were also for several other occupations, the most represented being plumbers and pipe-fitters (OR 9.13) and painters (OR 2.17). OR could not be calculated for occupations 952, 955, 957, 872, 873, and 973.

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 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	3.17-4.19
Blue collars (55, 56, 581, 628, 631, 7-9)	1993	151	4.52	3.87-5.29
Bricklayers, carpenters, and other construction workers (95)	1367	79	5.83	4.75-7.15
Bricklayers, stonemasons and tile setters (951)	1054	50	7.17	5.58-9.21
Bricklayers (95120)	988	47	7.05	5.45-9.12
Reinforced concreters, cement finishers and terrazzo workers (952)	12	0	NC	
Roofers (953)	27	1	12.3	2.28-66.1
Carpenters, joiners and parquetry workers (954)	73	4	6.88	2.92-16.2
Plasterers (955)	14	0	NC	
Insulators (956)	57	4	6.27	2.64-14.8
Glaziers (957)	0	4	NC	
Construction workers not elsewhere classified (959)	320	22	4.66	3.21-6.77
Other blue collar occupations				
Electrical wiremen (855)	97	16	2.34	1.48-3.69
Electrical linemen and cable jointers (857)	41	4	3.79	1.58-9.13
Plumbers and pipe fitters (871)	305	12	9.13	5.58-14.9
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	2.51-71.6
Painters, construction (931)	104	18	2.17	1.41-3.36
Crane and hoist operators (973)	17	0	NC	
Earth-moving and related machinery operators (974)	48	7	2.39	1.20-4.75
Motor-vehicle drivers (985)	14	4	1.05	0.39-2.81
Labourers not elsewhere classified (999)	31	3	3.43	1.24-9.48

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

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

Figures 2 and 3 here

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 years (there were no positive trends when we excluded the reference category, except for the minor group 95) (Supplementary Table 1).

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 remarkably lower (Supplementary Table 2). Also in this case the time or/and space restricted analyses A2-A4 yielded results in general quite similar to those of the overall analysis A1 (Supplementary Figures 4-5).

DISCUSSION

In this nationwide Italian study covering a long period (2000-2018), with the primary approach (in which subjects ever employed in non-construction blue collar occupations for >5 years were excluded) we found in males markedly elevated risks of pleural mesothelioma for most blue collar occupations in the construction industry, in particular (in order of number of cases): bricklayers; general construction workers (i.e., 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 an erectors; labourers; roofers. Findings of this primary approach were in general highly consistent across various supplementary analyses with different study base samples (i.e., with space/time restriction inclusion of cases)..

These results cannot be generalized to countries with different patterns/degrees of industrialization or which used different type of asbestos. Unlike other countries (e.g., France where almost all the asbestos used was imported and chrysotile was the most common used type),[21] in Italy asbestos was produced and used in all forms to produce asbestos-cement products for the construction industry.[22] Moreover, in Italy there are many small and medium construction 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] Finally, 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, e.g., use of ISCO-68 code 95120 instead of less specific codes 95910 (Housebuilders) or 95990 (Other construction workers), as already noted in a large pooled analysis of case-control study on lung cancer.[24] These factors might explain the large number of bricklayers among cases in our study and the elevated risks we found for most occupations in the construction sector.

Our findings are in agreement with many studies published in various countries. Just to name a few, studies that showed increased mesothelioma risks in the construction sector and in various occupations therein were performed in Canada,[25] France,[26] Italy,[11] Spain,[27] Nordic countries,[28-31] UK,[19 32 33] and USA.[34 35] Our results are largely plausible. 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 (e.g., pipes, 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 (e.g., insulators and roofers, plumbers and pipe fitters), while other might have been exposed indirectly because they worked in areas where other workers handled asbestos (e.g., electricians, carpenters, painters, concrete workers, maintenance workers).[37] Finally, many workers have been exposed because involved in removal of asbestos-containing materials. It should be added that preventive measures (technical, organizational, and personal) are difficult to implement in this complex

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 difficulty of implementing 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 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 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 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 fibers/cc) and occasionally also the European action limit at 0.1 fibers/cc.[42]

Strengths and limitations

The study has several strengths. First, the pleural mesothelioma 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, standardized 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%) randomly sampled from the general population (EAGLE and MISEM studies). Fourth, in analogy with others 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 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 eight 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 criticized, proved to be valid also in case-control studies on pleural mesothelioma in France.[43-45] A second limitation regards information quality, since in the various studies different persons performed data collection. However, the personnel was 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

This work was made possible thanks to data collected through an epidemiological surveillance system of mesothelioma covering the whole Italian territory since more than 20 years. In this nationwide case-control study with almost all controls sampled from the general population, we found clearly increased pleural mesothelioma risk for most occupations in the construction industry. This is largely plausible given 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, organizational, 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.

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Contributors SS: statistical analysis, manuscript drafting; DC, conceptualization, study design, statistical supervision, manuscript drafting; EM: manuscript drafting and statistical analysis (MISEM study); DCa, LV: data collection (MISEM study); MTL, NEC: principal investigators (EAGLE study); SC, SM, GB: principal investigators, data collection (CARA study); AS, LM, SP, CG, SE, SMu, VC, VCo, CN, FDA, CGe, LB, AR, IG, GM, IC, ER, TS, FC, ML, FT, GC, MM: data collection (Regional Operating Centers); AM: director (ReNaM), study conceptualization; AB: data management (ReNaM); CM: study design, data collection, manuscript drafting. All authors contributed to interpretation of findings and discussion. All authors revised and approved the manuscript for intellectual content.

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Competing interests DC, SM, CM served as consultants in trials concerning asbestos-related diseases.

Patient consent for publication As reporting of mesothelioma to the National Mesothelioma Registry (ReNaM) is compulsory by law (277/1991 and 81/2008), ethics approval is not required for cases. In the EAGLE, MISEM, and CARA studies, enrolled subjects signed an informed consent form.

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/MariaAdelaide di Torino, Turin, Italy: CEI-589 (MISEM); Comitato Etico del Policlinico di Sant'Orsola, Bologna, Italy: 111/2013/U/OssN (CARA).

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Figure legends

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.

Figure 1 footnotes

Abbreviations: 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

Figure 2 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 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.

Figure 3 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 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.

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**	
	2001	207/734		
	2002	214/760		**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		
	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		

1

Figure 1

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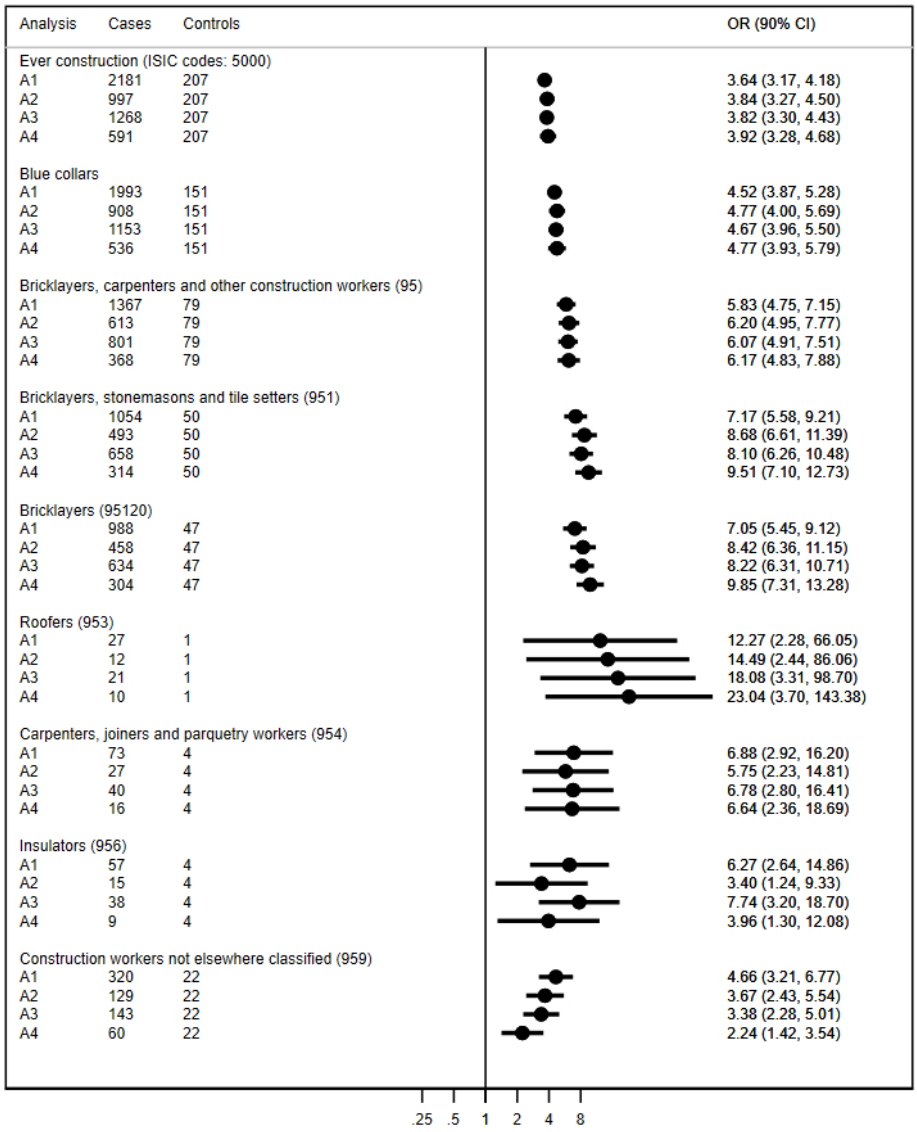

Figure 2

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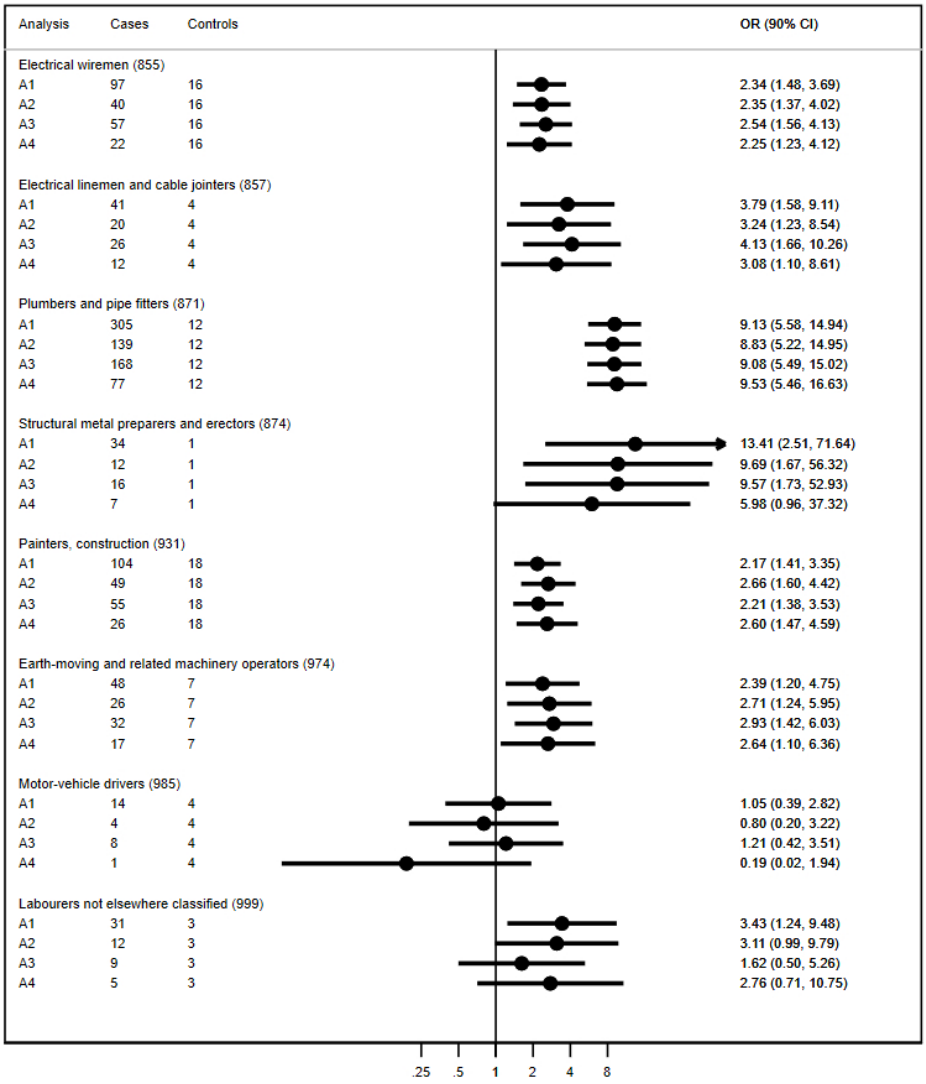

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Supplementary Figure 1 Diagram showing numbers of male pleural mesothelioma cases and controls across the years and their main characteristics, Italy, 2002-2004 and 2012-2016. Cases selected from the **same periods** of controls **(analysis A2)**. 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.

<table>
<tr><th>Period</th><th>Year</th><th>N. cases Primary/ secondary approach</th><th>Case source</th><th>Control source</th></tr>
<tr><td rowspan="8">2002-2004 and 2012-2016</td><td>2002</td><td>214/760</td><td rowspan="8">NATIONAL MESOTHELIOMA REGISTRY
Living in any Region
ReNaM questionnaire
Primary/secondary approach:
N. 2156/6910</td><td rowspan="3">EAGLE Living in 216 municipalities in five Lombardy Provinces
(Milan, Monza, Brescia, Pavia, Varese)
EAGLE questionnaire
Primary/secondary approach:
N. 778/1617</td></tr>
<tr><td>2003</td><td>238/758</td></tr>
<tr><td>2004</td><td>246/768</td></tr>
<tr><td>2012</td><td>288/886</td><td rowspan="5">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</td></tr>
<tr><td>2013</td><td>304/979</td></tr>
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</table>

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 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

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.

<table>
<tr><th>Period</th><th>Year</th><th>N. cases Primary/ secondary approach</th><th>Case source</th><th>Control source</th></tr>
<tr><td rowspan="8">2002-2004 and 2012-2016</td><td>2002</td><td>114/405</td><td rowspan="8">NATIONAL MESOTHELIOMA REGISTRY
Living in six Regions (Lombardy, Piedmont, Veneto, Tuscany, Apulia, Emilia-Romagna)
ReNaM questionnaire
Primary/secondary approach:
N. 1237/4051</td><td rowspan="3">EAGLE Living in 216 municipalities in five Lombardy Provinces
(Milan, Monza, Brescia, Pavia, Varese)
EAGLE questionnaire
Primary/secondary approach:
N. 778/1617</td></tr>
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ReNaM questionnaire
Primary/secondary approach: N. 250/490

CARA Living in one Region
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ReNaM questionnaire
Primary/secondary approach: N. 57/103</td></tr>
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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	

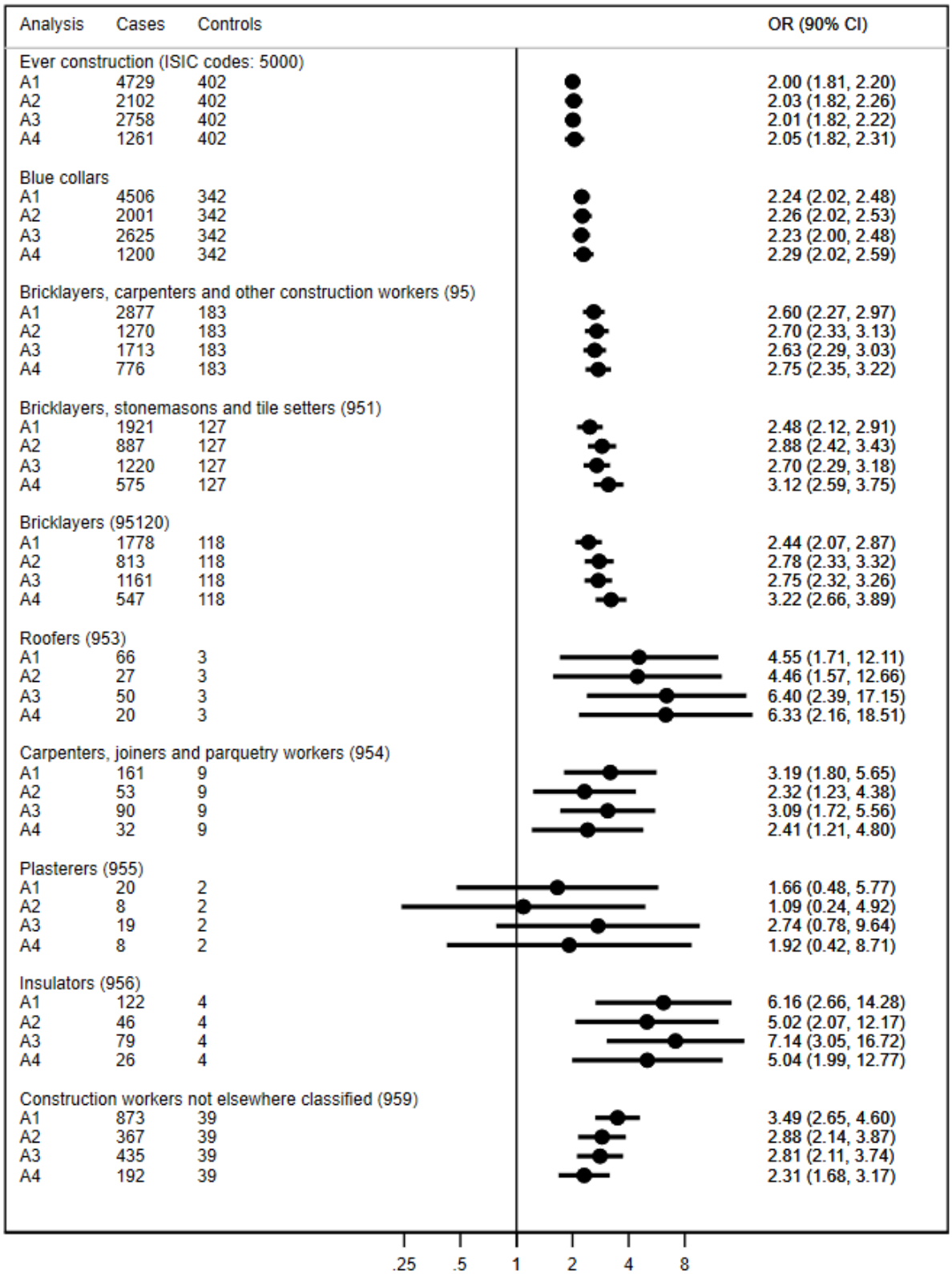
ISCO, International Standard Classification of Occupations (1968); ISIC, International Standard Industry Classification (1971)
[a]OR calculated with unconditional logistic regression models adjusted for age (categorical) and period

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**

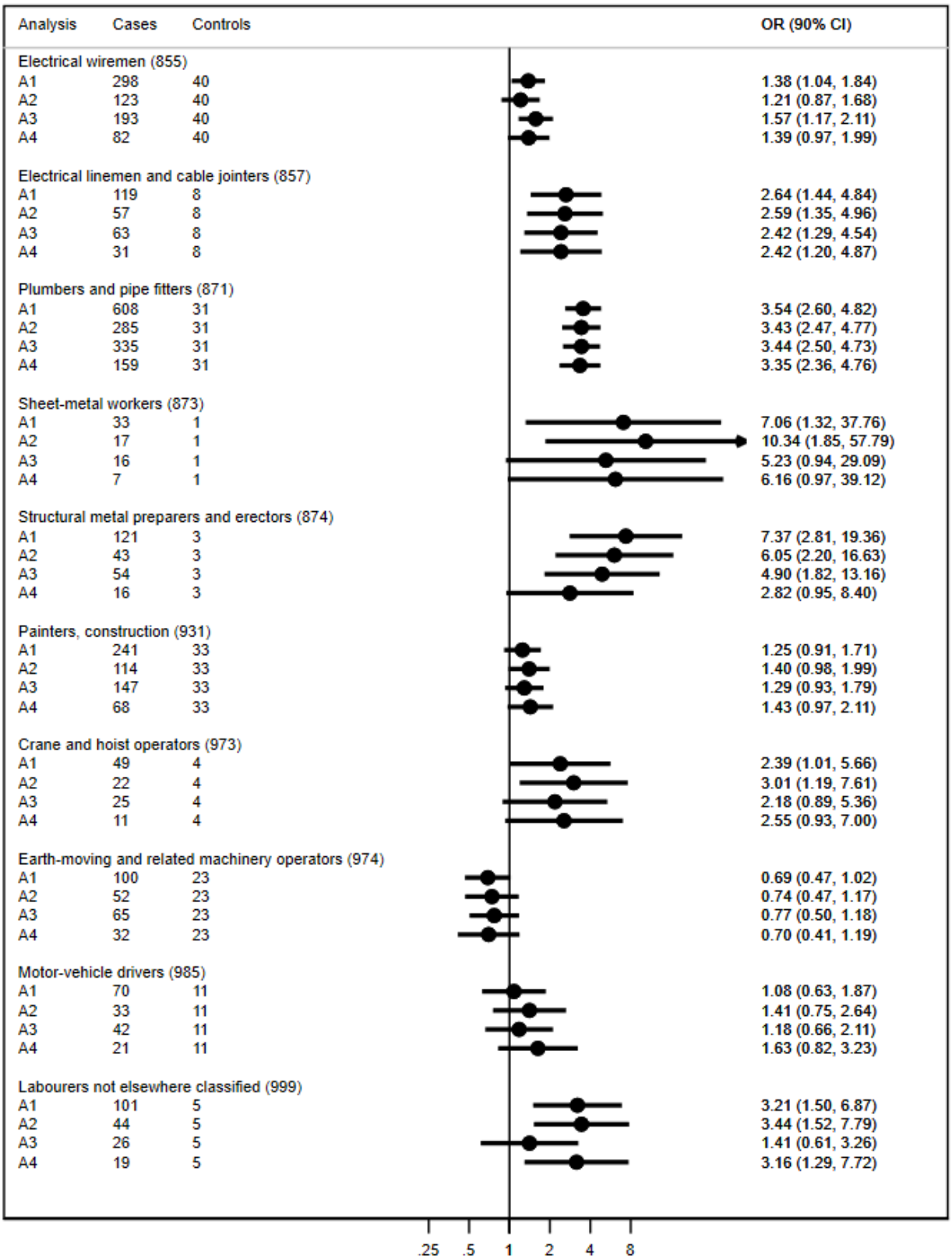
Occupation (ISCO-68 code)	Cases	Controls	OR*	90% CI
Total	15 592	2210		
Never employed in construction	10 863	1808	1.00	Reference
Ever employed in construction	4729	402	2.00	1.82-2.21
Blue collars (55, 56, 581, 628, 631, 7-9)	4506	342	2.24	2.02-2.48
Bricklayers, carpenters, and other construction workers (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.



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.



STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Comment
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Pag.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pag.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pag.5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	Pag.6
Methods			
Study design	4	Present key elements of study design early in the paper	Pag.6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pag.6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Pag.6-8
		(*b*) For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pag.6-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pag.6-9
Bias	9	Describe any efforts to address potential sources of bias	Pag.8-9
Study size	10	Explain how the study size was arrived at	Pag.6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pag.8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pag.8-9
		(*b*) Describe any methods used to examine subgroups and interactions	Pag.8-9
		(*c*) Explain how missing data were addressed	Pag.11
		(*d*) If applicable, explain how matching of cases and controls was addressed	Not applicable.
		(*e*) Describe any sensitivity analyses	Pag.8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pag.8-9, Figure 1, Suppl. Figures 1-3
		(b) Give reasons for non-participation at each stage	Participation been reported in the original studies

		(c) Consider use of a flow diagram	Figure 1, Suppl. Figures 1-3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pag.9-10, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Pag.10 (Table 1)
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Pag.2 (Table 2) and Suppl. Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Since previous studies were matched, crude analysis is not appropriate
		(*b*) Report category boundaries when continuous variables were categorized	Pag.10 (Table 1), and Suppl. Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pag.10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pag.12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pag.13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pag.12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pag.12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Pag.15

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Pleural mesothelioma risk in the construction industry: a case-control study in Italy. 2000-2018

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

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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 datasets, 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- and period-adjusted unconditional logistic regression models were fitted to estimate odds ratios (ORs) 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 dataset included 15 592 cases and 2210 controls. With the primary approach (4797 cases, 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.

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

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 (ReNaM), an epidemiological surveillance program organized as a network of regional operating centers which perform active search of mesothelioma cases
- Using a control-initiated case-control approach, we exploited three existing control datasets, mostly population-based, covering different periods and regions
- To minimize 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.

INTRODUCTION

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibers of the serpentine and amphibole series. These include the serpentine mineral chrysotile ("white asbestos"), and the five amphibole minerals actinolite, 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 mesothelioma (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 25-38 thousand 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, 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 industries with the largest asbestos use in the past andis paying the largest toll: of 17 191 cases with occupational exposure, 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, 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 relative 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 datasets of controls: 1) Controls from the Environment 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 "Multicentre Italian Study on the Etiology 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 "Cholangiocarcinoma 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 analyzed 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 occupations) and "reference" (never employed in construction occupations) groups, thus overcoming potential

confounding from asbestos exposure in other occupations; 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 National Mesothelioma Registry (ReNaM) is an epidemiological surveillance program organized as a network of regional operating centers (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 immunohistochemical confirmation), "probable" (usually, cytological 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 standardized 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, 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 six 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, 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 analyzed 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); 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% confidence intervals (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 minimize 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, i.e., 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. Supplementary Figures 1-3 show numbers of cases and controls included in time or/and space restricted analysis A2-A4 under primary and secondary approach).

Figure 1 here.

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

Patients and public involvement

We used existing datasets 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, 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.

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

Variable	Ever construction				Never construction			
	Cases		Controls		Cases		Controls	
	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		

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

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 Bricklayers (OR 7.05) and construction workers not elsewhere classified (OR 4.66), and also for other less represented occupations, although withfewer 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.

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 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	3.17-4.19
Blue collar occupations (55, 56, 581, 628, 631, 7-9)	1993	151	4.52	3.87-5.29
Bricklayers, carpenters, and other construction workers (95)	1367	79	5.83	4.75-7.15
Bricklayers, stonemasons and tile setters (951)	1054	50	7.17	5.58-9.21
Bricklayers (95120)	988	47	7.05	5.45-9.12
Reinforced concreters, cement finishers and terrazzo workers (952)	12	0	NC	
Roofers (953)	27	1	12.3	2.28-66.1
Carpenters, joiners and parquetry workers (954)	73	4	6.88	2.92-16.2
Plasterers (955)	14	0	NC	
Insulators (956)	57	4	6.27	2.64-14.8
Glaziers (957)	0	4	NC	
Construction worker, not elsewhere classified (959)	320	22	4.66	3.21-6.77
Other blue collar occupations				
Electrical wiremen (855)	97	16	2.34	1.48-3.69
Electrical linemen and cable jointers (857)	41	4	3.79	1.58-9.13
Plumbers and pipe fitters (871)	305	12	9.13	5.58-14.9
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	2.51-71.6
Painters, construction (931)	104	18	2.17	1.41-3.36
Crane and hoist operators (973)	17	0	NC	
Earth-moving and related machinery operators (974)	48	7	2.39	1.20-4.75
Motor-vehicle drivers (985)	14	4	1.05	0.39-2.81
Labourers, not elsewhere classified (999)	31	3	3.43	1.24-9.48

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

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

Figures 2 and 3 here

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) (Supplementary Table 1).

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 (Supplementary 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 (Supplementary Figures 4-5).

DISCUSSION

In this nationwide Italian study covering nearly two decades (2000-2018), we found markedly elevated risks of pleural mesothelioma among males for most blue collar occupations in the construction industry, in particular (in order of number of cases): bricklayers; general construction workers (i.e., 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 (i.e., with space/time restriction inclusion of cases).

These results may not fully generalized to countries with different patterns of asbestos use. Among these use factors are differential quantity of asbestos-containing products employed, work practices, organization of the construction industry, differences in work tasks by occupation, and relative quantities of different fiber types used in the Italian construction industry. Unlike other countries (e.g., 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 organized 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, e.g., use of ISCO-68 code 95120 instead of less specific codes 95910 (Housebuilders) or 95990 (Other construction workers), as already noted in a large pooled analysis of case-control study on lung cancer.[24] These factors might explain the 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 (e.g., pipes, 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 (e.g., 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, organizational, and personal) may be difficult to implement in this complex 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 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 fibers/cc) and occasionally also the European action limit at 0.1 fibers/cc.[42]

Strengths and limitations

The study has several strengths. First, the pleural mesothelioma 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, standardized 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 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 eight 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 criticized, proved to be valid also in case-control studies on pleural mesothelioma 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 e more than 20 years enabled this nationwide case-control study with almost all controls sampled from the general population. We found clearly increased pleural mesothelioma 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, organizational, 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.

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Contributors SS: statistical analysis, manuscript drafting; DC, conceptualization, study design, statistical supervision, manuscript drafting; EM: manuscript drafting and statistical analysis (MISEM study); DCa, LV: data collection (MISEM study); MTL, NEC: principal investigators (EAGLE study); SC, SM, GB: principal investigators, data collection (CARA study); AS, LM, SP, CG, SE, SMu, VC, VCo, CN, FDA, CGe, LB, AR, IG, GM, IC, ER, TS, FC, ML, FT, GC, MM: data collection (Regional Operating Centers); AM: director (ReNaM), study conceptualization; AB: data management (ReNaM); CM: study design, data collection, manuscript drafting. All authors contributed to interpretation of findings and discussion. All authors revised and approved the manuscript for intellectual content.

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Competing interests DC, SM, CM served as consultants in trials concerning asbestos-related diseases.

Patient consent for publication As reporting of mesothelioma to the National Mesothelioma Registry (ReNaM) is compulsory by law (277/1991 and 81/2008), ethics approval is not required for cases. In the EAGLE, MISEM, and CARA studies, enrolled subjects signed an informed consent form.

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).

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Figure legends

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.

Figure 1 footnotes

Abbreviations: 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

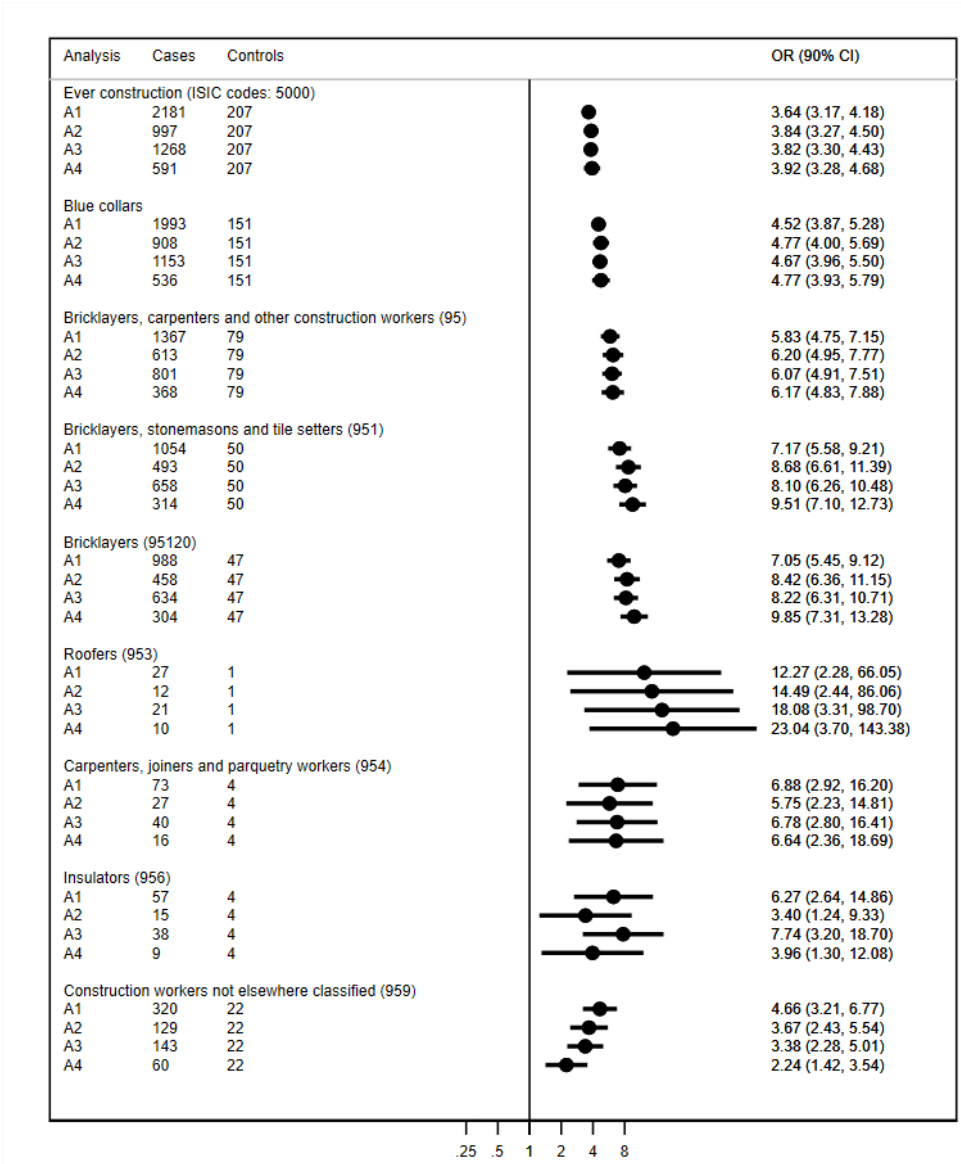
Figure 2 Pleural mesothelioma odds ratios (OR) and 90% confidence intervals (CI) for selected occupations in men in the construction industry (ISIC-71 code 5000) in four analyses, Italy, 2000–2018. Results of the primary approach (subjects ever employed in non-construction blue collar occupations for >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.

Figure 3 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 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.

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**	
	2001	207/734		
	2002	214/760		**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		
	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		

1

210x297mm (200 x 200 DPI)



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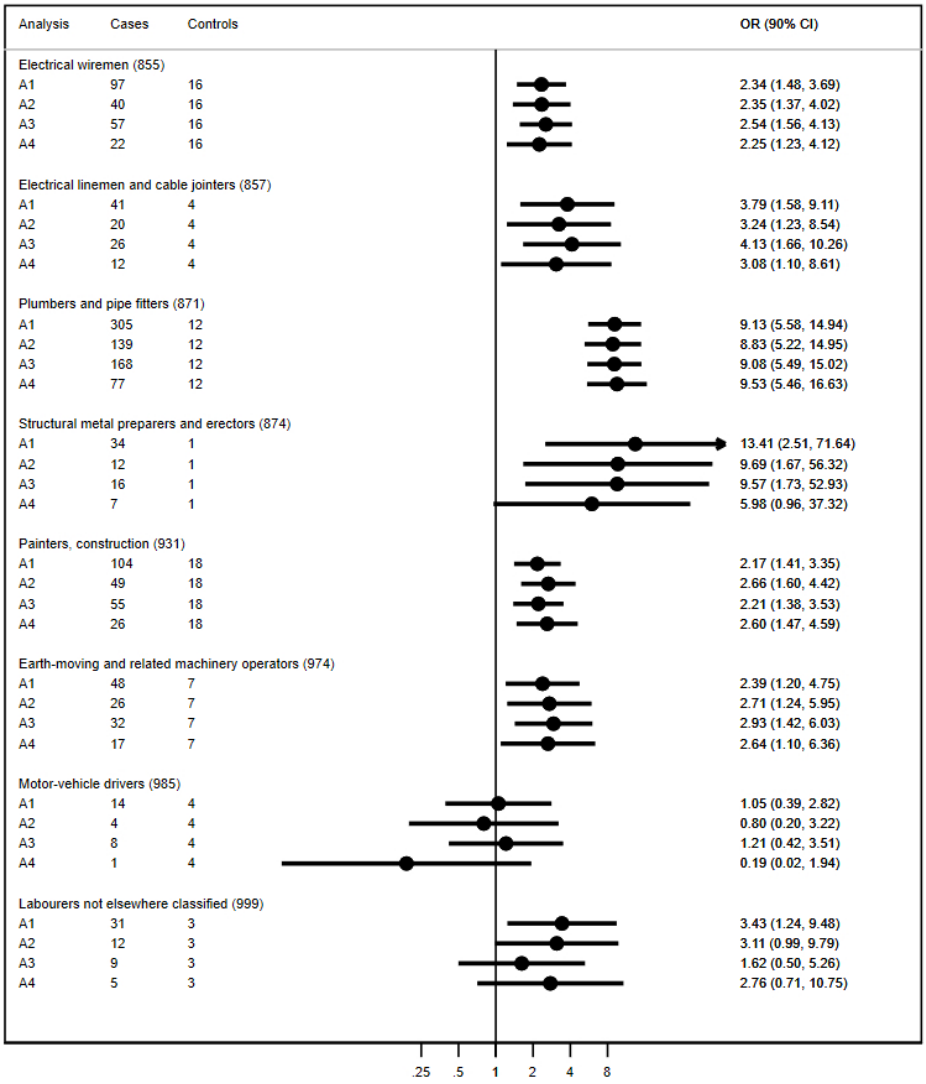

285x329mm (72 x 72 DPI)

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.

<table>
<tr><th>Period</th><th>Year</th><th>N. cases Primary/ secondary approach</th><th>Case source</th><th>Control source</th></tr>
<tr><td rowspan="8">2002-2004 and 2012-2016</td><td>2002</td><td>214/760</td><td rowspan="8">NATIONAL MESOTHELIOMA REGISTRY
Living in any Region
ReNaM questionnaire
Primary/secondary approach:
N. 2156/6910</td><td rowspan="3">EAGLE Living in 216 municipalities in five Lombardy Provinces
(Milan, Monza, Brescia, Pavia, Varese)
EAGLE questionnaire
Primary/secondary approach:
N. 778/1617</td></tr>
<tr><td>2003</td><td>238/758</td></tr>
<tr><td>2004</td><td>246/768</td></tr>
<tr><td>2012</td><td>288/886</td><td rowspan="5">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</td></tr>
<tr><td>2013</td><td>304/979</td></tr>
<tr><td>2014</td><td>289/928</td></tr>
<tr><td>2015</td><td>283/921</td></tr>
<tr><td>2016</td><td>294/910</td></tr>
</table>

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 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

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.

<table>
<tr><th>Period</th><th>Year</th><th>N. cases Primary/ secondary approach</th><th>Case source</th><th>Control source</th></tr>
<tr><td rowspan="8">2002-2004 and 2012-2016</td><td>2002</td><td>114/405</td><td rowspan="8">NATIONAL MESOTHELIOMA REGISTRY
Living in six Regions (Lombardy, Piedmont, Veneto, Tuscany, Apulia, Emilia-Romagna)
ReNaM questionnaire
Primary/secondary approach:
N. 1237/4051</td><td rowspan="3">EAGLE Living in 216 municipalities in five Lombardy Provinces
(Milan, Monza, Brescia, Pavia, Varese)
EAGLE questionnaire
Primary/secondary approach:
N. 778/1617</td></tr>
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(Apulia, Lombardy, Piedmont, Tuscany, Veneto)
ReNaM questionnaire
Primary/secondary approach: N. 250/490

CARA Living in one Region
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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	

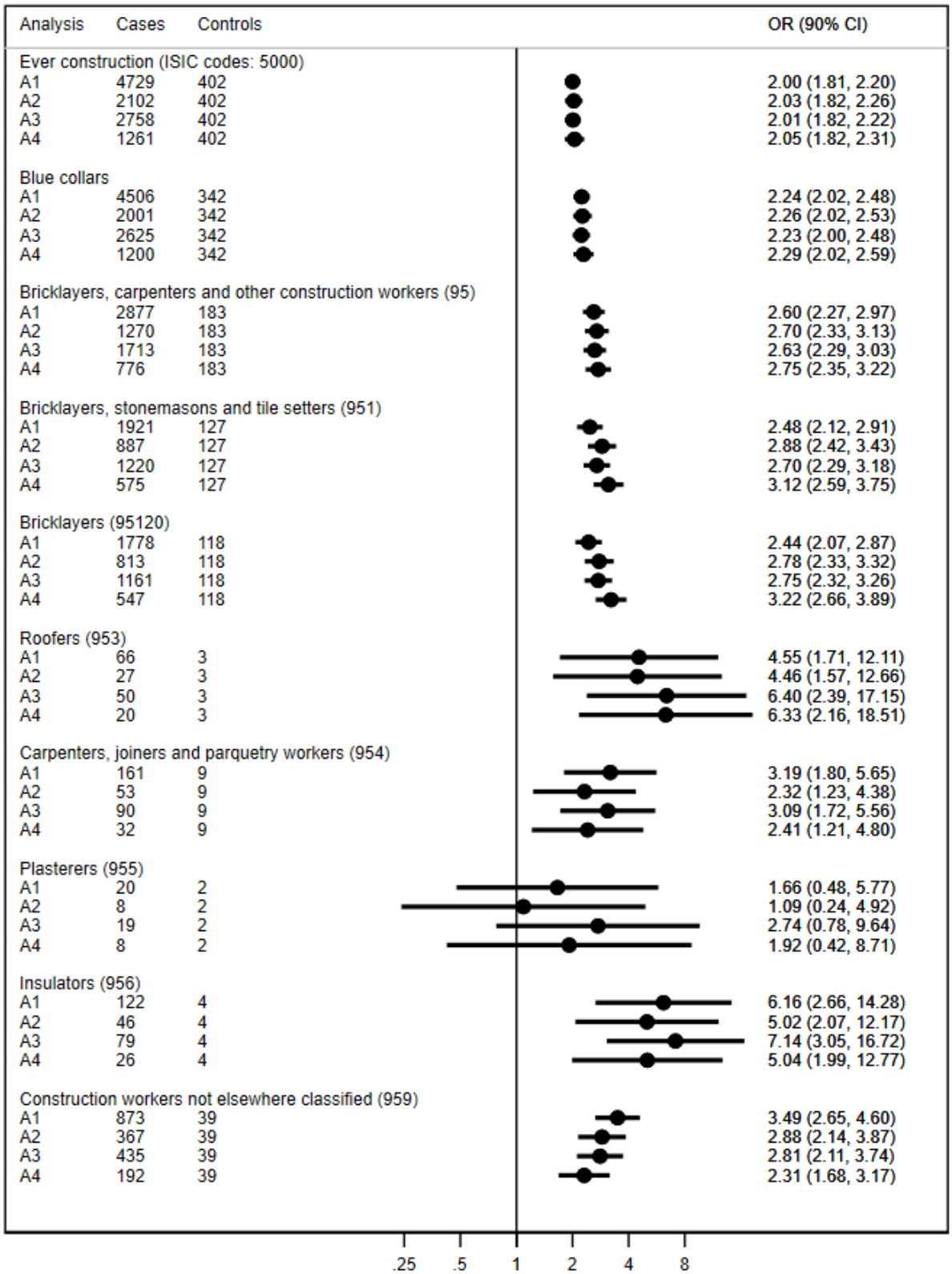
ISCO, International Standard Classification of Occupations (1968); ISIC, International Standard Industry Classification (1971)
[a]OR calculated with unconditional logistic regression models adjusted for age (categorical) and period

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**

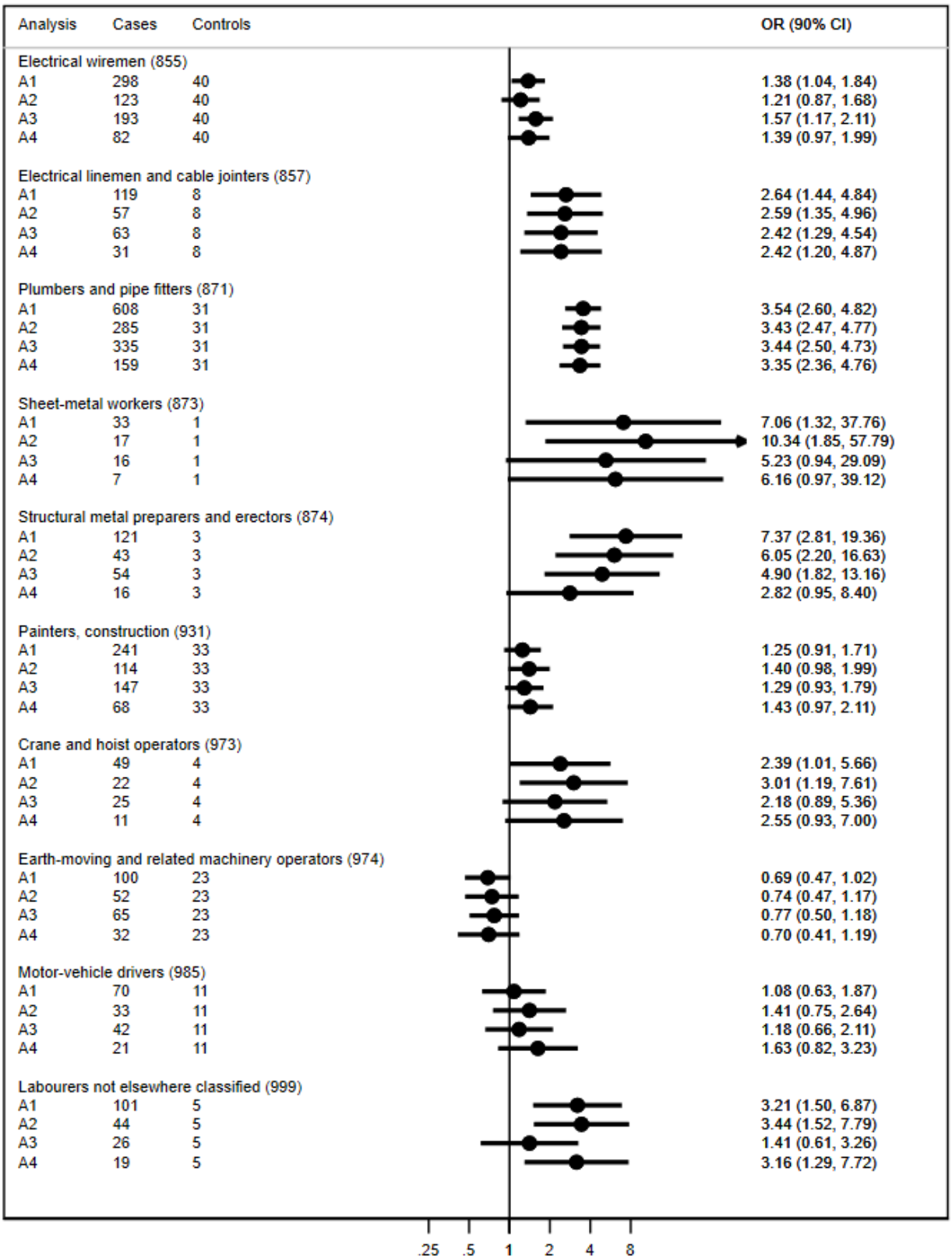
Occupation (ISCO-68 code)	Cases	Controls	OR*	90% CI
Total	15 592	2210		
Never employed in construction	10 863	1808	1.00	Reference
Ever employed in construction	4729	402	2.00	1.82-2.21
Blue collars (55, 56, 581, 628, 631, 7-9)	4506	342	2.24	2.02-2.48
Bricklayers, carpenters, and other construction workers (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.



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.



STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Comment
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Pag.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pag.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pag.5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	Pag.6
Methods			
Study design	4	Present key elements of study design early in the paper	Pag.6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pag.6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Pag.6-8
		(*b*) For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pag.6-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pag.6-9
Bias	9	Describe any efforts to address potential sources of bias	Pag.8-9
Study size	10	Explain how the study size was arrived at	Pag.6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pag.8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pag.8-9
		(*b*) Describe any methods used to examine subgroups and interactions	Pag.8-9
		(*c*) Explain how missing data were addressed	Pag.11
		(*d*) If applicable, explain how matching of cases and controls was addressed	Not applicable.
		(*e*) Describe any sensitivity analyses	Pag.8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pag.8-9, Figure 1, Suppl. Figures 1-3
		(b) Give reasons for non-participation at each stage	Participation been reported in the original studies

		(c) Consider use of a flow diagram	Figure 1, Suppl. Figures 1-3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pag.9-10, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Pag.10 (Table 1)
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Pag.2 (Table 2) and Suppl. Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Since previous studies were matched, crude analysis is not appropriate
		(*b*) Report category boundaries when continuous variables were categorized	Pag.10 (Table 1), and Suppl. Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pag.10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pag.12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pag.13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pag.12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pag.12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Pag.15

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.