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Early mortality from malignant mesothelioma in Italy as a proxy of environmental exposure to asbestos in children

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Abstract
Malignant mesothelioma (MM) is a rare neoplasm caused by asbestos. Mortality from MM in ≤50 years old people, considering the long latency, is likely related to asbestos exposure in childhood. Mortality from MM (C45, ICD10 code) is described among ≤50 years (ys) old people in Italy, in 2003-2016. National and regional Standardized Rates (SRs) were computed by age-class. The North-South trend of regional SRs, increasing in >50ys age-class, showed a flat cline in ≤50ys old people. Municipal Standardized Mortality Ratios (SMRs) were computed, with respect to regional figures, for ≤50 ys old population. In Italy, 487 people ≤50 ys old died from MM, in 2003-2016 (2.5% of all MM deaths), corresponding to 35/year. The highest SMRs were observed in Northern Regions, the most industrialized areas. Exceeding SMRs were found in 10 municipalities where former asbestos-cement plants, shipyards, and a quarry contaminated by fluoro-edenite fibres were present. Early mortality from MM, proxy of childhood environmental asbestos exposure, deserves particular concern.

Key words
- epidemiology
- mesothelioma
- mortality
- asbestos
- young adults

INTRODUCTION

Malignant mesothelioma (MM) is a rare neoplasm, originating from mesothelial cells of serous cavities (pleura, peritoneum, pericardium, and vaginal tunic of the testicle). Pleural MM represent about 80% of all MM cases. MM is highly lethal and characterised by a long period of latency (about 40 years and over) [1]. More than 80% of MM cases are attributable to asbestos exposure. All asbestos types are ascertained carcinogenic to human (Group 1), causing with sufficient evidence mesothelioma and lung, larynx and ovary cancers. A positive association with cancers of pharynx, stomach and colon-rectum was also reported [2]. Erionite, a naturally occurring fibrous mineral, was also confirmed to be an ascertained carcinogenic to human, causing mesothelioma [2]. In addition, in 2017 IARC defined fluoro-edenite, a previously unknown asbestos-like fibrous mineral, as carcinogenic to humans (Group 1), on the basis of the ascertained causal link with MM [3].

The number of deaths from MM is currently used to estimate the population burden of this neoplasm, in light of its high lethality. Incidence data, as a matter of fact, are not always available. Odgerel and colleagues estimated the global burden of MM in the range from 36,300 to 38,400 deaths per year, in a 20 year-period (1994-2014), considering 230 countries [4].

Asbestos is one of the most widespread occupational carcinogens: the World Health Organization (WHO) has estimated that around 125 million people worldwide are currently exposed to asbestos at workplace (www.who.int/ipcs/assessment/public_health/asbestos/

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en/). The Global Burden of Diseases (GBD) study estimated about 63% of occupational cancers attributable to asbestos in 2017 at global level, including 27,000 cases of mesothelioma [5].

Estimating the burden of MM cases due to non-occupational exposure is particularly difficult, though the risk of pleural mesothelioma caused by the residence near asbestos fibres sources (quarries, asbestos-cement plants) is known [1, 6]. Some estimates show that about 20% of MM cases at global level could be caused by non-occupational exposure to asbestos [6].

Italy was one of the main producers and importers of raw asbestos until the ban in 1992 [7]. In Italy, in 2003-2014 period, 16,086 persons died from MM, corresponding to 1,340 per year. Temporal trends show an increase of mortality from MM, in particular from pleural MM among men, in the last years [8]. The most recent report of the Italian Registry of Mesothelioma (ReNaM) identified 27,356 incident cases of mesothelioma from 1993 to 2015, corresponding to about 1,600 incident cases per year in the last period [9]. Information on the exposure context was available for 21,387 cases (78.2%): among these, 70.0% experienced occupational exposure (certain, probable, possible), 4.9% domestic and 4.4% environmental exposure, meanwhile for 1.5% of them the asbestos exposure was related to leisure or hobby activity. For 20% of cases, asbestos exposure was unlikely or unknown [9]. On the basis of exposure ways reported in ReNaM database, clusters of MM cases due to environmental exposure were mainly related to the presence of asbestos-cement plants, shipbuilding and repair activities and soil contamination [1]. Regarding the last asbestos exposure source, local investigations reported an exceeding risk of MM in some Italian areas with naturally asbestos fibres presence [10, 11]. MM cases were reported in excess in an area of Pollino Mount (Basilicata Region, Sothern Italy), where naturally serpentine and metabasite outcrops, containing asbestos fibres (namely, tremolite, actinolite and chrysotile), occurred [10]. In early 2000s, pleural and peritoneal malignancies were found in excess in some municipalities of Upper Susa Valley (Piedmont Region, Northern Italy), where tremolite asbestos in rocks surfaced by natural ground erosion or originating from construction activities [11]. MM cases environmentally exposed were reported in areas close to chrysotile and fluoro-edenite fibres containing quarries [12, 13]. An investigation focused on female MM cases found that non-occupational case-list of ReNaM is characterized by the prominence of women [14].

The improvement of early diagnosis of MM and the establishment of registries recording people exposed to asbestos are among the public health actions recommended by WHO (www.who.int/ipcs/assessment/public_health/asbestos/en/). Moreover, during the Sixth Ministerial Conference on Environment and Health, the 53 countries of WHO European Region committed to develop national programs to eliminate asbestos-related diseases, in agreement with the objectives of 2030 UN Agenda for Sustainable Development [15].

The issue of health risks originating from asbestos exposure in children is rarely addressed, mainly due to the low number of young mesothelioma cases and to the difficulties to detect a causal role of past exposure occurred during childhood. A systematic review on the age at first exposure to asbestos and the risk of asbestos-related diseases reported the studies published up to July 2012 [16]. The object of the review was highlighting the difference in MM risk, on the basis of the age at first asbestos exposure. Six studies reporting risk of MM mortality by age-class, childhood included, among occupational and environmental asbestos exposed subjects [17-22] were considered. Four studies found the highest risk in subjects aged 15 years (ys) or less at first exposure [17-20], meanwhile the other one reported a lower risk in subjects exposed at young age (less than 20 ys) than in adulthood [21]. The subjects exposed at birth showed the highest risk in the only study that included birth as age at first exposure [22]. Regarding the highest risk age at first asbestos exposure, the results of all studies, also restricting to only residential exposure investigations, were not consistent. The Authors concluded that because of the low number of the studies and their limitations the results are inconclusive and further studies are needed [16].

More recently, some cohort studies analysed the risk of MM among populations residentially exposed to asbestos in childhood. Dalsgaard and colleagues performed a cohort study on the incidence of MM in former children attending four schools located near an asbestos-cement plant in Aalborg [23]. The median age at diagnosis (similar in school and reference cohort) was 61 years (34-74 ys). MM was diagnosed more than 30 years after the school attendance in the majority of cases. Higher risk (Hazard Ratio: HR) in school cohort, adjusted for occupational and familial occupational exposure, was found and the results were confirmed also restricting the analysis to the subjects without occupational or familial occupational exposure. Similar HRs were shown in men and women, with M/F ratio in the school cohort equal to 1.2:1, as assumed for environmental exposure. The results suggested that childhood environmental exposure is an important risk factor for MM in late life [23]. Increased risk (OR = 3.3; 95% CI: 1.4-7.7) in subjects attending grammar school in Casale Monferrato, where the largest Italian asbestos-cement plant operated, was also reported in a case-control study on pleural MM incidence [24].

The risk of asbestos-related diseases in the population living near the Wittenoom crocidolite mine in Australia was investigated in several studies [21, 25, 26]. In the cohort analysis after 30 years and more of follow-up, increased incidence and mortality risk from several cancers, including mesothelioma, were found among adults living at Wittenoom in childhood (aged <15 ys) [25]. However, in a subsequent analysis of MM incidence, difference in risk between the subjects exposed in childhood (<15 ys) and adulthood was not observed [26], confirming the previous findings [21].

In 2017 a study on the association between residential exposure to Libby amphibole asbestos (LAA) prior to age 18 and respiratory symptoms in late life (median age: 25 ys) was published [27]. Pleural or interstitial changes on chest x-ray or HRCT were not found, but several respiratory symptoms, including self-reported pleural chest pain, among young adults were associated to childhood environmental exposure to LAA and were highlighted as a possible indicator of future respiratory diseases [27].

The Surveillance, Epidemiology and End Results (SEER) database reported a lower M/F rates ratio for MM cases aged under 65, with respect to those aged 65 and over [28].

Few studies on MM risk have been performed in Latin-American countries. A recent mesothelioma case-series in the municipality of Sibaté, where a major Colombian asbestos-cement facility is located was published. Some of the characteristics of the observed MM cases are represented by the early age at diagnosis, the sex-ratio approaching one and the absence of occupational exposure to asbestos, thus suggesting a major role of environmental exposure [29].

In Italy, the mortality from pleural mesothelioma by age-class was reported for 2003-2009 period [30]. In 0-39 age-class, 8 male and 7 female deaths were observed, corresponding to 0.01 (95% CI: 0.005-0.02)/100,000 in men and 0.01 (95% CI: 0.004-0.02)/100,000 in women. In the same period the corresponding rate in the overall population was 2.8 (95% CI: 2.7-2.9) and 0.8 (95% CI: 0.8- 0.9) /100,000, in men and women, respectively. The M/F ratio in 0-39 year age-class was equal to 1, meanwhile in the older age-classes male death rate was about 3-fold that of females rate: M/F = 3.4 in subjects aged 40-75 and M/F = 3.3 in 76-99 age-class [30].

The incidence of MM cases in Italy, in different age-classes by modality of exposure, on the basis of ReNaM database, was reported in Marinaccio, *et al.* 2015 [1]. MM cases aged less than 45 ys at diagnosis were rare, accounting for 2.4% of all cases recorded in 1993-2008 period (15,845 MM cases). Significantly, lower mean age at diagnosis was observed in non-occupationally exposed, in particular in those with an environmental exposure, compared to the cases exposed in occupational settings (67.2 and 66.1, respectively, *vs* 68.1). The mean age at first exposure was significantly lower in subjects environmentally exposed than in those occupationally exposed (17 *vs* 22.5 years, p value <0.001) [1].

Considering the long period of latency, the high mortality rate and the high attributable fraction to asbestos exposure, early deaths from MM could represent a *proxy* of exposure in childhood. Studying the early occurrence of mesothelioma has relevant public health and ethical implications in terms of health protection by unintentional exposure to environmental hazards in children, also considering the hypothesis of a highest vulnerability to environmental risk of this age-class population [31, 32]. Temporal and spatial distributions of early MM deaths could contribute in estimating the health impact of non-occupational exposure to asbestos in childhood. This is the case, for example, of the children living in areas contaminated by asbestos fibres or indirectly exposed to asbestos in domestic context, because of occupational activities of the parents.

In Italy, a preliminary analysis of early malignant pleural neoplasms (MNP) mortality, showed 1,594 early deaths (≤50 ys) from MNP in 1980-2010 period (55 per year on average, annual standardized rate = 0.2/100,000) and identified 147 municipalities where early mortality from MNP was significantly higher than the expected (mainly located in Regions mostly affected by activities involving asbestos exposure) [33].

The present study describes mortality from MM in Italy in people younger than 50 years (≤50 ys) and its geographical distribution, as a possible marker for environmental exposure to asbestos in children.

MATERIALS AND METHODS

This study is based on data of mortality from malignant mesothelioma (MM) at municipal level that are included in the cause-specific mortality database managed by the Statistical Service of the National Institute for Health, and provided by the Italian National Institute of Statistic (Istat).

Mortality from MM was analysed in a 14 year-period (2003-2016), the most recent years available at the beginning of the study, from ICD10 revision application. The MM deaths included in the study were all those recorded in the specific diagnostic category of malignant mesothelioma C45 (ICD-10).

National and regional standardized mortality rates (SR, direct method, 2013 European population as reference: https://ec.europa.eu/eurostat/web/products-manuals-and-guidelines/-/KS-RA-13-028) and their 90% Confidence Intervals (90% CI), in the population ≤50 and >50 ys old, were computed by gender.

Standardized Mortality Ratios (with 90% CI) in the subpopulation ≤50 ys old were computed for each of the 21 Italian Regions and Autonomous Provinces and for the 8,047 Italian municipalities, using national and regional age-class and gender specific rates as references, respectively. 90% CIs were estimated based on Poisson's distribution, if the observed cases were less than 100, otherwise on Byar method. Considering the low number of cases, SMRs were computed for the overall population, including both men and women, to reach a less broad CI.

RESULTS

In Italy, during 2003-2016 period, 487 persons ≤50 ys old died from MM (34.8 cases/year, on average), corresponding to 0.096 cases/100,000 inhabitants. These cases represent 2.5% of all deaths from MM in the same period (19,315 cases). *Table 1* shows the number of all MM cases and the corresponding standardized rates (SR), by age-class (≤50 and >50 ys) and gender.

The number of deaths from MM, by site, age-class and gender is reported in *Table 2*. The percentage of peritoneal MM, with respect to all MM deaths, is higher in ≤50 ys old people than in >50 ys old, among both sex (12.5% *vs* 3.8% in men and 16.7% *vs* 5.7% in women). Among young adults, the percentage of pleural MM, with respect to all MM, in men is higher than in women (73.5% *vs* 66.7%); in the latters, the percentage of peritoneal and other MM, equal to 16.7%, is higher than in male population.

The ratio of male to female standardized rates (SRm/SRf) is equal to 1.8 in the young sub-population (≤50

Table 1
Mortality from malignant mesothelioma: cases and age-standardized death rate, by age-class and gender. Reference: 2013 European population. Period: 2003-2016

	Men	
Age (years)	**Cases**	**ASR (90% CI)**
≤50	313	0.16 (0.14-0.18)
>50	13,511	9.34 (9.21-9.18)
	Women	
≤50	174	0.088 (0.074-0.105)
>50	5,317	2.73 (2.67-2.80)
	Overall	
≤50	487	0.12 (0.11-0.14)
>50	18,828	5.57 (5.50-5.63)

ASR: Age Standardized death Rate (n. deaths/100,000 inhabitants); 90% CI: Confidence Interval.

Table 2
Mortality from malignant mesothelioma (MM), by site, sex and age-class: number of cases and percentage with respect to all MM deaths. Period: 2003-2016

Cause of death	ICD	Men cases (%)	Women cases (%)	Overall cases (%)
Age ≤50				
Mesothelioma of pleura	C45.0	230 (73.5)	116 (66.7)	346 (71)
Mesothelioma of peritoneum	C45.1	39 (12.5)	29 (16.7)	68 (14)
Other mesothelioma	C45.2-C45.9	44 (14.1)	29 (16.7)	73 (15)
Mesothelioma (all)	C45	313 (100)	174 (100)	487 (100)
Age >50				
Mesothelioma of pleura	C45.0	11080 (82)	4246 (79.9)	15326 (81.4)
Mesothelioma of peritoneum	C45.1	514 (3.8)	303 (5.7)	817 (4.3)
Other mesothelioma	C45.2-C45.9	1917 (14.2)	768 (14.4)	2685 (14.3)
Mesothelioma (all)	C45	13511 (100)	5317 (100)	18828 (100)

ys) and 3.4 in older population (>50 ys), in overall period 2003-2016. *Figure 1* shows the national M/F ratio by year.

The geographical trend of regional MM mortality standardized rates, by Istat macroarea (North-West, North-East, Centre, South and Islands) and age-class is shown in *Figure 2*. In ≤50 ys old population the cline is flat, meanwhile a decreasing North-Southern trend is observed in overall and >50 ys old people *(Figure 2)*.

Regional SMRs from MM in young population (≤50 old) are showed in *Table 3* and *Figure 3* reports the geographical distribution.

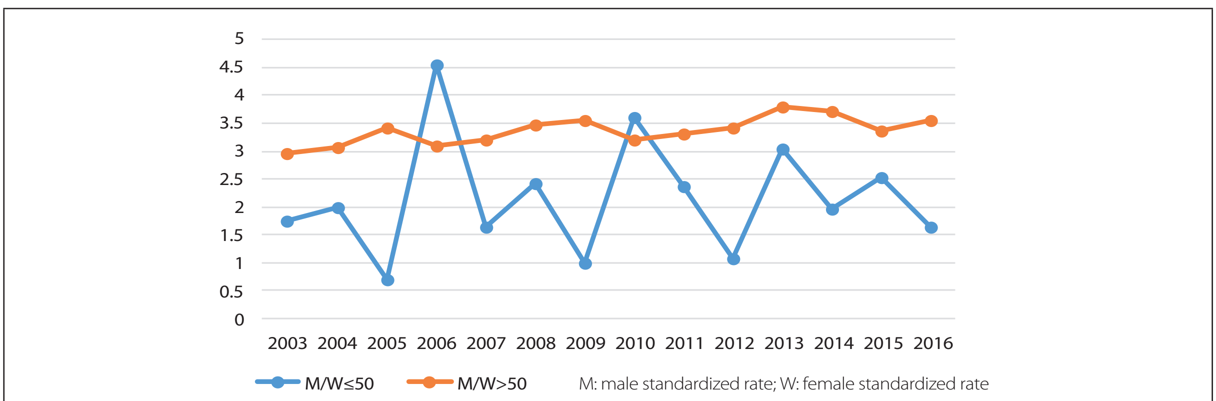

Figure 1
Mortality from malignant mesothelioma. Annual trend of sex ratio (male standardized rate/female standardized rate), by age-class. Period: 2003-2016.

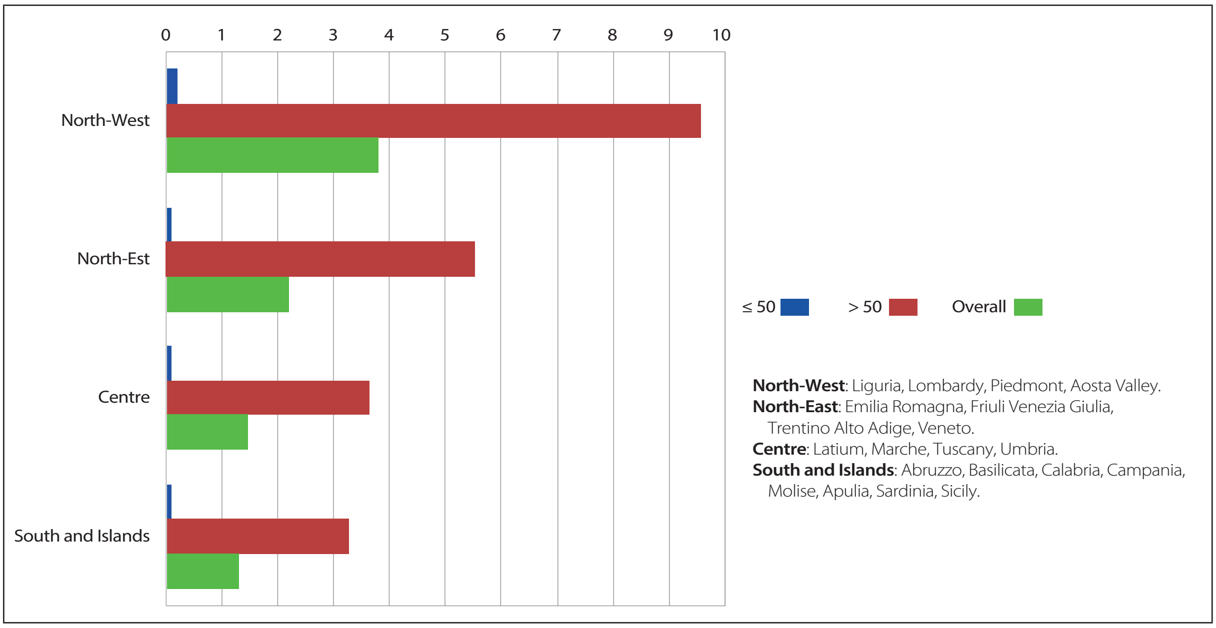

Figure 2
Mortality from malignant mesothelioma. Regional standardized rates (/100,000), by Istat macroarea (North-West, North-East, Centre, South and Islands) and age-class. 90% Confidence Intervals. Period 2003-2016.

Table 3
Mortality from malignant mesothelioma, in ≤50 years old population. Standardized Mortality Ratio by Region. Reference: National Rate. Period: 2003-2016

Region	OBS	SMR (90% CI)
Piedmont	73	204.0 (168.4-247.3)
Aosta Valley	1	93.2 (20.8-417.7)
Lombardy	115	141.1 (121.1-164.5)
Bolzano	5	120.3 (58.6-247.1)
Trento	1	23.1 (5.16-103.8)
Veneto	25	60.9 (43.9-84.4)
Friuli-Venezia Giulia	5	49.7 (24.2-102)
Liguria	18	141 (95.9-207.2)
Emilia-Romagna	35	97.7 (74.1-129)
Tuscany	28	93.7 (68.8-127.7)
Umbria	5	71.8 (34.9-147.5)
Marche	10	81.3 (48.6-136)
Latium	34	72.6 (54.8-96.2)
Abruzzo	4	37.9 (17.0-84.5)
Molise	2	79.7 (26.4-241)
Campania	46	99.7 (78.3-126.6)
Apulia	26	81.1 (58.8-111.9)
Basilicata	2	42.9 (14.2-129.6)
Calabria	12	77.5 (48.4-124)
Sicily	35	89.4 (67.8-118)
Sardinia	5	35.8 (17.4-73.5)

OBS: Observed cases; SMR: Standardized Mortality Ration; CI: Confidence Interval.

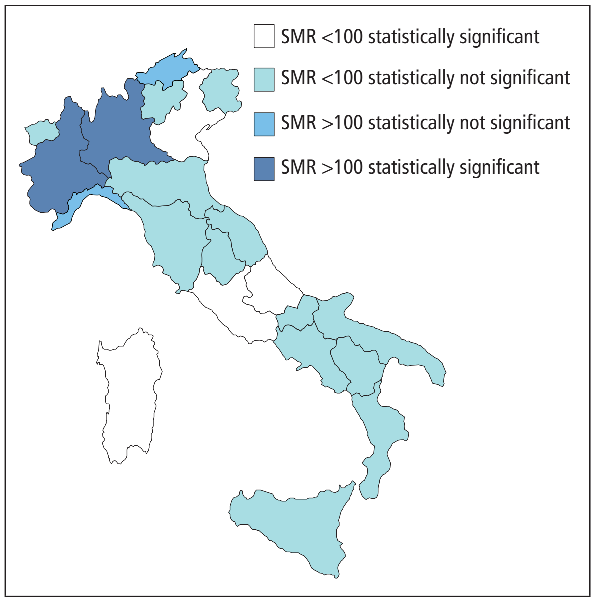

Figure 3
Mortality from malignant mesothelioma, in ≤50 years old population. Geographical distribution of Standardized Mortality Ratio (SMR), by Region. Period: 2003-2016.

The early mortality (≤50 ys) from MM at regional level as compared to national rates, show higher risks in some Northern Italian Regions: Piedmont and Lombardy display SMRs significantly higher than 100, Liguria and Bolzano Province have rates higher than the National one, even if the CI lower limit is <100.

In the analysis at municipal level, 357 out of the 8,078 Italian municipalities showed at least one MM death ≤50 years old, in the study period. In ten municipalities

Municipality	OBS	SMR (90% CI)
La Spezia	3	396.4 (158.4-991.8)
Stradella	3	3132.2 (1251.8-7837.4)
Quattro Castella	3	2728 (1090.2-6825.8)
Torre Annunziata	3	927.01 (370.5-2319.6)
Alessandria	4	538.2 (241.6-1198.8)
Biancavilla	4	2324.2 (1043.5-5177.1)
Monza	4	393.7 (176.8-877)
Broni	6	8095.0 (4186.0-15654.2)
Genova	11	229.9 (140.7-375.7)
Casale Monferrato	17	5805.9 (3906.1-8629.7)

OBS: Observed Cases; SMR: Standardized Mortality Ratio; CI: Confidence Interval.

Figure 4
Early mortality from malignant mesothelioma (≤50 years old). Municipalities with SMR and 90% Confidence Interval Lower Limit >100, based on at least 3 observed cases. Period: 2003-2016.

a statistically significant excess risk (based on at least 3 cases) was observed *(Figure 4)*.

DISCUSSION

In Italy, 2.5% of all deaths from MM occurred in ≤50 years old people (487 cases in 14 years, 2003-2016), corresponding to around 35 deaths per year, on average. Considering the long period of latency of the disease and the high attributable fraction to asbestos exposure, these deaths could be probably due to asbestos exposure occurred in childhood.

Several previous investigations, reporting excesses of early mortality from MM in people exposed to asbestos in childhood [23-26], corroborate this hypothesis. For this reason, localized excesses of MM mortality in ≤50 ys old people, could also be used as a sentinel event of past, or current, contexts of environmental exposure to asbestos.

Considering the causal link between MM and fibres [2, 3], we highlight that no information on the presence of erionite outcrops either erionite exposure contexts for the population in Italy has been reported. Contexts of exposure to fluoro-edenitic fibres were detected in a specific area that will be considered in the comments of the present findings.

The lower MM mortality ratio of male to female in young age-class, compared to that in >50 ys old population (1.8 *vs* 3.4), corroborates the hypothesis of a non-occupational asbestos exposure in early MM cases. This hypothesis is confirmed by data from ReNaM, that showed a significantly higher F/M gender ratio in environmentally exposed cases than in overall and occupationally exposed cases (1.19 *vs* 0.38 and 0.14, respectively) [14]. MM Female/Male rate ratio about 1:1 in under 65 people was reported also in US population [28] and among MM cases residentially exposed to asbestos in childhood, in Aalborg [23].

In addition, the percentage of incident cases reported in ReNaM database with a history of occupational exposure is lower among subjects ≤50 years than in >50ys old (37% *vs* 56%); the proportion of MM incident cases with environmental/familial exposure is around two-fold significantly higher in the young (≤50 ys) with respect to older cases (16% *vs* 8%) [9]. Furthermore, ReNaM findings provide evidence of a percentage of unknown or unlikely modalities of exposure higher in young MM patients (≤50 ys old at diagnosis) than in older cases (24.6% and 15.6%, respectively) [9].

The analysis of mortality by MM site, age-class and gender *(Table 2)* highlighted a higher percentage of peritoneal MM in young adult (≤50 old) than in >50 old people, among both gender (12.5% *vs* 3.8% in men and 16.7% *vs* 5.7% in women). In addition, our evaluation showed that in both age-classes the percentage of peritoneal MM, with respect to all MM deaths, is higher in women than in men. In a previous investigation on peritoneal mesothelioma risk in Italy, based on multiple-causes mortality and ReNaM incidence database, the 0-44 years age group had a higher proportion of incident peritoneal MM cases (6.2%) than of pleural MM (2.4%). In the same age group, 34.7% of deaths and 44.4% of incident cases for peritoneal MM occurred among women [39]. The issue of misclassification of ovarian cancers in peritoneal mesothelioma, as well as of other abdomen contiguous tumours, has been discussed in recent papers [39-42].

The analysis of regional SMR distribution showed the highest mortality risk from MM among young adults in some Northern Regions. The same geographical pattern was observed in the general population mortality from MM, following the industrial geographical distribution in the country, with the highest industrialization rate in Northern Italy [8, 30, 38]. In particular, the former Italian largest asbestos-cement plants were located in Broni and Casale Monferrato, Lombardy and Piedmont Region (North-West) respectively. In Liguria Region (North-West Italy), several shipyards and naval industries are still operating. The high SMR found in Bolzano Province has never showed before, and deserves further in-depth analysis.

The presence of these activities could explain the geographical North-South trend observed in overall and >50 ys old people, with the highest SRs in North-West macroarea. The flat cline observed in young adults (≤50 ys old) corroborates the hypothesis of a less contribute of occupational exposures in early MM mortality.

At municipal level, significant exceeding SMRs (based on 3 or more observed cases) in young adults (≤50 ys old) were observed in municipalities with known asbestos sources: asbestos-cement plants (Broni and Stradella, Casale Monferrato), shipbuilding and repair activities (Torre Annunziata, La Spezia and Genova) and a quarry contaminated by fluoro-edenite fibres (Biancavilla), characterized by a high mortality from MM in the general population also [8]. The presence of the same asbestos sources was related to clusters of non-occupationally exposed MM incident cases [1].

The case of Biancavilla municipality (Sicily Region, South Italy) represents an example of appropriateness of using early mortality as a marker of residential asbestos exposure in children. A high risk of mesothelioma in the population living in this municipality related to environmental exposure to fluoro-edenitic fibres contained in the stone quarry located in the municipality has been highlighted, since the late Nineties [34]. The epidemiological investigations performed in Biancavilla, corroborated by animal studies, contributed to the evaluation by IARC of the carcinogenicity of fluoro-edenite [3]. In 1980-2010 period, 6 deaths from MNP *vs* 0.6 expected were observed in this municipality (SMR = 1,003, CI 90%: 437-1,980) among people aged 50 ys or less. Extending the analysis to municipalities located wit:hin a radius of 10 km from Biancavilla, the number of MNP deaths rose to 11 (SMR = 367, CI 90%: 206-608) [35]. Same results were found by the analysis of MM incident cases living at the diagnosis in Biancavilla, based on Regional Operating Centre of ReNaM database. A higher value of Standardized Incidence Ratio (SIR), with respect to regional figures, was shown in people aged less than 50 years (5 cases, SIR = 2,134, 95% CI: 693-5,000) than among older people (19 cases, SIR = 474, 95% CI: 285-739), even if based on a low number of cases [13].

Regarding Alessandria, Monza and Quattro Castella, the other municipalities reported in *Figure 4*, no specific etiological hypotheses have so far been raised. An excess of mortality from pleural mesothelioma, in the male population, was previously observed in Quattro Castella [36]. In these contexts, *ad hoc* in-depth studies appear to be warranted.

In spite of the uncertainty of the computed estimates, due to the low number of observed and expected cases, these results deserve specific concerns, in view of the rarity of the phenomenon and the ethical implications, considering the possibility of a childhood exposure to environmental risks.

Some limitations of the present study need to be discussed.

A limitation is related to the use of mortality data in the detection of mesothelioma cases. A possible underestimate of MM cases in asbestos occupational cohort studies using mortality data, with respect to incidence data, was debated [37]. Misclassification caused by the use of death certificates was discussed also in previous papers on the surveillance of mesothelioma mortality in Italy [30, 38]. The use of the 10th revision ICD code, available in Italy at national level since 2003, including the specific morphological code of malignant mesothelioma reduces the possible misclassification. In addition, the high mortality rate of the disease mitigates the possible bias, but a remaining effect could not be ruled out, and some prudence in the interpretation of the data is appropriated.

Moreover, a limitation could be represented by the use of the residence at death as a *proxy* of the childhood residence. The geographical analysis, performed in order to identify the areas with possible asbestos sources, was carried out on the basis of the residence transcribed in death certificate (as Istat database) while, taking into account the long period of the latency, the place of residence during childhood, where exposure to asbestos probably occurred, might have been different.

In addition, regional and municipal SMRs have been computed for men and women combined to improve the precision of the estimates, considering the ratio F/M close to one in early MM mortality. Studies analysing the distribution of early MM deaths by site and gender, with suitable methods, appear appropriated.

Further investigations, based on the integration of MM mortality and incidence data, the latter from ReNaM database, could reduce parts of these limitations and furnish a useful focus on this issue. The analysis of early MM occurrence, by site of MM, sex and exposure modality, based on individual database, appears of particular concern, taking into account also the specific F/M ratio among young adults.

CONCLUSION

The analysis of early mortality from MM showed that in Italy, in 2003-2016 period, 487 people ≤50 ys old died from MM, corresponding to 2.5% of all MM deaths, due to a likely non-occupational asbestos exposure in childhood.

Geographical distribution highlighted regions and, particularly, municipalities with the highest risks of MM mortality for this specific population age group.

These signals, though characterised by uncertainty, require to implement specific public health and environmental remediation actions, and further in-depth investigations, in the light of their ability to identify past, or still on-going, environmental sources of exposure that could impact on childhood population.

The findings of the present study provide evidence of the usefulness to use early MM mortality data as a *proxy* of asbestos exposure in people affected in young age, particularly where individual assessment of exposure is not available. This possibility might be common in low- and middle-income countries where environmental exposure to asbestos in children is a critical issue [43] and where suitable experiences of surveillance systems of mesothelioma incident cases, including the individual evaluation of the modalities of exposure, still lack.

The use of the adopted methods, based on mortality data, to replicate the study in other countries could give an important information on the environmental exposure to asbestos, at global level.

Author's contributions statement

Conception: II, LF, PC, SC, GM, CB, AZ; Acquisition and analyses of data: GM, MDS; Interpretation of data: AB, AM, AZ, CB, CM, II, LF, PC, SC; Writing-Original draft: LF, II; Writing: Revising and final approval: LF, AB, AM, AZ, CB, CM, GM, MDS, PC, SC, II.

Conflict of interest statement

The Authors declare that neither they nor their Institutions have financial or personal relationship with other people or organizations that could inappropriately bias conduct and findings of the study.

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