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Factors Affecting Asbestosis Mortality Among Asbestos-Cement Workers in Italy

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Abstract

Objectives: This study was performed with the aim of investigating the temporal patterns and determinants associated with mortality from asbestosis among 21 cohorts of Asbestos-Cement (AC) workers who were heavily exposed to asbestos fibres.

Methods: Mortality for asbestosis was analysed for a cohort of 13 076 Italian AC workers (18.1% women). Individual cumulative asbestos exposure index was calculated by factory and period of work weighting by the different composition of asbestos used (crocidolite, amosite, and chrysotile). Two different approaches to analysis, based on Standardized Mortality Ratios (SMRs) and Age-Period-Cohort (APC) models were applied.

Results: Among the considered AC facilities, asbestos exposure was extremely high until the end of the 1970s and, due to the long latency, a peak of asbestosis mortality was observed after the 1990s. Mortality for asbestosis reached extremely high SMR values [SMR: males 508, 95% confidence interval (CI): 446–563; females 1027, 95% CI: 771–1336]. SMR increased steeply with the increasing values of cumulative asbestos exposure and with Time Since the First Exposure. APC analysis reported a clear age effect with a mortality peak at 75–80 years; the mortality for asbestosis increased in the last three quintiles of the cumulative exposure; calendar period did not have a significant temporal component while the cohort effect disappeared if we included in the model the cumulative exposure to asbestos.

Conclusions: Among heaviest exposed workers, mortality risk for asbestosis began to increase before 50 years of age. Mortality for asbestosis was mainly determined by cumulative exposure to asbestos.

Keywords: asbestos exposure; asbestos-related diseases; asbestosis; cohort mortality study; retrospective assessment

Introduction

Asbestosis is an occupational lung disease caused by the inhalation and deposition of asbestos fibres in the lung, thereby leading to diffuse interstitial fibrosis. It can be asymptomatic in the early stages but its progression over time entails disability, respiratory insufficiency, and premature death (CDCP, 2004; Lippmann, 2014), thus causing an average loss of 13.0 potential years of life per decedent (Diandini *et al.*, 2013). All forms of asbestos cause asbestosis (Collegium Ramazzini, 2010). Although the diagnosis of asbestosis is usually made via radiography, initial interstitial fibrosis can be established either by histology (Lippmann, 2014) or by High-Resolution Computed Tomography (HRCT); in the latter, either bilateral honeycombing (Wolff *et al.*, 2015) is evident or the sum grade of irregular opacities comes to be more than 2 on the International Classification for Occupational and Environmental Respiratory Diseases (ICOERD) scale (Kusaka *et al.*, 2005). After deposition, the asbestos fibres continue to injure the lungs, depending largely upon the nature and concentration of the dust (Lippmann, 2014).

Asbestos-Cement (AC) facilities have reported a high asbestos-fibre concentration at the workplace with the use of crocidolite and amosite fibres as well as chrysotile. The presence of a consistent lung asbestos burden among AC workers provided a further evidence of heavy asbestos exposures (Gylseth *et al.*, 1983; Merler *et al.*, 2017).

In general, to become clinically evident asbestosis requires heavy exposures and epidemiological studies provide evidence that there is a threshold fibre dose in the range of 25–100 ff/ml-years (Mossman and Churg, 1998), but lower exposure has been also observed by autopsy (Sluis-Cremer *et al.*, 1990). In the 1950s–1960s, the diagnosis of asbestosis was based on X-ray views or lung biopsy, while since 1986 the use of HRCT improved the early detection of asbestosis (Oksa *et al.*, 1994) without substantial changes in more recent periods. The death rate for asbestosis, especially for men (Lin *et al.*, 2007),

is associated with past asbestos consumption (Lin *et al.*, 2007; Antao *et al.*, 2009). Among the general population of England and Wales in the period 1968–2008, the asbestosis mortality rate was higher in males and reached a peak in the recent calendar periods and in older ages (Hanley *et al.*, 2011). A similar tendency was observed in Australia between 1979 and 2002, with a higher risk among males (Smith and Leggat, 2006). In the USA, the death rate due to asbestosis increased from 1970 till 2000 and declined thereafter (Bang *et al.*, 2008). In spite of the increasing trend in the number of deaths from asbestosis registered in Western countries (Bang *et al.*, 1999; Hanley *et al.*, 2011), the associated mortality rates tend to decline (Antao *et al.*, 2009) after the peak of asbestosis mortality is attained among the workers of earlier birth cohorts (Darnton *et al.*, 2012). This behaviour is a consequence of the peculiarities of asbestosis, characterized by a high survival implying a long latency between the death and the first exposure. The historical worldwide consumption of asbestos fibres increased from the 1920s reaching a peak in the 1980s and declined in intensity only after 1980 (Stayner *et al.*, 2013; Abelmann *et al.*, 2015).

Few occupational cohorts have been studied in order to quantify the risk from asbestosis in relation to their past asbestos exposure. Chrysotile textile workers showed a strong exposure–response relationship between the exposure to chrysotile and asbestosis mortality (Hein *et al.*, 2007; Deng *et al.*, 2012). Harding *et al.* (2009) carried out a study on British asbestos workers undergoing regular medical examinations and detected that incidence for asbestosis was associated with the birth cohort, age at first exposure, year of first exposure, duration of exposure, latency, and job type. The occupational sector is a good predictor of asbestosis since heavily exposed tasks report an elevated risk for asbestosis (Markowitz *et al.*, 2013).

In the absence of detailed information on exposure, most epidemiological studies have reported a birth cohort effect on asbestosis rate (Harding *et al.*, 2009; Harding and Darnton, 2010; Darnton *et al.*, 2012), with a strong decline for recent birth cohorts (Hanley *et al.*, 2011; Farioli *et al.*, 2018). The present study is a part of a large project on epidemiological surveillance of asbestos workers (Ferrante *et al.*, 2017). The aim of this investigation was to explore the temporal components of asbestosis mortality in relation to the intensity of asbestos exposure, among a pooled cohort of AC workers.

Material and methods

AC cohorts

This study included workers employed in 21 Italian AC facilities: these cohorts have already been discussed by two previous studies (Ferrante *et al.*, 2017; Luberto *et al.*, 2019). The production cycle of AC industries in Italy was similar in the different companies and was based on the 'Hatschek process' using 13–15% of asbestos, mostly chrysotile with lower fractions of crocidolite and amosite depending on the product type (Patroni *et al.*, 1987; Luberto *et al.*, 2019).

The 21 cohorts of the study met the following requirements: (i) a follow-up investigation completed and updated; (ii) a period of observation longer than 40 years by the pooling of individual records for all the workers in the cohorts retrieved by the official rosters for each factory. Only anonymized data were pooled, identifiable data remaining at the local study level. Table 1 describes the characteristics of 21 cohorts. This research was performed on 13 076 AC workers, with a predominance of males (81.9%). The factories that have been included are a sample of those involved in the production of AC products in Italy, but can be supposed to be representative of the occupational sector, since they have adopted a standard production cycle (Patroni *et al.*, 1987). Different activities were often conducted in the same environment. The main production of the industries included plain or corrugated sheets, as well as pipes, slabs, tanks, chimneys, and other products. In many factories, the production also included the manually manufacture of small pieces (Luberto *et al.*, 2019).

Statistical analysis

Standardized Mortality Ratio (SMR) was used, as is conventional, as a descriptive measure of asbestosis mortality. Vital status was ascertained through the Registrar Office of the municipality of the last residence. The beginning of the follow-up varied across factories; the end of follow-up was at least 31 December 2010, for four cohorts (Table 1 factory no. 3, 4, 10, and 21) and at least 31 December 31 2012, for the remaining 17 cohorts (Supplementary Tables S1 and S2, available at *Annals of Work Exposures and Health* online). The cause of death was obtained by municipalities in case of death prior to 1986, and by Local Health Authority of residence thereafter, and was coded according to the 9th revision of the International Classification of Diseases (ICD) (Table 1).

Duration of the exposure was computed by summing up all work durations, while the latency was calculated as Time Since the First Exposure (TSFE) in years in this occupational setting. The number of expected deaths was based on regional mortality rates provided by the National Institute of Health in terms of region, cause, gender, age, and calendar year from the year 1970 (Pirastu *et al.*, 2016). Therefore, deaths and person-years (p-ys) before 1970 were excluded from the SMR analysis for 498 workers who were lost or died before 01/01/1970

Table 1. Characteristics and causes of death of the cohorts under study.

		Total (n = 13 076)	Males (n =10 714)	Females (n = 2362)
Factory (locality), n (%)	1) Artclit (Cadelbosco di Sopra)	53 (0.4)	52 (0.5)	1 (0.0)
	2) Eternit (Bagnoli)	1451 (11.1)	1229 (11.5)	222 (9.4)
	3) Baraclit (Bibbiena)	725 (5.5)	725 (6.8)	0 (0.0)
	4) Cemamit (Ferentino)	81 (0.6)	80 (0.7)	1 (0.0)
	5) Cemental (Correggio)	554 (4.2)	479 (4.5)	75 (3.2)
	6) Cemiant (Cadelbosco di Sopra)	107 (0.8)	24 (0.2)	83 (3.5)
	7) Edilit (Vigodarzere)	540 (4.1)	324 (3.0)	216 (9.1)
	8) Eternit (Casale Monferrato)	3376 (25.8)	2618 (24.4)	758 (32.1)
	9) Eternit/ICAR (Rubiera)	556 (4.3)	487 (4.5)	69 (2.9)
	10) Fibronit (Avenza)	226 (1.7)	189 (1.8)	37 (1.6)
	11) Fibronit (Bari)	414 (3.2)	414 (3.9)	0 (0.0)
	12) Fibronit (Broni)	1334 (10.2)	1295 (12.1)	39 (1.7)
	13) Fibrotubi (Bagnolo in Piano)	290 (2.2)	232 (2.2)	58 (2.5)
	14) Itamiant (Castelnovo di Sotto)	1189 (9.1)	886 (8.3)	303 (12.8)
	15) Maranit (Poggio Renatico)	202 (1.5)	185 (1.7)	17 (0.7)
	16) Saca (Cavagnolo)	860 (6.6)	578 (5.4)	282 (11.9)
	17) Sacelit (Senigallia)	589 (4.5)	450 (4.2)	139 (5.9)
	18) Sidercam (Boretto)	134 (1.0)	123 (1.1)	11 (0.5)
	19) Superlit (Novi di Modena)	175 (1.3)	169 (1.6)	6 (0.3)
	20) Uprocem (Boretto)	63 (0.5)	47 (0.4)	16 (0.7)
	21) Veronit (Livorno)	157 (1.2)	128 (1.2)	29 (1.2)
Vital status, n (%)	Alive	5806 (44.4)	4559 (42.6)	1247 (52.8)
	Deceased	7057 (54.0)	5973 (55.7)	1084 (45.9)
	Emigrated	73 (0.6)	59 (0.6)	14 (0.6)
	Lost to follow-up	140 (1.1)	123 (1.1)	17 (0.7)
Birth cohort, n (%; years)	≤1919	2346 (17.9)	1960 (18.3)	386 (16.3)
	1920–1929	3047 (23.3)	2525 (23.6)	522 (22.1)
	1930–1939	3520 (26.9)	2681 (25.0)	839 (35.5)
	1940–1949	1947 (14.9)	1610 (15.0)	337 (14.3)
	≥1950	2216 (16.9)	1938 (18.1)	278 (11.8
Year at first employment, n (%; years)	≤1949	1719 (13.1)	1210 (11.3)	509 (21.5)
	1950–1959	3158 (24.2)	2260 (21.1)	898 (38.0)
	1960–1969	4453 (34.1)	3937 (36.7)	516 (21.8)
	1970–1979	2088 (16.0)	1831 (17.1)	257 (10.9)
	≥1980	1658 (12.7)	1476 (14.0)	182 (7.7)

Table 1. Continued

		Total (n = 13 076)	Males (n =10 714)	Females (n = 2362)
Age at first employment, n (%; years)	<20	2586 (19.8)	1615 (15.1)	971 (41.1)
	20–29	5169 (39.5)	4375 (40.8)	794 (33.6)
	30–39	3210 (24.5)	2804 (26.2)	406 (17.2)
	40–49	1615 (12.4)	1443 (13.5)	172 (7.3)
	50+	496 (3.8)	477 (4.5)	19 (0.8)
Duration of employment, n (%; years)	<10	6999 (53.5)	5640 (52.6)	1359 (57.6)
	10–19	2916 (22.3)	2428 (22.7)	487 (20.6)
	20–29	2314 (17.7)	1955 (18.2)	360 (15.2)
	≥30	847 (6.5)	691 (6.5)	156 (6.6)
CAEI, n (%; ff/ml-years)	1st Q—<12.9	2616 (20.0)	2275 (21.2)	341 (14.4)
	2nd Q—(12.9–103.4]	2616 (20.0)	2150 (20.1)	465 (19.7)
	3rd Q—(103–456]	2616 (20.0)	2055 (19.2)	560 (23.7)
	4th Q—(456–981]	2616 (20.0)	2220 (20.7)	395 (16.7)
	5th Q—>981	2616 (20.0)	2014 (18.8)	601 (25.4)
	Deceased	(n = 7057)	(n = 5973)	(n = 1084)
Cause of death (ICD IX), n (%)	Lung cancer (162)	884 (12.5)	844 (14.1)	40 (3.7)
	Pleural mesothelioma (163	400 (5.7)	309 (5.2)	91 (8.4)
	Peritoneal mesothelioma (158)	137 (1.9)	105 (1.8)	32 (3.0)
	Cardio-vascular diseases (390–459)	1856 (26.3)	1539 (25.8)	317 (29.2)
	Respiratory diseases (460–519)	818 (11.6)	723 (12.1)	95 (8.8)
	Pneumoconiosis (501–505)	452 (6.4)	400 (6.7)	52 (4.8)
	Asbestosis (501)	416 (5.9)	365 (6.1)	51 (4.7)

(431 dead, 15 emigrated, and 52 lost to follow-up). The 95% confidence interval (CI) of SMR was estimated according to Poisson's distribution of observed deaths. SMRs for asbestosis were computed stratifying for gender, birth cohort, year at first exposure, age at first exposure and for the combination of TSFE (<20, 20–39, and ≥40 years) and quintiles (Q) of Cumulative fibre-weighted Average Exposure Index (CAEI) whose calculation formula is reported in more detail in Supplementary File S3, available at *Annals of Work Exposures and Health* online weighting for the type of asbestos fibre.

An Average Exposure Index (AEI) was applied to all members of a given cohort, without gender differences, considering the exposure geometric mean (E) and the proportional size of the workforce (F) by factory (f), time period (t), and type of occupational exposure (d for direct or i for indirect), according to the following formula:

$$\mathrm{AEI}_{\mathrm{ft}} = (E_{\mathrm{ftd}} * \ F_{\mathrm{ftd}} + E_{\mathrm{fti}} * \ F_{\mathrm{fti}})$$

To account for the commercial type of asbestos used in each factory, we considered in the analysis a fibre-weighted AEI based on the proportion of chrysotile ($\mathrm{CH}_{\mathrm{ft}}$), amosite ($A_{\mathrm{ft}}$), and crocidolite ($\mathrm{CR}_{\mathrm{ft}}$) used by each factory and time period. The weights were the power factors estimated for the asbestos type by Hodgson and Darnton (2010) corresponding to 1 for chrysotile, 14 for amosite, and 71 for crocidolite. The fibre-weighted AEI index was computed as below

$$\text{fibre-weighted } \mathrm{AEI}_{\mathrm{ft}} = \mathrm{AEI}_{\mathrm{ft}} * (1 * \mathrm{CH}_{\mathrm{ft}} + 14 * A_{\mathrm{ft}} + 71 * \mathrm{CR}_{\mathrm{ft}})$$

which provided the average chrysotile equivalent asbestos concentration in fibres per cubic centimetre. From the fibre-weighted AEI a CAEI was computed on the basis of the occupational history of each worker summing the contribution of all his periods of activity T_i at each factory F_i:

$$\text{fibre-weighted } \mathrm{CAEI}_{\mathrm{ft}} = \sum_{t \in T_i \cap f \in F_i} \text{fibre-weighted } \mathrm{AEI}_{\mathrm{ft}}$$

where CAEI values were reported in chrysotile equivalent asbestos concentration in fibres per millilitre for years (ff/ml-years).

Mortality rates for asbestosis were investigated by means of an Age-Period-Cohort (APC) regression model, assuming a Poisson distribution for number of death for asbestosis and computing person-years from the hiring date to the end of follow-up without left restriction. APC models were used to explore the temporal patterns by providing an evaluation of the effects of age at risk, cohort of birth, and calendar period on mortality rates and on the combined estimation of the relative risk of each effect. A Bayesian procedure was applied to estimate an APC model where age, cohort and calendar were assumed to be random variables in order to easily overcome problem of model identifiability. Considering a hierarchical structure, the factory of employment was also considered a further random variable. Summarizing, the considered random variables were age at risk (13 five-year age groups from 30 to 90+ years old), calendar period (20 five-year calendar periods covering 1920–2015), birth cohort (19 five-year birth cohorts covering 1890–1980), factory of employment (21 factories). To account for factors potentially affecting the mortality rate for asbestosis, the following fixed effects were also included: gender, quintiles of the cumulative fibre-weighted exposure index and age at first exposure in binary form (≤30 years and >30 years). Cut-offs for quintiles derived from the overall fibre-weighted CAEI; cumulative exposure was a time-dependent variable changing across classes of age and calendar period. Technical details about the Bayesian APC model specification and fitting are reported in Supplementary File S4, available at *Annals of Work Exposures and Health* online.

The posterior marginal distribution of the parameters was obtained by numerical approximations by means of the Integrated Nested Laplace Approximation (INLA) framework (Rue *et al.*, 2009). The risk associated with the fixed and the random effects were reported as Mortality Rate Ratios (RR), by the exponential transformation of the *a posteriori* parameter estimates calculating their 95% credible intervals (CIs) according to the 2.5 and 97.5% quantile of *a posteriori* distribution.

In order to assess the effect of CAEI on temporal components, an additional analysis was performed estimating coefficients of an APC model excluding CAEI. Statistical analyses were performed using the program R 3.5.2 (R Core Team R, 2014) and appropriate packages (INLA for Bayesian APC model; tscount for time series functions; Epi for statistical functions in epidemiology).

Results

The cohort included 13 076 workers (Table 1; 10 714 males and 2362 females) and 388 914 p-ys beginning from the year 1970. Almost half of the workers were employed in three factories (Eternit of Casale Monferrato 25.8%; Eternit of Bagnoli 11.1%; Fibronit of Broni 10.2%). The study achieved a good level of completeness (140 subjects were lost at follow-up, 73 migrated abroad before the end of follow-up). The year of first employment was before 1960 for 37.3% of the workers with a marked gender

difference (32.3% males versus 59.5% females). More than half of the workers were younger than 30 years of age at the time of recruitment (59.3%) with a higher proportion among the subgroup of female workers (74.7%).

A difference in gender in relation to the duration of employment was observed, with a somewhat higher percentage of females being employed for less than 10 years. Overall, 7057 subjects (54.0%) died during the follow-up with a slight difference by gender (males: 55.7%; females: 45.9%). The cause of death was known for 95.9% and for 97.6% of the male and female deaths, respectively.

The study reported 416 deaths from asbestosis (5.9% of total deaths). These deaths mostly occurred after 1990 (66.4%) and involved an increasing proportion of females over time from 3.2% before 1979 to 17.5% after the year 2000 (Supplementary Table S5, available at *Annals of Work Exposures and Health* online). We registered an increased number of asbestosis deaths by calendar period because of the long time since first exposure to death. A marked difference between males and females was observed in the distribution of the amount of death for asbestosis by calendar period [mean ± standard deviation (SD): males 1993 ± 13.0 years; females 1999 ± 9.9 years] and by TSFE (mean ± SD: males 42.1 ± 12.3 years; females 55.3 ± 10.7 years), consistent with higher exposure among men leading to earlier deaths from asbestosis (Fig. 1) The cohort reported an asymmetric distribution of CAEI (mean: 471 ff/ml-years; median: 230 ff/ml-years) with a substantial variation (1st Q–3rd Q: 30.4–705 ff/ml-years; min–max = 0–3857 ff/ml-years). The five quintiles had the following cut-offs: 1st Q <12.9, 2nd Q 12.9–103, 3rd Q 103–456, 4th Q 456–981, and 5th Q >981 ff/ml-years. Asbestos exposure before 1960 was extremely high and levelled-off only after 1980 (Fig. 2).

Estimates of SMR were 543 (CI: 491–599) for the overall cohort 1028 (CI: 771–1336) among the female workers and 508 (CI: 456–563) among males. Asbestosis SMR decreased with increasing values among categories of year at birth and year at first exposure in both genders; the highest SMR values were reported for workers born before 1919 and for those at work before 1949. A higher SMR for asbestosis was showed by workers starting their exposure before an age of 20 years with respect to those exposed in later ages (Table 2).

SMR analysis by CAEI, TSFE, and gender is reported in Table 3. Among males, SMR for asbestosis increased monotonically by quintiles of CAEI (from 42.4 in the 1st Q to 830 in the 5th Q), and by categories of TSFE (from 208 to 1101 from the category 0–19 years to >60 years). The presence of few male deaths for asbestosis in the first two quintiles and for latency less than 19 years resulted in SMRs with large CI. Among the female workers, no deaths were recorded in the 1st Q of exposure and for less than 20 years of TSFE. However, SMR increased across the remaining categories of CAEI and TSFE. In considering these figures it should be borne in mind that SMRs for men and women should not be compared, and that within quintiles of CAEI men's exposure is higher than women's. For both genders, the largest SMR was recorded in the highest combination of CAEI and TSFE.

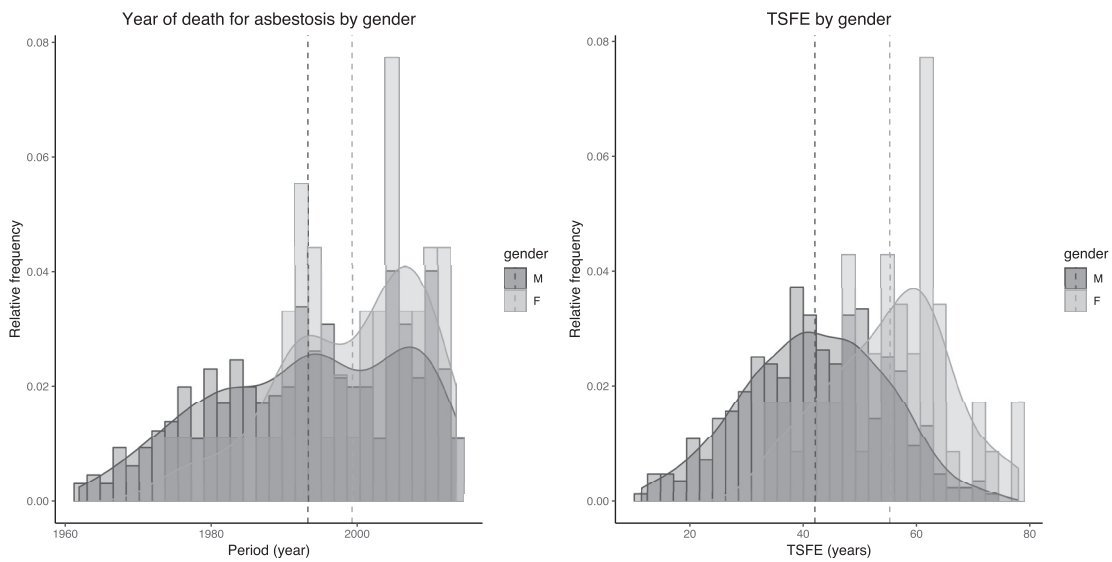

Figure 1. Histogram of the relative frequency of asbestosis death by calendar period and by TSFE for male in black and female in grey with a non-parametric estimation of the density function (vertical dotted line indicates the mean value).

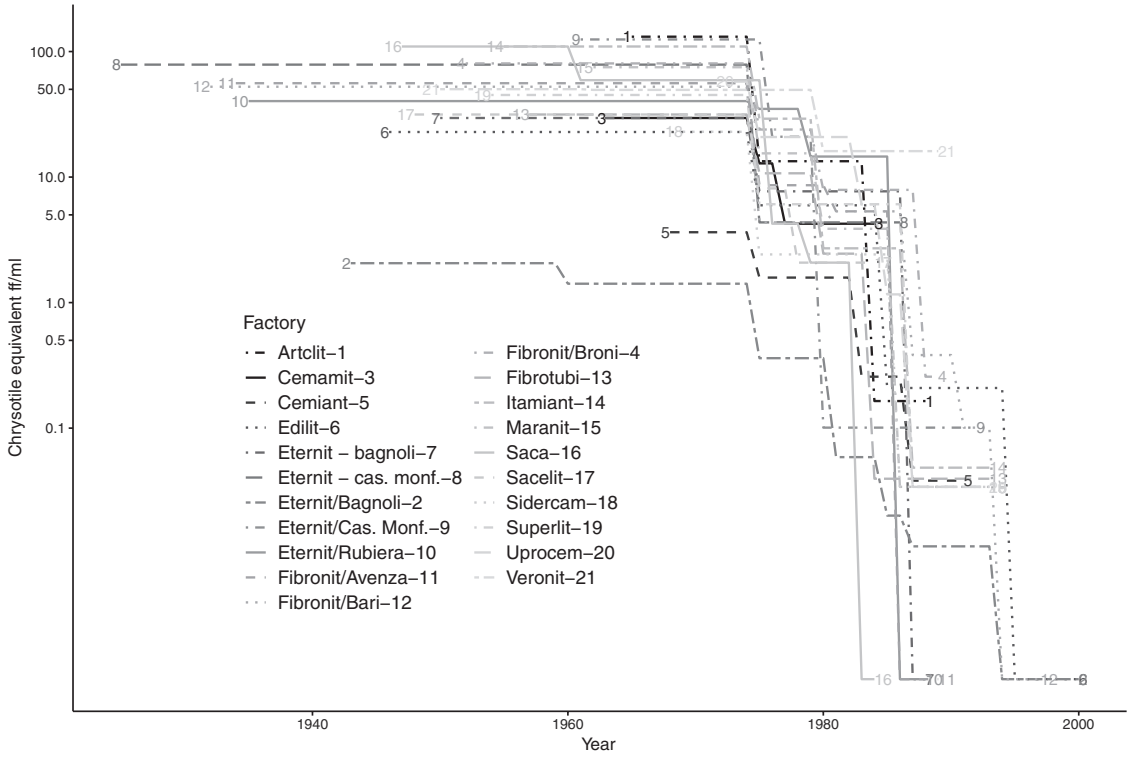

Figure 2. Chrysotile equivalent asbestos concentrations by calendar year across factories (log scale, ff/ml).

In APC analysis, an increased mortality RR for asbestosis in second to fifth quintiles of CAEI, as compared with the reference (1st Q), was recorded (2nd Q RR: 2.49, CI: 0.64–13.29; 3rd Q RR: 5.34, CI: 1.50–26.7; 4th Q RR: 13.6, CI: 3.88–66.5; 5th Q RR: 19.9, CI: 5.66–98.3). Mortality RR for asbestosis was lower among female workers as compared with male workers (RR: 0.34, CI: 0.25–0.46). Workers starting their exposure after an age of 30 years showed a slightly decreased risk (RR: 0.87, CI: 0.70–1.08). The mortality RR from asbestosis showed a marked excess for the major Eternit production facilities at Bagnoli and Casale Monferrato and for the smaller Fibronit plant at Bari (Fig. 3).

Estimated mortality RR increased exponentially with age, starting from 65 years and reaching a peak in the 85 years age class (RR: 20.8, CI: 13.7–32.7). The cohort and period components showed a flat RR trend (Supplementary Fig. S6, available at *Annals of Work Exposures and Health* online). The estimate of an APC model without the inclusion of the CAEI as a covariate shows an apparent cohort effect associated with an increased RR among the workers born in the years 1905–1928 and for those at work before an age of 30 years (RR: 1.56, CI: 1.27–1.93), but these findings disappeared when exposure was accounted for (Supplementary Fig. S6, available at *Annals of Work Exposures and Health* online).

Discussion

The analysis of 21 cohorts of AC workers in Italy and the occurrence of a large number of deaths from asbestosis allowed to investigate the temporal components of asbestosis mortality, exploring several determinants. The study accomplished a long follow-up (more than 40 years) and achieved a satisfactory level of completeness (1.3% lost to follow-up, 95% causes of death are known); the existence of an adequate number of deaths from asbestosis, in both genders, allowed gender-specific analyses.

Due to the lack of individual data on jobs and work activities for all members in the cohorts, the evaluation of asbestos exposure in this study was based on the construction of an asbestos exposure index that considered the probability, intensity, and mineralogical composition of asbestos exposure at the cohort, rather than at the

Table 2. SMR for asbestosis by birth cohort, year at first exposure, age at first exposure, and gender.

		Males		Females		Total	
		O/E	SMR (CI)	O/E	SMR (CI)	O/E	SMR (CI)
Birth cohort	≤1919	138/0.16	839 (710–991)	23/0.01	1554 (1033–2338)	161/0.18	898 (769–1048)
	1920–1929	152/0.34	450 (384–527)	22/0.02	1157 (762–1756)	174/0.36	483 (420–566)
	1930–1939	49/0.16	314 (238–416)	5/0.01	354 (147–851)	54/0.17	318 (243–415)
	1940–1949	9/0.02	387 (201–744)	1/0.01	863 (122–6126)	10/0.02	409 (220–761)
	≥1950	0/0	—	0/0	—	0/0	—
Year at first exposure	≤1949	124/0.13	927 (778–1106)	33/0.02	1452 (1032–2043)	157/0.16	1004 (855–1169)
	1950–1959	120/0.23	511 (434–621)	14/0.02	776 (460–1311)	134/0.25	538 (452–634)
	1960–1969	94/0.26	366 (299–448)	3/0.01	455 (147–1412)	97/0.26	363 (300–447)
	1970–1979	9/0.05	181 (94.1–347)	1/0.01	542 (76.3–3844)	10/0.05	194 (97.0–340)
	≥1980	1/0.01	71.3 (10.1–507)	0/0	—	1/0.01	69 (3.95–305)
Age at first exposure	<20	40/0.06	650 (469–873)	23/0.02	1282 (827–1879)	63/0.08	793 (613–1006)
	20–29	132/0.24	554 (465–654)	17/0.02	1014 (605–1575)	149/0.26	591 (495–683)
	30–39	125/0.25	499 (417–592)	7/0.01	610 (262–1179)	132/0.26	510 (423–595)
	40+	51/0.13	378 (284–491)	4/0.01	1167 (362–2710)	55/0.14	398 (302–512)
		348/0.69	508 (456–563)	51/0.05	1028 (771–1336)	399/0.73	543 (491–599)

Table 3. SMR for asbestosis by quintiles of CAEI, TSFE, and gender.

	CAEI	TSFE									
		0–19 years		20–39 years		40–59 years		60+ years		Total	
		O/E	SMR (CI)	O/E	SMR (CI)	O/E	SMR (CI)	O/E	SMR (CI)	O/E	SMR (CI)
M	1st Q	0/0.01	—	2/0.03	73 (18.3–292)	0/0.01	—	0/0	—	2/0.05	42.4 (10.6–169)
	2nd Q	0/0.01	—	8/0.04	197.2 (99–394)	1/0.03	30.2 (4.1–204)	0/0	—	9/0.08	106 (55.3–204)
	3rd Q	2/0.01	226 (56.4–902)	14/0.06	236 (140–398)	16/0.06	264 (162–431)	1/0.01	731 (103–5186)	33/0.13	253 (180–356)
	4th Q	5/0.01	467 (194–1122)	42/0.07	567 (419–767)	53/0.09	588 (449–770)	0/0	—	100/0.18	564 (463–686)
	5th Q	2/0.01	273 (68.4–1093)	69/0.09	757 (598–959)	109/0.13	838 (695–1011)	24/0.02	1396 (936–2083)	204/0.25	830 (724–952)
	Total	9/0.04	208 (108–400)	135/0.29	461 (390–546)	179/0.33	548 (473–634)	25/0.02	1101 (744–1629)	348/0.69	508 (456–563)
F	1st Q	0/0	—	0/0	—	0/0	—	0/0	—	0/0.00	—
	2nd Q	0/0	—	0/0	—	2/0.01	617 (154–2466)	0/0	—	2/0.01	378 (94–1510)
	3rd Q	0/0	—	0/0	—	3/0.01	459 (147–1422)	1/0.01	1275 (180–9054)	4/0.01	407 (153–1085)
	4th Q	0/0	—	0/0	—	8/0.01	1409 (705–2818)	2/0.01	1572 (393–6287)	10/0.01	1088 (586–2023)
	5th Q	0/0	—	5/0.01	1519 (632–3648)	14/0.01	1039 (615–1755)	16/0.01	2401 (1471–3919)	35/0.02	1489 (1068–2071)
	Total	0/0.00	—	5/0.01	501 (209–1204)	27/0.03	913 (626–1331)	19/0.01	2113 (1348–3312)	51/0.05	1028 (771–1336)

worker's level (Hodgson and Darnton, 2010; Luberto *et al.*, 2019). For each worker, the CAEI was calculated by summing up all indices assigned to the factory where the study participants worked through their period of employment. The effect of the exposure was measured by means of diverse and complementary analyses (SMR and APC regression model) in order to explore mortality patterns, not as thoroughly evaluated in the previous studies (Harding *et al.*, 2009; Deng *et al.*, 2012; Farioli *et al.*, 2018); Our study, however, was restricted to a single occupational sector. SMR analysis is commonly used in mortality studies, but SMRs from asbestosis are strongly influenced by the proportion of asbestos workers in the reference population, When this proportion varies across the strata of the reference population, for example by gender or geography, caution is needed in making inferences based on SMR comparisons, as it may not be a reliable measure of risk. APC regression was included to permit an analysis based on internal rate ratios.

The mortality from asbestosis was assessed on the basis of the underlying cause of death. Previous reports on some of the cohorts included in the study (Magnani *et al.*, 2008; Menegozzo *et al.*, 2011) revealed that additional cases had been reported as concomitant causes; therefore, an underestimation of the burden of asbestosis-related mortality is possible in this study. Furthermore, 35 deaths in males and 1 in females were recorded as 'other pneumoconiosis'. It is unlikely that a substantial number of AC workers could have died from pneumoconiosis different from asbestosis, so these deaths might have been at least partly misclassified but the lack of information about possible other exposing tasks in their work history prevents us from drawing further conclusions. Overall, the high number of deaths for asbestosis is the consequence of high exposure to asbestos in the AC sector. The results of this study may also be extended to other occupational sectors with high asbestos exposures, such as insulators or asbestos-textile workers, both reporting a high mortality risk for asbestosis (Bang *et al.*, 2008; Harding *et al.*, 2009). The results obtained in this study suggest that the higher SMR for asbestosis among females with respect to males does not reflect a real higher risk, but a larger impact of the AC sector on rates of the reference female population compared with males. This is supported by the internal analysis based on relative risks demonstrating a lower mortality risk for asbestosis among female workers, consistent with previous reports (Darnton *et al.*, 2012; Farioli *et al.*, 2018). This result, stemming also from the analyses adjusted for cumulative exposure and time since first exposure, may be

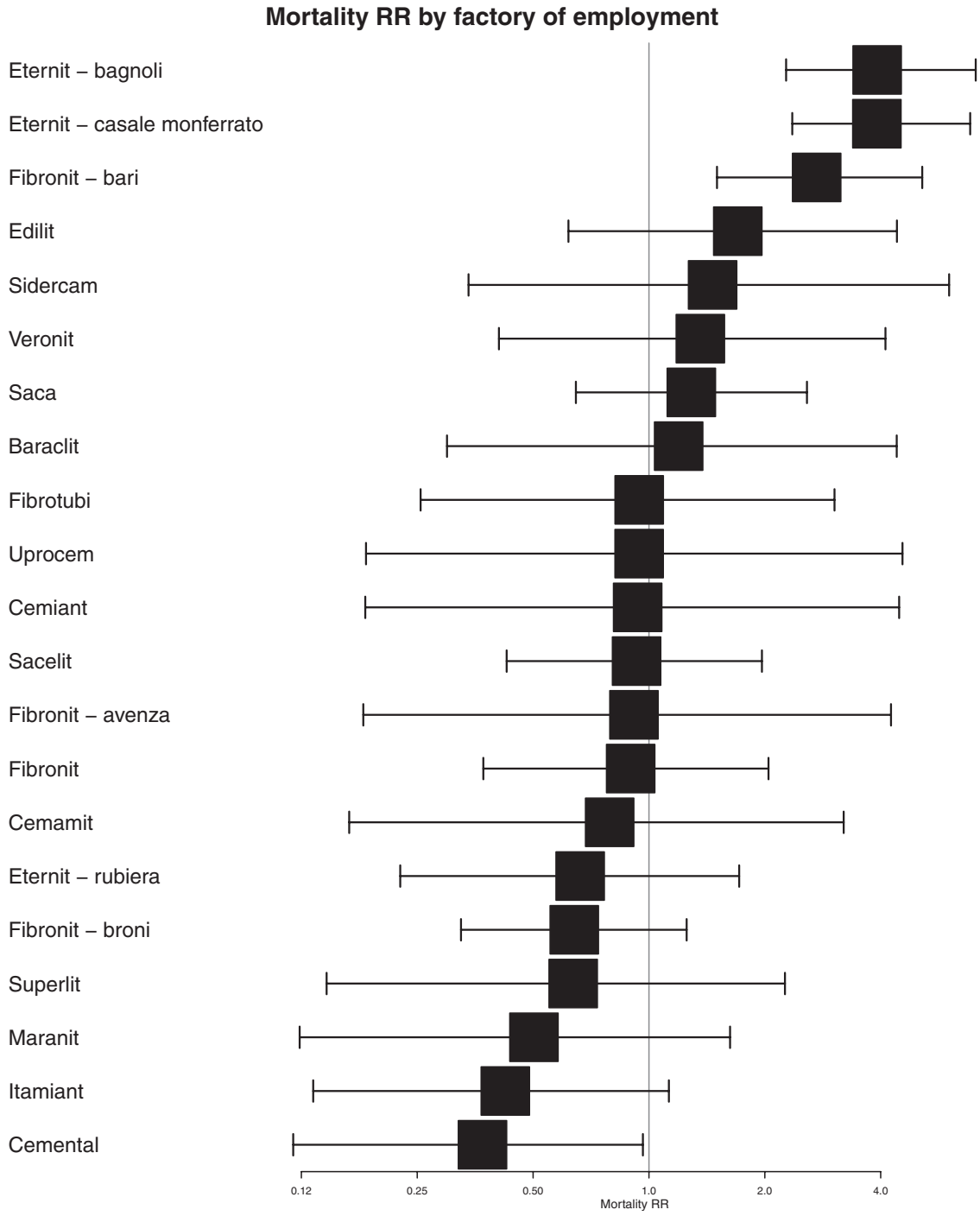

Figure 3. Mortality Relative Risk (log scale) estimated by APC regression model by factory adjusted for other model covariates.

viewed as an indication that females performed tasks associated with a lower asbestos, not completely captured by the average exposure and cumulative exposure indices. In our view, this is justified by the fact that CAEI calculations were based on estimates for exposure intensity representing factory-specific average values and

could not take into account the jobs of cohort members, whereas women were mainly employed in specific tasks, with less demand for physical strength (such as manufacture of 'special' products) and, presumably, different exposure patterns.

A further potential limitation in exposure assessment was the adjustment of exposure estimates by fibre type. Whereas, given the variation in use of different asbestos varieties across the factories included in this study, there was a need to adjust exposure estimates by fibre type, the power factors for amosite and crocidolite relative to chrysotile were derived from the meta-analysis of studies on mesothelioma risk by Hodgson and Darnton (2010), and do not necessarily represent correctly their fibrogenicity.

No cases were observed in women in the first quintile of cumulative exposure, corresponding to the nominal category 'up to 12.9 ff/ml-years', in agreement with previous estimates of risk (Tossavainen *et al.*, 1997); two male workers died from asbestosis in the first quintile, possibly because of misclassification of the exposure, given the lack of information on their other work activities, or due to higher exposures of males within the CAEI quintiles.

Both SMR and APC analyses reported a dose–response relationship between cumulative asbestos exposure and asbestosis mortality that did not level off at the highest exposures. This result differed from that of the previous reports (Finkelstein, 1989; Farioli *et al.*, 2018), but is consistent with a log-quadratic trend as found in a cohort of chrysotile textile workers (Berry *et al.*, 1979; Deng *et al.*, 2012).

The APC analysis was adjusted for mineralogical variety and time-dependent variables which make the results obtained in this study comparable with other cohorts exposed only to chrysotile fibres (Harding *et al.*, 2009). The different estimates of mortality risk for asbestosis among factories imply that, despite similar cycle processes among cohorts (Patroni *et al.*, 1987), the circumstances and levels of exposure differed and were not completely captured by the cumulative exposure index and its parameters reported in the present study.

In APC analysis exposure at earlier ages was associated with a higher RR, but this result almost completely disappeared adjusting by CAEI. The same behaviour was observed for the temporal cohort effect: in fact adjusting by CAEI, the APC model failed to find a significant cohort effect, implying such cohort effect was due to the presence of birth cohorts hired during periods at high asbestos exposures. The studies that analysed the temporal dynamics of mortality for asbestosis are restricted to Western countries and report a clear cohort effect associated with reduced risk among the birth cohort starting from 1930 (Harding *et al.*, 2009). Asbestos exposure, however, had not been adjusted for. A calendar period effect was not observed in the present study: this result differs from that observed in studies carried out on the general population (Hanley *et al.*, 2011), but is conceivable in occupational studies.

No information on smoking habits was available. Previous studies found a higher risk of mortality from asbestosis in current and former compared with never smokers (Wraith and Mengersen, 2008; Harding *et al.*, 2009; Frost *et al.*, 2011). Tobacco smoking is indeed a well-known risk factor for many cardiovascular diseases, as well as lung cancer and other malignancies as the larynx, bladder, head, and neck, blood, and others and may be a powerful cause of competing mortality. Our inability to adjust for smoking is indeed a limitation of our study. However, there are no indications that the proportion of smokers in this pooled cohort differed from that in the general population and across the levels of exposure.

The present study allowed us to estimate the adjusted exposure–response relationship between asbestos exposure and asbestosis mortality. However, we had observed just the tip of the iceberg since mortality from asbestosis differs from its incidence: among Italian female workers compensated for asbestosis (Germani *et al.*, 1999), the percentage of deaths from asbestosis was only 13.7% (38/277), while among a selection of workers who were compensated for asbestosis in Canada (Finkelstein *et al.*, 1981) and Poland (Szeszenia-Dąbrowska *et al.*, 2002), the proportion of deaths for respiratory diseases (mainly asbestosis) reached 36.1 and 14.7%, respectively. Studies based on incidence may be more appropriate to estimate the real burden of asbestosis because subjects with asbestosis have a relative long survival and competing causes of death may affect the asbestosis mortality.

The findings of this study confirmed that mortality from asbestosis has mainly been determined by cumulative exposure to asbestos (Darnton *et al.*, 2012). As a consequence of the rapid decline in exposures after 1980 in Italy, deaths from asbestosis may be expected to sharply decrease in the next decades. Further research is needed to assess the influence of the different varieties of asbestos on asbestosis mortality.

Supplementary Data

Supplementary data are available at *Annals of Work Exposures and Health* online.

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Ethical review

The main study was approved by the University of Eastern Piedmont's Ethical Review Board (authorization CE 112/13, 12 July 2013).

Competing interest

No authors declared financial conflict of interest.
The following authors reported that they served as expert witness in court trials on asbestos-related diseases: AA, AB, FB-A, LB, CM, LM, SM, EM, DM, MM, EO, VP, and SS.

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