



Estimate of environmental and occupational components in the spatial distribution of malignant mesothelioma incidence in Lombardy (Italy)



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ABSTRACT

Introduction: Measuring and mapping the occurrence of malignant mesothelioma (MM) is a useful means to monitor the impact of past asbestos exposure and possibly identify previously unknown sources of asbestos exposure.

Objective: Our goal is to decompose the observed spatial pattern of incidence of MM in the Lombardy region (Italy) in gender-specific components linked to occupational exposure and a shared component linked to environmental exposure.

Materials and methods: We selected from the Lombardy Region Mesothelioma Registry (RML) all incident cases of MM (pleura, peritoneum, pericardium, and tunica vaginalis testis) with first diagnosis in the period 2000–2016. We mapped at municipality level crude incidence rates and smoothed rates using the Besag York and Mollié model separately for men and women. We then decomposed the spatial pattern of MM in gender-specific occupational components and a shared environmental component using a multivariate hierarchical Bayesian model.

Results: We globally analyzed 6226 MM cases, 4048 (2897 classified as occupational asbestos exposure at interview) in men and 2178 (780 classified as occupational asbestos exposure at interview) in women. The geographical analysis showed a strong spatial pattern in the distribution of incidence rates in both genders. The multivariate hierarchical Bayesian model decomposed the spatial pattern in occupational and environmental components and consistently identified some known occupational and environmental hot spots. Other areas at high risk for MM occurrence were highlighted, contributing to better characterize environmental exposures from industrial sources and suggesting a role of natural sources in the Alpine region.

Conclusion: The spatial pattern highlights areas at higher risk which are characterized by the presence of industrial sources - asbestos-cement, metallurgic, engineering, textile industries - and of natural sources in the Alpine region. The multivariate hierarchical Bayesian model was able to disentangle the geographical distribution of MM cases in two components interpreted as occupational and environmental.

1. Introduction

Almost all malignant mesothelioma (MM) cases are attributable to asbestos (or other asbestiform fibers) exposure. Measuring occurrence of MM is therefore a useful mean to monitor the impact of past asbestos exposure and possibly identify previously unknown sources of asbestos exposure.

Several countries established MM registries to monitor MM incidence over time, identify sources of asbestos exposure, provide forensic assistance to patients and their families, evaluate survival, and

forecast future trends of MM incidence (Ferrante et al., 2019).

Italy had been using large quantities of two kinds of commercial asbestos - chrysotile and amphiboles – with more than 3.5 million tons produced or imported from 1945 to the 1992 ban. Italy is currently among the countries with higher MM frequency – either in term of absolute number of cases or crude mortality rates (Nuyts et al., 2018; Marinaccio et al., 2012; Corfiati et al., 2015; Park et al., 2011; Odgerel et al., 2017).

The Lombardy region, North-West Italy is the most populated (currently, 10.06 million inhabitants, one-sixth of the Italian

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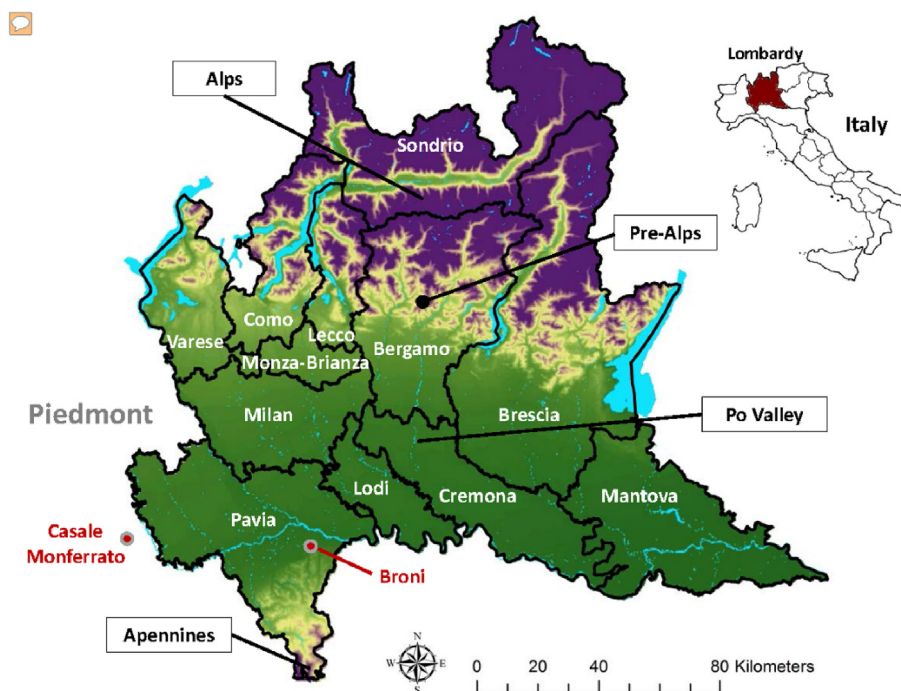


Fig. 1. Lombardy Region and its 12 Provinces.

population) and industrialized of the 20 Italian regions. It is the fourth largest Italian region, covering an area of 23,844 km², with 12 Provinces and 1546 municipalities (Fig. 1).

In 2002, a national MM registry (ReNaM) was set up, organized as a network of regional registries (some of which had started activities earlier). About one fourth of all Italian MM are recorded in Lombardy (Binazzi et al., 2018).

Mensi et al., 2016a studied the geographical distribution of MM incidence in the Lombardy Region at municipality level in the period 2000–2012. This study analyzed separately men and women and reported in both genders a strong spatial pattern with many common high risk areas and some gender specific ones.

There are examples in the literature where the spatial distribution of risk of disease in men and women is jointly studied. This approach is useful to identify presence and extent of shared risk factors which are not gender specific. Two examples are in Richardson et al. (2006) and Biggeri et al. (2009) where the spatial distribution of lung cancer was jointly studied in men and women in UK and Tuscany (Italy) respectively.

In the case of MM incidence, to jointly study the spatial distribution of disease risk in men and women is of particular interest. Indeed, “questions remain unanswered about the contribution of environmental asbestos exposure to MM occurrence”, particularly among women (Bertazzi, 2005). In the MM case registries in general and the Lombardy MM case registry in particular, the percentage of mesothelioma incident cases with no identified asbestos exposure (IAE) is usually higher among women, while among men occupation was the main source of IAE. An analysis which aimed to disentangle the effect of occupational and environmental exposures could also be useful in explaining non-occupational (in particular not IAE) cases in women.

An interesting contribution to the study of the geographical distribution of mesothelioma rates and the role of environmental exposures is in Goldberg et al. (2010). These authors evaluated the degree of correlation between men and women incidence rates and concluded that using data from MM registries «the burden of environmental exposure to asbestos can be estimated from mesothelioma cases without IAE»

Following this line of reasoning, the goal of this work is to estimate

the environmental and occupational components in the geographical distribution of MM incidence in Lombardy by fitting shared multi-variate Bayesian models.

2. Material and methods

2.1. Malignant mesothelioma registry of Lombardy Region (IT)

In Lombardy, a regional MM registry (Registro Mesoteliomi Lombardia, RML) was established in 2000. The RML records all confirmed MM cases (definite, probable, or possible) of the pleura, peritoneum, pericardium, and tunica vaginalis testis reported among Lombardy residents at the time of diagnosis. Patients or their next-of-kin are interviewed using a standardized questionnaire to investigate past asbestos exposure and other relevant information (interview rate > 95%). In particular, lifetime occupational history (industries, occupations) is collected at interview and stored in the RML database. Detailed description of workplaces and specific job tasks is used to assign asbestos exposure but not archived in the electronic dataset. Sources of non-occupational asbestos exposure (see below) are collected and stored electronically. Finally, complete residential history (birth place and municipalities of residence) is also investigated, but only residence periods in known asbestos contaminated sites is recorded in electronic format. Asbestos exposure is classified as occupational (definite, probable, or possible) or - only in absence of occupational exposure - as familial or para-occupational exposure (e.g., from contaminated clothes of a family member); domestic or home-related (e.g. ironing on asbestos boards, small insulation works); indoor environmental (presence of asbestos containing material within the house); outdoor environmental (residence near factories that used asbestos). Note that these outdoor environmental cases refer to a few well-characterized situations with definite and high asbestos exposure, in particular Broni, a small municipality in which the second largest Italian asbestos-cement factory has been in operation (Mensi et al., 2015; Consonni et al., 2019). If no exposure source is identified at interview, cases are labelled as without any identified asbestos exposure (IAE). Finally, cases without or with low quality interview are labelled as “not classified”. More details on the characteristics of the RML are

described in Mensi et al. (2016a, 2016b).

For the present study we selected from the RML database all MM occupational IAE cases (certain, probable, or possible) and all the non-occupational cases operationally defined as all other MM cases including MM cases without IAE or “not classified” MM cases. The analysis was then restricted to MM cases with date of first diagnosis between January 1, 2000 and December 31, 2016, the period in which all activities of case ascertainment, evaluation, and interview had been completed.

Population data by municipality, year, sex, and age were downloaded from the Italian National Institute of Statistics (*Istituto Nazionale di Statistica*, ISTAT) (<http://demo.istat.it/>).

2.2. Correlation analysis

For a simple descriptive analysis, we calculated the Pearson's Correlation coefficients between the rates of occupational/non occupational MM in men and women. For each of the 1546 municipalities of the Lombardy region we calculated the crude incidence rate. In detail, Y_{ik} , the number of observed incident cases for MM for the i -th municipality ($i = 1, \dots, 1546$) and k -th gender ($k = M$ men, W women), follows a Poisson distribution with mean $(pop_{ik} \times \theta_{ik})$ where pop_{ik} indicates the population-time at risk and θ_{ik} the incidence rate. The maximum likelihood estimates of θ_{ik} is $\hat{\theta}_{ik} = \frac{Y_{ik}}{Pop_{ik}}$. The weighted Pearson's correlation coefficient is

$$r = \frac{\sum w_i^2 (\hat{\theta}_{iM} - \bar{\theta}_M)(\hat{\theta}_{iW} - \bar{\theta}_W)}{\sqrt{\sum w_i^2 (\hat{\theta}_{iM} - \bar{\theta}_M)^2 \sum w_i^2 (\hat{\theta}_{iW} - \bar{\theta}_W)^2}}$$

where the weights w_i are inversely proportional to the variance of each observation; that is, assuming a Gaussian approximation to the Poisson likelihood, the variance of the i -th observation is assumed to be proportional to the reciprocal of the population-time at risk. Notice that the weights are specific for each i -th municipality and not specific by gender, therefore $w_i = Pop_i = Pop_{iM} + Pop_{iW}$. Pearson's correlation coefficient was also computed for rates of occupational/non occupational MM in men and women. We repeated this analysis also for Standardized Incidence Ratios for comparison with the literature (see Supplemental material S2).

2.3. Spatial exploratory analysis

We use the so called BYM model (Besag et al., 1991) to account for overdispersion and stabilize municipalities rates. In detail let Y_{ik} be the number of observed incident cases for MM for the i -th municipality ($i = 1, \dots, 1546$) and k -th gender ($k = M$ men, W women) which follows a Poisson distribution with mean $pop_{ik} \times \theta_{ik}$ where pop_{ik} indicates the population-time at risk and θ_{ik} the incidence rate. A spatial random effect model is used to account for spatially structured and unstructured terms and to stabilize rates estimates toward the local and the general mean. We followed the convolution BYM model in which

$$\log(\theta_{ik}) = \alpha_k + u_{ik} + v_{ik}$$

where α_k represents a gender-specific intercept, u_{ik} a spatially structured term by area and gender and v_{ik} a spatially unstructured term by area and gender. The term u_{ik} , called gender specific clustering random term, captures Poisson overdispersion which is spatially structured and shrinks the relative risk towards a local mean. The gender specific clustering component – the a priori in Bayesian terminology – is modelled, conditionally on u_{l-i} terms ($\sim i$ indicates areas adjacent to i -th ones, $l = 1, \dots, 1546$), as Normal $(\bar{u}_i, \lambda_{kl}n_i)$ where $\bar{u}_i = \sum_{l \sim i} \frac{u_l}{n_i}$.

The term v_{ik} , called gender specific heterogeneity random term, captures the overdispersion which is not spatially structured and stabilizes the relative risk toward the global mean. The gender specific heterogeneity a priori distribution is modelled as a weakly informative Normal $(0, \lambda_{\gamma k})$.

The hyperprior distributions of the precision parameters $\lambda_{\gamma k}$, $\lambda_{\gamma k}$ are assumed to be Gamma $(0.5, 0.0005)$ (Kelsall and Wakefield, 1999).

2.4. Shared multivariate bayesian model

The basic idea is to decompose the observed spatial pattern of incidence of MM in two parts: one attributable to environmental exposure and one to occupational exposure. To model the part attributable to occupational exposure, we specify two shared spatial distributions between occupational and non-occupational MM rates separately for men and women. To model the part attributable to the environmental component, we specify a shared spatial distribution of non-occupational MM rates between men and women.

Let define MO occupational cases of MM in men, WO occupational cases of MM in women, MN non-occupational cases of MM in men and WN non-occupational cases of MM in women.

The observed number of cases (Y_{ki}) for the four k -th categories in the i -th municipality are assumed to follow a Poisson distribution:

$$Y_{MOi} \sim \text{Poisson}(\theta_{MOi} \times pop_{Mi})$$

$$Y_{WOi} \sim \text{Poisson}(\theta_{WOi} \times pop_{Wi})$$

$$Y_{MNI} \sim \text{Poisson}(\theta_{MNI} \times pop_{Mi})$$

$$Y_{WNI} \sim \text{Poisson}(\theta_{WNI} \times pop_{Wi})$$

Where $i = 1, \dots, 1546$ is the number of municipalities in the region and the terms θ_{ki} are the rate ratios, and pop_{i} are the gender specific population denominators.

We assume log-linear random effect models for the rate ratios, that is

$$\log(\theta_{MOi}) = \alpha_{MO} + \psi_{Mi} * \delta_1$$

$$\log(\theta_{WOi}) = \alpha_{WO} + \psi_{Wi} * \delta_2$$

$$\log(\theta) = \alpha_{MN} + \psi_{Mi} / \delta_1^\delta + \phi_{MWi} * \delta$$

3

$$\log(\theta_{WNI}) = \alpha_{WN} + \psi_{Wi} / \delta_2 + \phi_{MWi} / \delta_3$$

Where α_k are group-specific intercepts with a priori uniform distribution, ψ_{Mi} is the shared clustering term between MO and MN, ψ_{Wi} is the shared clustering between WO and WN, and ϕ_{MWi} is shared clustering between MN and WN. The terms ψ_{Mi} and ψ_{Wi} capture the occupational spatial gender-specific distribution of the risk. The idea is that the two shared components capture a “residual” occupational part in the distribution of the non-occupational cases. The term ϕ_{MWi} captures the environmental spatial distribution of the rate in common between man and women driven by the geographical distribution of non-occupational cases. The parameters δ_1 and δ_2 explain the importance of occupational vs non-occupational cases in the estimation of the gender specific occupational components. The term δ_3 indicates if the environmental component, which is common in both gender, has a different association with rate distribution in men and women.

The scaling parameters δ_1 δ_2 and δ_3 are assumed a priori lognormal distributed.

2.5. Computational details

All the models were estimated using Markov Chain Monte Carlo methods using the WinBugs software (Lunn et al., 2000). For each model we have run two independent chains and convergence of the algorithm was evaluated according to Gelman and Rubin (1992). We discarded the first 30,000 iterations (burn-in) and stored 10,000 iterations for estimation.

Table 1
Characteristics of subjects with malignant mesothelioma by gender, Lombardy Region Mesothelioma Registry, 2000–2016.

	Men		Women	
	N	%	N	%
Total	4048	100	2178	100
Age at diagnosis, mean (SD)	70.8	(10.0)	73.5	(10.4)
Site				
Pleura	3837	94.8	2006	92.1
Peritoneum	180	4.4	165	7.6
Pericardium	8	0.2	7	0.3
Tunica vaginalis testis	23	0.6	–	–
Diagnosis				
Definite	3338	82.5	1659	76.2
Probable	296	7.3	184	8.4
Possible	414	10.2	335	15.4
Morphology (ICD-O code)				
Not otherwise specified (90503)	207	5.1	132	6.1
Fibrous/sarcomatoid/desmoplastic (90513)	342	8.5	104	4.8
Epithelioid (90523)	2474	61.1	1353	62.1
Biphasic (90533)	527	13.0	191	8.8
Unknown	498	12.3	398	18.3
Presence of pleural plaques	554	13.7	171	7.8
Interview				
Patient	2369	58.5	982	45.1
Relative	1472	36.4	1012	46.5
Not performed	207	5.1	184	8.5
Asbestos exposure at interview				
Occupational	2897	71.6	780	35.8
Familial (para-occupational)	20	0.5	87	4.0
Indoor/Outdoor environmental	85	2.1	106	4.9
Home-related	37	0.9	97	4.4
None ^a	775	19.1	889	40.8
Not classified ^b	234	5.8	219	10.1

Abbreviations: ICD-O, International Classification of Diseases for Oncology, Third Edition.

^a Without any identified asbestos exposure (IAE).

^b Because of no or low quality interview.

3. Results

3.1. Characteristics of mesothelioma cases

We globally analyzed 6226 MM cases (pleura, peritoneum, pericardium, and tunica vaginalis testis) 4048 in men and 2178 in women with a male/female ratio of 1.86 (Table 1). Pleura was the

Site of MM origin in over 90% of cases. The majority had an epithelioid morphology.

Interview was obtained for more than 90% of affected subjects, either from the patients themselves (57%) or from one of their relatives.

Occupational exposure was identified in 2897 men (71.6%) and 780 women (35.8%). Familial, indoor/outdoor environmental and home related exposure at interview was 3.5% in men and 13.3% in women. Cases without any identified asbestos exposure (IAE) and cases not classified were much more frequent in women (40.8% and 10.1) than in men (19.1% and 5.8).

In both men and women, the Province of Pavia showed distinctly high crude and age-standardized incidence rates of MM (Fig. 2). Rates were higher than the regional average in the Provinces of Bergamo, Lecco, Milan (excluding the city of Milan) and Varese (men), and in the Provinces of Bergamo, Lodi, Monza and Brianza, Sondrio (women).

The percentage of cases with direct interview was 54% (58% in men, 45% in women). This percentage varies among provinces (min 44% Lodi – max 82% Brescia; men: min Lodi 47% – max Brescia 86%; women: min Lodi 27% – max Brescia 69%). There was a mild non-significant correlation, among provinces, between percentage of cases with direct interview and percentage of cases with identified asbestos exposure (Pearson's $r = 0.38$, $p = 0.246$; among men Pearson's $r = 0.54$ $p = 0.069$ and among women Pearson's $r = 0.45$ $p = 0.144$).

For the provinces with low incidence the percentage of direct interviews is equal or greater than the percentage of identified asbestos exposures in both sexes (see Supplemental material S6, Figure S6.1). This could be a consequence of a contextual effect, i.e. the higher the incidence of malignant mesothelioma the greater the probability of information from the relatives. However, the statistical model adopted takes into account for potential gender-specific misclassification.

3.2. Correlation analysis

The Pearson's r correlation coefficients between occupational MM rates in men and women was 0.28 (IC 95% 0.23; 0.33- For correlation analysis we computed 95% CI instead of 90% CI to make comparisons with the results reported in Goldberg et al., 2010). Between non-occupational MM rates in men and women Pearson's r was 0.67 (IC 95% 0.64; 0.70). This rough empirical observation of a substantial correlation between non-occupational IAE MM rates confirms the intuition of Goldberg et al. (2010) and suggests the presence of a shared environmental exposure (see Supplemental material S2 for detailed comparisons).

A moderate correlation between males and females non-occupationally exposed is also present when not classified cases are included in the analysis ($r = 0.41$, 95% CI 0.37; 0.45). This is suggestive of a gender-specific misclassification of exposure, as shown by a correlation between rates for occupationally exposed and rates for not occupationally exposed (including not classified cases) in men of $r = 0.29$ (95% CI 0.24; 0.33) and in women of $r = -0.10$ (95% CI -0.15; -0.05).

In interpreting these results, we have to remind that the use of correlation coefficient when data are spatially structured has limitations and has been criticized in the literature (Clifford et al., 1989).

3.3. Spatial exploratory analysis

The crude rates (upper panels) and the BYM smoothed rates (lower panels) by gender (left panels: men right panels: women) are reported in Fig. 3. The spatial pattern is more evident when using smoothed BYM rates (lower panels). The most affected area (south-west), in the Province of Pavia, is the area which includes the town of Broni.

3.4. Shared multivariate bayesian model

In Fig. 4 we report the maps of the gender-specific occupational components (upper panels) and the environmental component from the shared multivariate Bayesian model. The components are expressed on a log scale and centered to zero. In other words, they are interpretable as the log ratio of the component of the generic i -th municipality to the regional average. As reported in the figure the range span from -0.5 to $+2.8$ – i.e. a ratio between 0.60 and 16.5. For example, the high observed rate of occupationally classified MM cases in men in the municipality of Broni is 98.27 per 100,000 person-years vs the average observed regional rate of 3.48: the log ratio is therefore 3.34. The smoothed Bayesian estimate of the occupational component for Broni is 2.8.

The spatial pattern of occupational gender-specific components highlights areas in common between men and women. In particular, in the Province of Pavia (south west part of the region), which includes the Broni area. In the central part of the Region high occupational risk is present in the highly industrialized provinces of Varese, Monza and Brianza, Bergamo, and Brescia. The geographical distribution of occupational component in women shows two hot-spot municipalities in the province of Bergamo (Calcio) and of Cremona (Romanengo) where asbestos textile industries were present.

The spatial distribution of the environmental component (lower panel) highlights, as expected, the area of Broni in the province of Pavia: however, the number of municipalities identified at higher risk

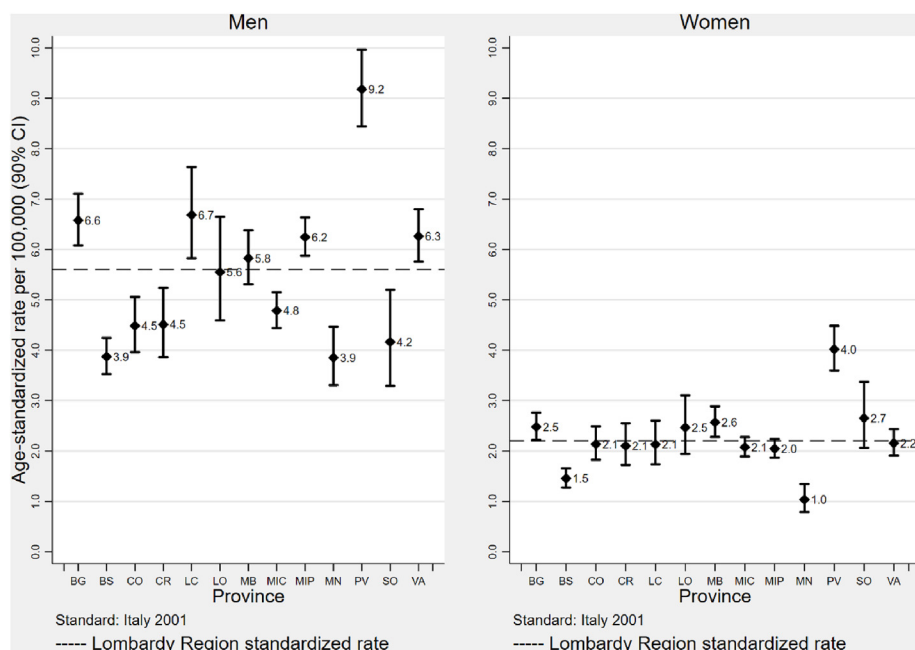


Fig. 2. Directly age-standardized rates and 90% Confidence Interval CI (per 100,000 person-years, age 0–99 years; standard population: 2001 Italian population) of malignant mesothelioma by gender and Province of residence at diagnosis. Lombardy Region Mesothelioma Registry 2000–2016. Dashed line: average regional MM age-standardized rates. BG: Bergamo; BS: Brescia; CO: Como; CR: Cremona; LC: Lecco; LO: Lodi; MB: Monza-Brianza; MIC: Municipality of Milan; MIP: Province of Milan; MN: Mantua; PV: Pavia; SO: Sondrio; VA: Varese.

by the environmental component is larger than those identified by the occupational component, which is restricted to the municipality of Broni and a small number of adjacent towns.

The second large area identified by the environmental component is located in the northern mountain territories of Lombardy region. This is a large territory around the Valmalenco valley which is a non-

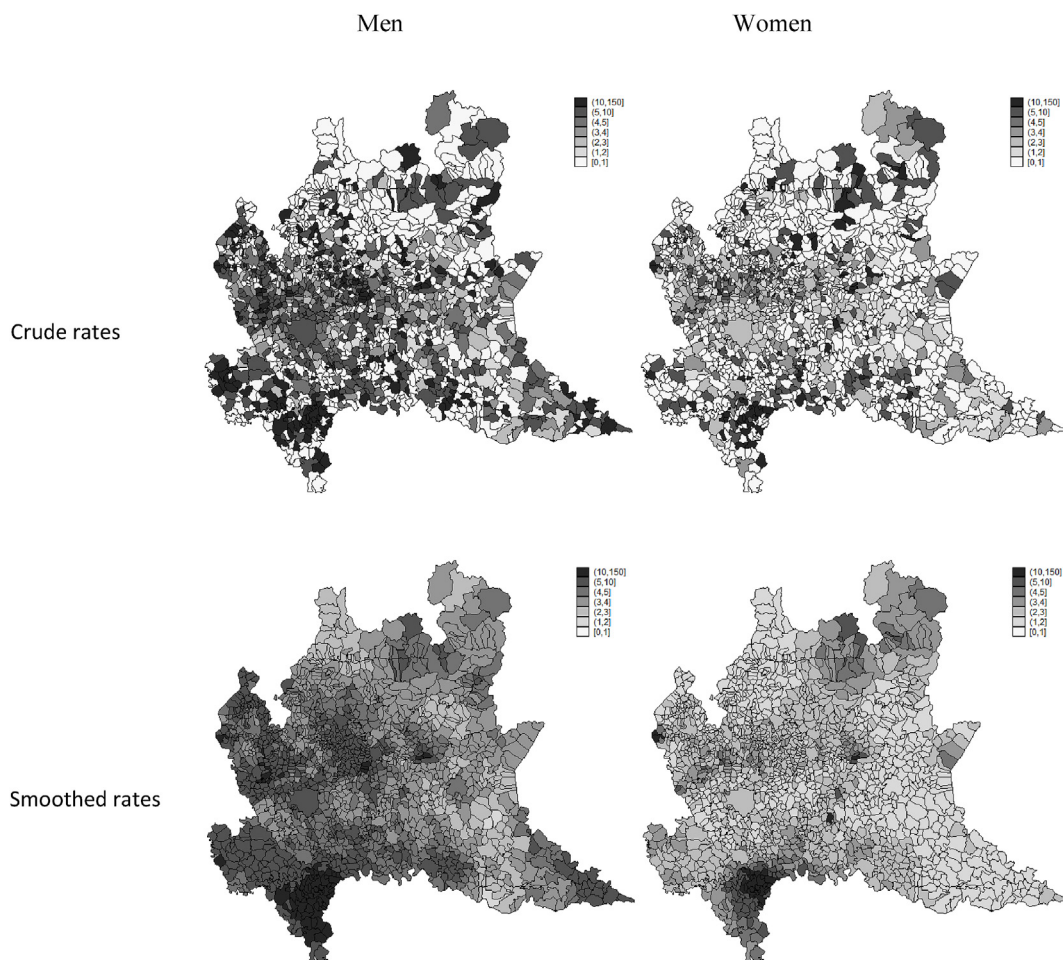


Fig. 3. Choropleth maps of Crude (upper panels) and Bayesian smoothed (lower panels) Incidence Rates, per 100,000 person-years, of malignant mesothelioma by gender (left panels: men, right panels: women) (see text for details). Lombardy Region Mesothelioma Registry, 2000–2016. Absolute scale.

Gender specific occupational components

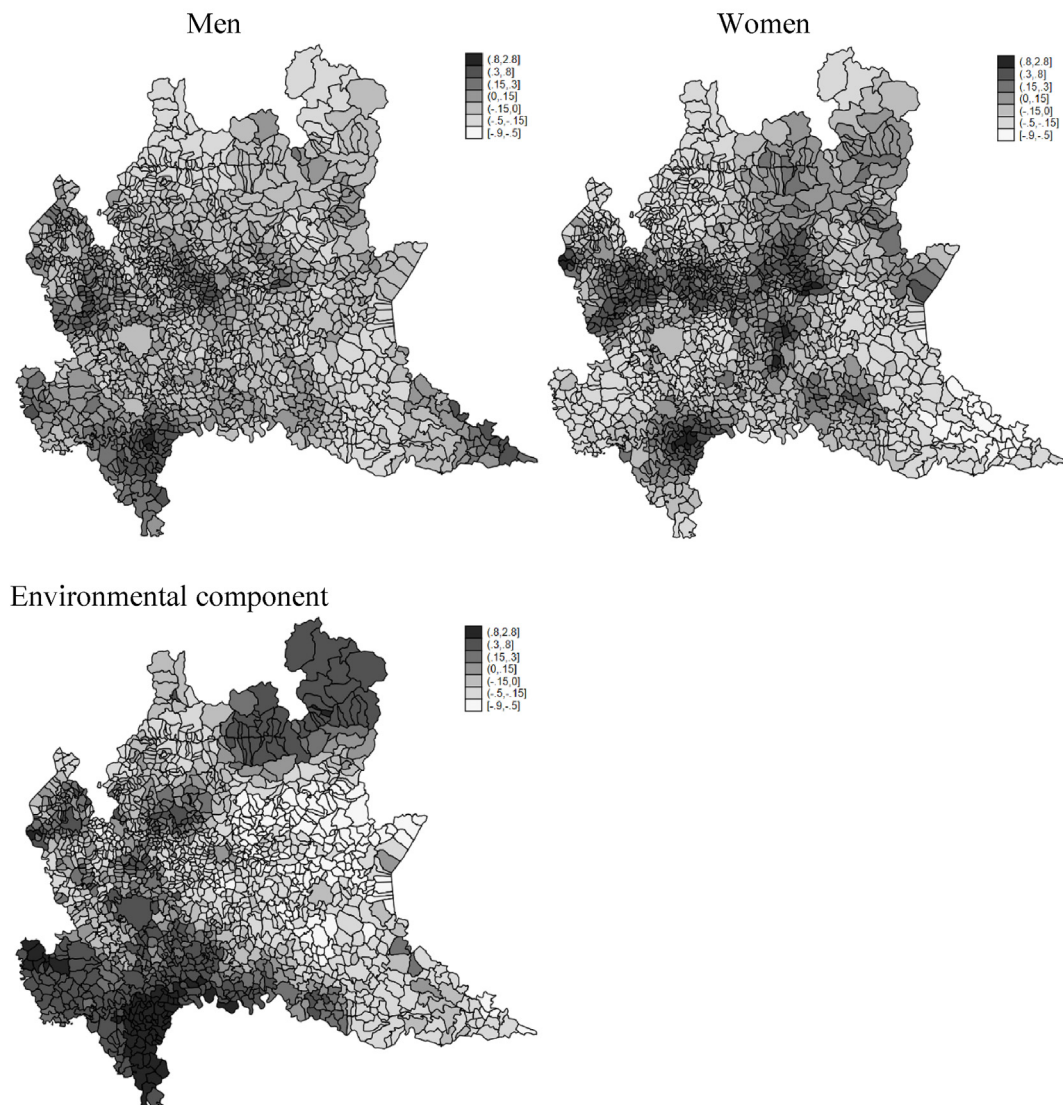


Fig. 4. Choropleth maps of malignant mesothelioma gender-specific occupational components (upper panels, left panel: men, right panel: women) and shared environmental component (lower panel) estimated by the multivariate hierarchical Bayesian model. Lombardy Region Mesothelioma Registry, 2000–2016. Absolute scale. (see text for details).

industrialized, mountain area in the Province of Sondrio with a low population density where MM incidence rates are particularly high. In this area, occupational – although limited in absolute number of workers - exposures to asbestos and ambient contamination – potentially large due to the geological structure of the Valley - arise from extraction and processing of Malenco serpentinites. Chrysotile and antigorite were found as polymorphic states of the Malenco serpentinite, and between the two, chrysotile was the more prevalent (Cattaneo et al., 2012).

Lastly, an interesting spatial cluster is highlighted by the higher estimated environmental component for the municipalities located at the south-western border of Lombardy Region close to the Piedmont province of Alessandria. This cluster is part of the larger cluster centered in the municipality of Casale Monferrato (Alessandria, Piedmont), one of the most asbestos contaminated towns in Europe.

The mean of the posterior distribution for the two scaling parameters δ_1 and δ_2 for the shared components in the multivariate hierarchical Bayesian model were 2.66 (90% credible interval, CrI 1.91; 3.54) and 2.20 (90% CrI 1.67; 2.99) respectively. This means that, as

expected, a small fraction of non-occupational cases contributes to the shared occupational spatial component.

This observation is particularly useful for women. The fraction of MM cases in women not attributable to occupational exposure was high and our model-based estimate – which is function of the scaling parameters δ 's - was 59% (1287/2178, 90% CrI 39%; 94%). The number of cases erroneously classified as non-occupational was estimated as 111 over 1398 cases in the Registry according to the interviews.

The posterior mean for the scaling parameter δ_3 is 0.91 (90% CrI 0.85; 0.98) that is mean, according to our model parameterization, that the environmental component is more important among women than among men.

3.5. Sensitivity analysis

We rerun all the analysis using SIRs instead of rates. We evaluated SIRs using internal indirect standardization for the calculation of expected number of cases (see Supplemental material S1). The differences in the results compared to the analysis by crude rates (see Figures S1.1,

S1.2, S1.3) were minimal.

The shared multivariate Bayesian analysis was conducted using all cases, including “not classified” MM as non-occupational cases. We count 426/6229 “not classified” MM cases (6.84%), of them 213/4049 among men (5.26%) and 213/2180 among women (9.77%). In Supplemental materials S2 we added some analyses which suggest a misclassification of exposure and some details on how our model can recover information from the not classified cases. The exclusion of “not classified” MM cases resulted in zero events for municipalities with small population denominators - 23 in men and 29 among women. The Bayesian analysis excluding “not classified” cases did not lead to notable differences for the occupational gender-specific components (see Supplemental material S3, Figure S3.1 top panel). Some difference was observed for the Environmental component because the Alpine area was strongly smoothed (Figure S3.1 bottom panel). In fact, seven “not classified” cases occurred in seven distinct municipalities of the Alpine area. Dropping these cases from the analysis the residual empirical information to support the estimation of the environmental component in the Alpine area is poor. Figure S3.2 shows the map of the number of cases “not classified” by municipality. On percentage there was no clear pattern in the geographical distribution of not classified cases, nor the Alpine area showed a higher rate of “not classified” cases. The problem is simply linked to the small number of events, since MM is a rare disease.

The percentage of MM with definite, probable and possible exposure are 80%, 8% and 12% respectively. Notice that definite cases represent the great majority (80%) of total cases. There was little variation among provinces with the exception of the capital City of Milan (see Supplemental material S4, Table S4.1). Maps of the distribution of MM crude rates and definite MM crude rates are quite similar (see Figure S4.1 and Figure S4.2). Maps of the distribution of MM crude rates for probable and possible exposure showed only random fluctuations related to the small number of events. Therefore, analyses on definite cases only would yield comparable results to those obtained using all cases (see Supplemental material S4).

In the literature the environmental determinants to MM were studied by the male to female incidence ratios. The M/F crude rate ratios are shown in Supplemental material S5, figure S5.1. The observed M/F crude rate ratios are confused by the occupational and environmental components. For this reasons they are difficult to interpret. Even using M/F SIRs ratios could produce a confused picture, because the two standard reference rates are gender-specific. The confusion stands on the fact that ratios close to unity are the results of mixing of effects: equal occupational risk between the two sexes, presence of environmental only risk (which should be not gender-specific), absence of risk. M/F ratios away from unity vary among areas only due to the occupational component. In Figure S5.1 the dark area corresponds to the industrialized area in the north of Milan (where mainly engineering industries are located).

To obtain a model based version of the M/F ratios we simply re-parametrized the adopted shared Bayesian model (see Supplemental material S5 for details). We provided maps of the estimated log M/F ratios in Figure S5.2: in the left panel (Occupational Male to Female log ratio) the map highlighted in grey tones the areas with greater occupational risk for men compared to women; in the right panel the map (Occupational Female to Male log ratio) highlighted areas with greater occupational risk for women compared to men. These maps did not provide additional information respect to those presented in Fig. 4.

4. Discussion

The association between MM and non-occupational asbestos exposure is widely debated in the literature (Noonan, 2017) although the number of studies is small (Xu et al., 2018). MM is a well-known disease related to asbestos exposure in the workplace and several pathways for environmental asbestos exposures have been described and associated

with MM – as reflected by the recording rules of the Regional Mesothelioma Registry of Lombardy, for example: para-occupational exposure, home-related, indoor environmental for presence of asbestos containing material within the house, outdoor environmental i.e. residence near factories that used asbestos, and, finally, exposure to naturally occurring asbestos materials. Some of these various asbestos exposure pathways follow a geographical pattern. In fact, para-occupational exposure depends on exposed workers acting as vectors for transporting fibers – e.g. through contact with worker clothes. Therefore, we expect some geographical clustering since the workforce is usually resident close to the industrial plant. Exposure from industrial operations or airborne emissions from nearby mines, industrial waste materials and reuse of asbestos materials from the industry in housing materials are all affecting neighborhood communities and show some extent of geographical clustering. Commercial asbestos-containing products can induce various home-related indoor environmental exposures which are not geographically structured. Some outdoor environmental exposure like asbestos in automotive brakes could have some weak spatial pattern. Lastly, exposure to naturally occurring asbestos can occur when asbestos materials are used for roads and soil amendments and as building materials, or through natural erosion and wind. Generally speaking, exposure to natural occurring asbestos may show a clear geographical pattern on a larger spatial scale than that associated with industrial or mining sources of exposure.

In our geographical study we took advantage of small scale municipality level of analysis to decompose the occupational and non-occupational spatial pattern of MM incidence. The evidence of para-occupational exposure and MM risk is well established in the literature. However, residential workers' communities can also be subject to neighborhood contamination and it can be difficult to disentangle para-occupational exposures from residential exposures attributable to industrial point sources – either airborne or waste disposal. In the literature a small radius of less than 10 km from the exposure source for neighborhood contamination is commonly used - for example in Xu et al. (2018). It is expected that the radius be much larger if we focus on para-occupational exposures linked to workers' home residence.

In our results the environmental component shows a large spatial cluster around the municipality of Broni – a well described case of asbestos exposure due to industrial source – with a radius up to 30 km around the town, while the occupational component is restricted to less than 10 km radius. Moreover, we found at the south-western border of the Lombardy Region a spatial cluster for the environmental component located at about 30 km from the town of Casale Monferrato in the adjacent Piedmont Region, another well-known example of asbestos exposure from an industrial source (Maule et al., 2007).

Exposure to asbestos via natural geological formations is a quite separate phenomenon. Several geographic foci have been described - in northwest Greece, northern Corsica, Cyprus, New Caledonia, Biancavilla (Sicily), Cappadocian villages (Turkey), and in rural areas of southwestern China. In such examples the male/female ratios were close to one. We found a large geographically structured Alpine area with higher environmental component in the Northern part of Lombardy region, where the geological characteristics of the mountains include the Serpentine rocks containing asbestos fibers (Cattaneo et al., 2012).

The estimated fraction of environmental MM cases in women is high (model-based estimate is 59%; 95% CrI 39%–73%). The observed Registry-based prevalence is an overestimate since some of those classified as non-occupational are misclassified. Actually, environmental exposure is difficult to investigate by Registry-based interview - except for few well-defined situations with high contamination from large industrial plants. Occupational exposure can be relatively well evaluated in men using data from interviews which cover lifetime job history. In fact, in most MM men it is possible to identify the source(s) of asbestos exposure. Conversely, for the majority of women the sources of asbestos exposure remain unknown. While part of those cases may be

attributable to still unknown occupational exposure, it is conceivable that many cases in women would originate from environmental exposure. Our model estimate of misclassification rate was 111 cases over 1398 cases classified as non-occupational.

Considering the statistical models adopted, we decided to model crude rates instead of the usual standardized incidence ratios (SIRs). Crude rates are directly interpretable as the burden of disease while standardized rates are fictitious, depending on the choice of an arbitrary standard population. Moreover, it is believed that the incidence rate of MM in absence of asbestos exposure (“background rate”) is around 2 per million person-years (McDonald, 1985). Hence, virtually each case can be seen as an indicator of exposure to asbestos. Under no asbestos exposure we therefore practically expect zero case count. In the literature the use of SIRs is frequent, a choice justified by a comparative approach. However, classifying some areas below the regional average, which is an inevitable consequence of using SIRs internally standardized, could induce the reader to erroneously consider these areas unimportant for MM. Our paper aimed to estimate the presence and extent of an environmental risk of MM and this reflects our choice to model crude incidence rates.

In Supplemental materials S1 we compared the results obtained using crude rates with those obtained using SIRs. The differences were minimal. This is due to the fact that we did not find relevant confounding by age in our dataset. We cannot exclude that this could happen in situations where important variations in occupational asbestos exposure occurred among birth cohorts. Comparison among SIRs is known to be potentially biased which is not the case of rates, however, our Bayesian model does not suffer the problem of lack of comparability, given the model be correctly specified (Breslow and Day vol II).

We advocate the use of rates from a public health perspective because virtually all MM cases are attributable to asbestos. If we use SIRs only (SIR-1)/SIR % of cases will be attributable. Moreover, using gender-specific SIRs the absolute difference in incidence between men and women will be obscured, since SIRs are scaled to the regional gender-specific average rate.

Age or cohort effects cannot be excluded and must be considered in interpreting the results of our cross-sectional analysis. However, the RML retrieves detailed information for each case and we were able to conduct an analysis separately for occupational and non-occupational IAE cases.

Many complex alternative model specifications are possible. In our model we did not consider the heterogeneity random terms in the original specification of Knorr-Held and Best (2001). Our choice is justified by identifiability argument. Indeed, the BYM model will fit a number of parameters which is 2 times the number of observations: it is well known that much care has to be taken in mapping random components – the clustering and the heterogeneity components – of the BYM model, since only the ratio of the variances of the two random terms be identifiable (Leroux et al., 2000).

To ensure identifiability of the random components we specified a parsimonious model with 3×1546 (ψ_{Mi} ψ_{Wi} ϕ_{MWi} , $i = 1, 1546$ areas) parameters on 4×1546 observations (Y_{MOi} Y_{WOi} Y_{MNi} Y_{WNI} , $i = 1, 1546$ areas). Our model assumes a gender-specific correlation between rates of occupational and non-occupational MM among areas, and a correlation between rates of non-occupational MM in men and women. A possible extension of the multivariate shared model would have been to augment the model with a second shared random component between occupational MM in men and women.

A potential limitation of this kind of study is that the relevant exposure for MM cases could be experienced at a different location than the residence at diagnosis. This point cannot be solved with our kind of data but there are examples in the literature of geographical clusters of MM due to re-immigration (Merler et al., 2000; Musk et al., 2019; for an Italian example see the geographical cluster of MM in the municipality of Triggiano, Bari, due to remigration after retirement of workers of an

asbestos cement plant in Switzerland; E. Merler Personal Communication).

In Italy we had a massive flux of internal migration from South to the industrial region of North-West, Lombardy and Piedmont, with a peak in the early seventies. These migrant populations showed a reduced risk of cancer (and lung cancer in particular) than the host populations but higher risk than the native populations of origin. The data considered in our study refers to the calendar period 2006–2016, forty years after the peak migration flux. A possible dilution effect could be occurred for the rate of MM among older age groups in the municipalities who experienced massive migration from the South, assuming that not exposed older relatives of migrant workers reached the householder in the incoming years after migration. These considerations are relevant for older birth cohorts, mainly relative to exposures experienced during the second world war and the immediate after war period. For more recent ones, after the seventies, a milder potential confounding by birth place (North-South) cannot be excluded as well as we cannot exclude a residual confounding induced by aggregate data, a common fallacy in ecological studies like ours despite the use of sophisticated spatial Bayesian modelling. Extra European Union migrants are a relatively recent phenomenon in Italy and Lombardy. We have for Lombardy a percentage between 7.6% and 11.4% in the period analyzed in our work with no correlation with crude rates of MM by Province (<http://www.comuni-italiani.it/03/statistiche/stranieri.html>) (see Supplemental material S7).

Lastly, we defined non-occupational cases all MM cases with or without evidence of non-occupational asbestos exposure. This choice reflects our assumption that the cases without any IAE and cases without or with low quality interview (“not classified”) may have been exposed to asbestos (occupationally or non-occupationally). If it is so, some correlation between occupational and non-occupational cases should be present and our model specification is consistent with this assumption. Differently, we could have restricted the analysis to only cases with valid information from the interview. We ran both analyses, and since we found evidence of some correlation between occupational and non-occupational components, we presented the analysis on all MM cases which is more powerful when considering a rare disease and small areas in term of population denominators.

5. Conclusion

The main message of the paper is that, using appropriate methodological analysis, we were able to disentangle occupational and environmental components in the MM spatial distribution. The methodology is new in the epidemiology of MM and the results show a larger than previously found impact of the environmental component.

The geographical analysis showed a strong spatial pattern in the distribution of incidence rates in both gender (Mensi et al., 2016a). The multivariate hierarchical Bayesian model decomposed the spatial pattern in an occupational and an environmental component and consistently identified some known occupational and environmental hot spots mainly linked to the presence of asbestos-cement, metallurgic, engineering and textile industries. Other areas at high risk for MM occurrence were highlighted contributing to better characterize environmental exposures from industrial sources – in particular in the area of Broni, a well-known hot spot due to a large polluting asbestos cement plant - and suggesting a role of natural sources in the Alpine region.

The estimated fraction of environmental MM cases in women is high (model-based estimate is 59%; 95% CrI 39%–73%) strengthening previous report based on observational data.

In conclusion, geographical studies like our can be useful to quantify the extent of environmental exposure to asbestos on malignant mesothelioma incidence.

Author contribution

Dolores Catelan: Conceptualization, Methodology, Software, Formal analysis, Writing: original draft; Writing: Review & editing. Dario Consonni: Data curation, Formal analysis, Writing: Review & editing. Annibale Biggeri: Supervision, Conceptualization, Methodology, Writing: Review & editing. Barbara Dallari, Luciano Riboldi: Resources. Angela C. Pesatori: Writing: Review & editing. Carolina Mensi: Resources, Writing: Review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2020.109691>.

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