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Exploring methods for the assessment of temporal trends in mortality and hospitalization in Italian industrially contaminated sites

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Abstract
Introduction. The Italian contaminated sites of interest for remediation are monitored by SENTIERI, an epidemiological surveillance system describing the health status of populations living nearby these sites. There is an increasing concern on how to assess temporal changes in the health status of these populations.
Methods. A sequence of three statistical techniques was adopted to analyse temporal trends of mortality and hospitalization, by using different indicators and reference populations, in a sample of 36 sites with industrial sources of contamination monitored by SENTIERI.
Results. Positive temporal trends in health risks are detected reflecting mainly long term effects of industrial activities. The adopted methodology identifies multiple factors influencing the temporal patterns: type of health outcomes, type of disease, and its link with gender and type of emission sources.
Conclusions. Reliable methods to assess health profile changes in local populations attributable to contaminations are key elements to measure the impact of remediation activities.

Key words
- contaminates sites
- mortality
- hospitalization

INTRODUCTION

In Italy, the health status of communities identified as living close to major contaminated sites is periodically monitored by the SENTIERI epidemiological surveillance system, using data at the municipality level [1]. Most of these contaminated areas are registered as National Priority Contaminated Sites (NPCS) and many of them are contaminated by still active industrial complexes. The main aim of SENTIERI is to describe health profiles of communities living close to each monitored site by looking at different health outcomes (mortality and hospitalization, cancer incidence, prevalence of congenital malformations) in order to provide evidence for local public health interventions.

All 20 Italian Regions, excluding Molise, have at least one site monitored by SENTIERI, with an overall interested population of 5,900,000 inhabitants in 319 municipalities (2011 Italian Census) [1].

Industrial plants have contaminated most of these sites for decades, compromising the surrounding areas by polluting soil, water, air, and the food chain with several chemical substances. The main polluting sources found in the monitored sites are chemical plants, petrochemical plants and refineries, steel industries, electric power plants, mines, harbour areas, asbestos, landfills, incinerators [2].

The first figures published by SENTIERI documented an overall excess of mortality in the 44 monitored areas (298 municipalities), with around 10,000 exceeding deaths among the 404,000 observed (men and women combined, all causes of mortality) in an 8-year period (1995-2002) [3]. About 3,600 deaths were associated with pollution present in the contaminated sites. A subsequent overall analysis of cancer incidence data in 10 years (1996-2005), limited to the 23 sites served by cancer registries, showed an overall excess of 9% in men and 7% in women [4]. The last SENTIERI publication regarded 319 municipalities in 45 sites, with data on

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mortality, hospitalizations, cancer incidence (for the overall population and children, separately), and congenital anomalies. Data on mortality documented an excess for all causes of 2.5% (around 5,300 deaths) and 3% (around 6,700 deaths) in men and women, respectively, in a period of 8 years (2006-2013) [1].

SENTIERI has provided figures on health profiles in different periods, updating such figures on the basis of data availability. At present, no formal statistical analysis on changes over time of such profiles has been carried out.

This is an explorative study aimed at proposing a possible methodological procedure for assessing temporal trends in mortality and hospitalizations to be applicable to SENTIERI and other epidemiological surveillance systems based on data aggregated at a population level (i.e. ecological-area level data). This will be reached by exploring the informational benefits of some statistical analysis by their application to data regarding a subgroup of sites monitored by SENTIERI. An in-depth analysis of temporal trends in contaminated sites via model estimation and the application of statistical methods for comparing them with regional reference trends were carried out.

METHODS

Selection of contaminated sites

The present contribution is primarily focused on exploring methods for the assessment of temporal trends in different groups of sites, and to suggest some possible clues for further *ad hoc* analyses, while did not aim to analyze, discuss and interpret results concerning different contamination sources. To achieve this aim we limited the analysis to the large subgroup of sites monitored by SENTIERI having chemical/petrochemical or steel industrial plants among the main sources of contamination and excluding other contaminated sites characterized by asbestos or asbestiform fibers or having landfills as the only source of contamination or combined with asbestos. Thirty-six sites were identified and classified in the following 5 categories:

- Chemical: sites that present just a chemical plant or a chemical plant and a landfill. The chemical plant is predominant in the contamination process since the landfill, in these cases, is used for waste produced by the chemical plant itself;
- Chemical+: sites that present a chemical plant and other relevant plants, in terms of contribution to pollution in the air, such as electric power plants, steel industries or harbour areas [5, 6];
- Petrochemical: sites that present a petrochemical plant and/or a refinery and a harbour area;
- Petrochemical+: sites that present a petrochemical plant and/or a refinery and other relevant plants, in terms of contribution to pollution in the air, such as electric power plants, steel industries or harbor areas [5, 6]. This label includes sites that present at least three pollution sources, up to a maximum of seven, so the contamination level is considered high;
- Steel: sites that present a steel industry and a landfill. The steel industry is predominant in the contamination process, since the landfill, in these cases, is usually used for waste that is produced by the industry itself.

Out of the thirty-six sites, 17 of them were classified as "Chemical", 5 as "Chemical+", 2 as "Petrochemical", 10 as "Petrochemical+" and 2 as "Steel".

The selected sites have industrial sources of chemical contamination of soil and water environmental matrices. The presence of important industrial sources of air pollution is associated with petrochemical plants and refineries and steel plants and is highlighted with the "+" if other industrial sources of air contamination (i.e., electric power plant, harbour area, steel industry) are present in the site.

This paper does not provide the names of the contaminated sites included in the analyses, nor it describes where they are located. We intentionally anonymized the study areas since the main objective is to explore useful methods and identifying a process of analysis to be used in epidemiological surveillance systems, rather than to produce and interpret results from an environmental public health perspective.

Source and description of health data

Two data sources available at the Statistical Service of the Italian National Institute of Health (Istituto Superiore di Sanità) were used: the National Mortality Database (NMD) managed by the Italian National Institute of Statistics (Istat) and the National Hospital Discharge Database (NHDD) managed by the Italian Ministry of Health. The NMD contains the underlying causes of death, coded using ICD-10 Revision since 2003. The NHDD records data of all patients discharged from all Italian hospitals, including not only acute admissions but also planned investigation treatment units, on a "day-hospital" basis. For each patient, demographic data (e.g., sex, date and place of birth) are recorded with the primary and up to five secondary discharge diagnoses, codified according to the WHO International Classification of Diseases-Clinical Modification, 9th Revision (ICD9-CM).

Mortality and hospitalization data for each selected site were analyzed for the period 2005-2016. Concerning hospitalization data, every hospitalized patient was considered just once each year, even if they had been hospitalized multiple times in the same year, for the same disease. Also, only the primary cause of hospitalization was considered. This procedure avoids multiple counts for the same subject and reduces the distortion of risk estimates.

This study refers to data observed in Italian selected contaminated sites and in the regions where these are located; the NPCS data were cleared from their respective regional data to avoid their contribution to the reference (the regional data).

Selection of causes of death and hospitalization

Multiple causes of mortality and hospitalizations were considered in this work following a sequence of three different phases.

In the first phase, standardized mortality and hospitalization rates for the selected contaminated sites were computed (see the statistical analysis section below) for each of the 52 causes of mortality (from the ICD-10) and 49 causes of hospitalization (from the ICD9-CM) selected in the SENTIERI study [1].

In the second phase, in order to compare the single NPCS figures with the corresponding regional reference values, hospitalization and mortality data were broken down into groups: all causes; all malignant tumours; trachea and lung malignant tumours; malignant tumours of the lymphatic-hematopoietic system; circulatory system diseases; ischemic heart disease; respiratory system diseases; digestive tract diseases; urinary system diseases; chronic lung diseases; acute respiratory diseases (asthma; acute respiratory infections, pneumonia and flu and chronic obstructive pulmonary diseases for hospitalizations).

These groups of causes were chosen due to prior knowledge on their association with the considered pollution sources, mainly petrochemical plants and refineries. Precisely, literature has been provided for lung cancer mortality [7] and incidence [8], risk of leukemia [9], respiratory symptoms [10] and hematological malignancies [11] on residents living near petrochemical industrial complexes.

In the third and final phase, with the aim of making comparisons between the contaminated sites and the reference regions, only the two larger groups of causes "General mortality" and "All causes of hospitalization" were analyzed in depth.

Statistical analysis

The three phases of analysis are here described.

In the first phase, for each cause of mortality (52 causes) and hospitalization (49 causes), standardized rates were computed for each year in 2005-2016, for males and females separately, marginalizing over the age factor and using the European population as reference [12].

The time series of standardized rates were studied by adapting linear regression models to the series, using time as the only covariate. The regression coefficients were evaluated to better describe hospitalization and mortality over time: a positive regression coefficient highlights increasing values over time, while negative regression coefficients highlight decreases. Significant linear trends can be detected by observing the p-value of each coefficient and setting a threshold: results are shown for a chosen threshold of 0.1. A chi-square dependence test was calculated for detecting the association between gender and significant linear trends, both increasing and decreasing.

In the second phase, the focus was on the selected groups of causes presented in the previous section. Increasing trends found among these causes were specified and further analyzed: time trends found to be associated with a specific gender in a contaminated site were compared to the corresponding region, to detect any differences or similarities between these geographical levels. This procedure was used to verify if increasing gender/cause time-trends are related to a specific site or if they are shared by all areas in the region where the site is located.

In the third phase, again, with the aim of comparing NPCS values and reference regional values, the focus was only on "All natural causes" of hospitalization and on "General mortality". For these two causes, ratios between rates in the contaminated sites and in the reference regions were computed, to detect possible risk excesses. With a ratio exceeding the threshold 1, the rate in the contaminated site is higher than the regional one, showing a risk excess; on the contrary, a ratio smaller than 1 correlates with a risk decrease; if the ratio equals the threshold, the site and the region have the same rate and no risk excess in either of them.

In addition, for the two groups of causes, a graphical comparison of the Local Estimated Scatterplot Smoothing (LOESS) curves built on the time series of the rates in the sites and in the regions was carried out in order to understand the general behaviour of the series. Confidence intervals were also calculated (with a 95% range) around approximations, to show the uncertainty surrounding these estimates.

By fitting simple regression models and using chi-square dependence tests, the first phase aims to get an overview of the trends in the time series of mortality and hospitalization.

In the second phase, a focus is made on increasing trends on a group of causes of interest, the ones that were chosen because of prior knowledge on their association with the selected sources of contamination, with the additional aim of comparing trends in the contaminated sites to those in the reference regions.

Focusing on an even smaller group of causes, the third phase gives further results on NPCSs-regions comparisons, through the application of rate-ratios analysis and LOESS curves graphical observation.

The three phases are displayed in *Figure 1*. Analyses were performed using the statistical software R and RStudio.

RESULTS

First phase

Out of 3,396 estimated regressions analyzing mortality rates, 768 (21.55%) show a significant trend, and among the latter 27.73% displays an increasing tendency. Significant gender differences in linear trends are also observed, as suggested by the chi-squared dependence test: there are more growing trends in the series due to women's death rather than men. The highest percentages of positive trends compared to the total for each type of site were observed for "Chemical+" and "Petrochemical", respectively 31.76% and 34%.

Out of 3,294 trends estimated for hospitalization data, 1,712 (51.69%) appear to be significant, 7.18% of which increasing; gender does not seem to influence the trend. Most significant trends have been observed for the "Chemical" and "Petrochemical+" sites, respectively 43.51% and 31.54% of the total.

Table 1 shows both significant and non-significant trends in mortality and hospitalization, which can be compared, for all causes. Regarding significant trends, although hospitalizations show a greater number of those, mortality has a four-fold higher percentage of increasing ones (27.7% *vs* 7.2%, respectively).

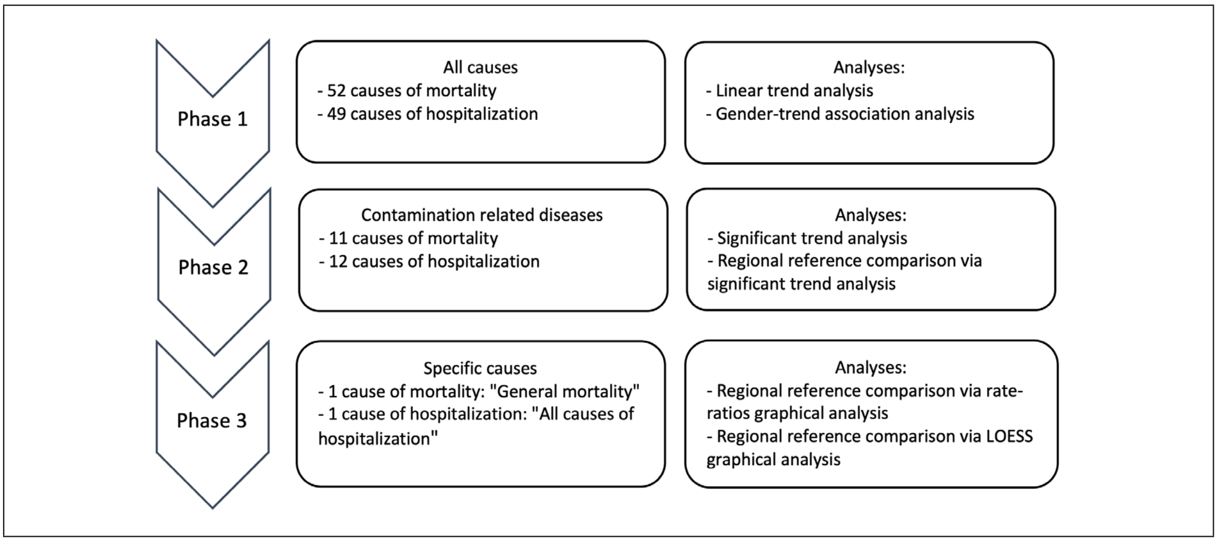

Figure 1
Diagram of the three phases of analysis.

Table 1
Significant and non-significant trends in mortality and hospitalization, for all causes. On each time series, a linear regression model is fitted and the regression coefficient, whether positive or negative, is evaluated; the coefficient is considered significant if its p-value is smaller or equal than the fixed threshold 0.1. For the five categories of NCPSs, absolute frequencies of the estimated trends are reported, both for hospitalization and mortality; frequencies are specified for both significant and non-significant trends, whether positive or negative, in both males and females

Significant trends												
Hospitalization	**Chemical**		**Chemical+**		**Petrochemical**		**Petrochemical+**		**Steel**		**Total**	**%**
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**		
Negative	356	320	98	101	49	46	270	236	61	52	1589	92.82%
Positive	33	36	4	7	1	3	14	20	3	2	123	7.18%
	389	356	102	108	50	49	284	256	64	54		
	745		210		99		540		118		1712	100%
Mortality	**Chemical**		**Chemical+**		**Petrochemical**		**Petrochemical+**		**Steel**		**Total**	**%**
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**		
Negative	130	109	35	23	18	15	95	91	22	17	555	72.27%
Positive	29	54	8	19	9	8	33	44	3	6	213	27.73%
	159	163	43	42	27	23	128	135	25	23		
	322		85		50		263		48		768	100%
Non-significant trends												
Hospitalization	**Chemical**		**Chemical+**		**Petrochemical**		**Petrochemical+**		**Steel**		**Total**	**%**
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**		
Negative	260	249	72	69	27	30	105	132	23	30	996	62.95%
Positive	128	171	54	48	15	13	71	72	5	8	585	37.05%
	388	420	126	117	42	43	176	204	28	38		
	808		243		85		379		66		1582	100%
Mortality	**Chemical**		**Chemical+**		**Petrochemical**		**Petrochemical+**		**Steel**		**Total**	**%**
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**		
Negative	365	364	93	111	35	42	197	192	46	47	1491	56.73%
Positive	268	262	98	68	34	31	168	153	27	27	1136	43.27%
	633	626	191	179	69	73	365	345	73	74		
	1259		370		142		710		147		2628	100%

Second phase

Results showing statistically significant estimated trends are reported, focusing on the selected groups of causes. Out of 792 estimated linear trends for the eleven causes of death, 290 are significant; of the significant ones, 30 (10.34%) are increasing. Of the 864 linear trends for the twelve hospitalization diseases, 685 appear to be statistically significant; only 7 (1.21%) of the significant ones increase, almost ten times smaller than the same percentage found for mortality results.

The absolute frequencies of the estimated decreasing and increasing significant trends, for each considered disease and type of pollution source, are described in *Figures 2a, 2b* and *Figures 2c, 2d*, for mortality and hospitalization, respectively.

In both scenarios, most of the estimated trends appear to be decreasing (89.66% in mortality, 98.79% in hospitalization), most of which are observed in "Chemical" (44.23% in mortality, 43.80% in hospitalization) and "Petrochemical+" (32.30% in mortality, 31.12% in hospitalization) types of sites. High frequencies of decreasing trends are also found for "Circulatory system diseases" and "General mortality" (*Figure 2a*), and for almost all hospitalization causes but "Trachea and lung malignant tumours" and "Lymphatic-hematopoietic system malignant tumours" (shown in *Figure 2c, 2d*).

Increasing trends are small in number, more frequent in mortality than in hospitalization, for a few selected causes.

All increasing mortality and hospitalization trends for the selected causes are shown in *Tables 2 and 3* by contaminated sites and gender; each regression coef-

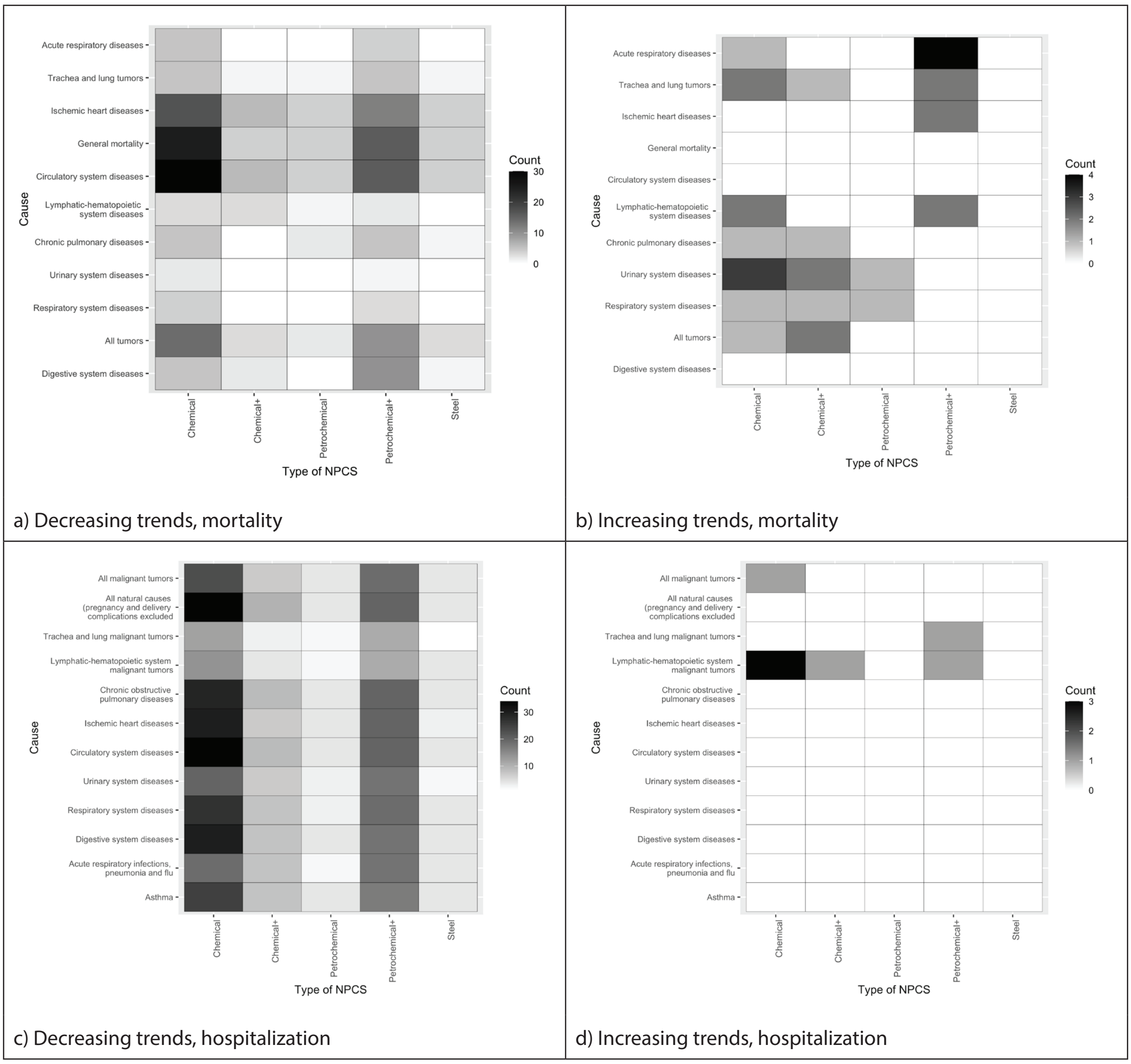

Figure 2

Absolute frequencies of the estimated significant trends, both increasing and decreasing, for mortality and hospitalization, separately. The shades of gray, ranging from white to black, correspond to the absolute frequencies. For the same phenomenon, whether hospitalization or mortality, the white shade corresponds to zero and the black shade corresponds to the maximum absolute frequency, depending on its value in decreasing or increasing trends.

Table 2
Increasing and statistically significant trends in mortality for the 11 selected groups of causes. When such a coefficient is estimated in a NCPS, for a specific gender and cause, a linear model for the same conditions is estimated in the region where the NCPS is located, as well. The regional coefficient is sided by an asterisk when statistically significant

Cause	Type of site	Gender	Coefficient	Coefficient in the region
Lymphatic-hematopoietic system diseases	Chemical	Male	2.03	-0.12
	Chemical	Female	1.50	-0.26*
	Petrochemical+	Male	1.43	0.08
	Petrochemical+	Female	1.11	-0.15
Respiratory system diseases	Chemical	Male	4.43	-1.08*
	Chemical+	Female	8.96	0.68*
	Petrochemical	Female	0.99	-0.44
Urinary system diseases	Chemical	Female	1.58	0.11
	Chemical	Female	0.82	0.075
	Chemical	Female	2.42	0.015
	Chemical+	Male	1.84	-0.009
	Chemical+	Female	2.68	-0.018
	Petrochemical	Male	1.20	-0.009
Ischemic heart diseases	Petrochemical	Male	5.16	-3.77*
	Petrochemical	Female	6.07	-2.60*
Chronic pulmonary diseases	Chemical	Male	5.16	-2.23*
	Chemical+	Female	4.93	0.44
Acute respiratory diseases	Chemical	Female	0.74	0.46*
	Petrochemical+	Female	0.57	0.057
	Petrochemical+	Male	1.95	0.40
	Petrochemical+	Female	0.81	0.099
	Petrochemical+	Female	1.09	-0.099
Trachea and lung tumors	Chemical	Female	1.56	0.50*
	Chemical	Female	1.33	0.42*
	Chemical+	Female	1.55	-0.02
	Petrochemical+	Female	1.10	0.55*
	Petrochemical+	Female	0.39	0.49*
All tumors	Chemical	Female	2.94	-0.11
	Chemical+	Male	15.02	-5.15*
	Chemical+	Female	2.33	-0.49

*Significant.

Table 3
Increasing and statistically significant trends in hospitalization for the 12 selected groups of causes. When such a coefficient is estimated in a NCPS, for a specific gender and cause, a linear model for the same conditions is estimated in the region where the NCPS is located, as well. The regional coefficient is sided by an asterisk when statistically significant.

Cause	Type of site	Gender	Coefficient	Coefficient in the region
Lymphatic-hematopoietic system malignant tumors	Chemical	Male	6.51	-1.8*
	Chemical	Female	3.39	-1.28*
	Chemical	Female	1.11	- 0.25
	Chemical+	Male	2.82	-3.38*
	Petrochemical+	Female	3.74	-1.28*
All malignant tumors	Chemical	Female	6.97	-6.18*
Trachea and lung malignant tumors	Petrochemical+	Female	0.67	0.25*

*Significant.

ficient can be compared to the regional one, which was estimated for the same disease and gender. An asterisk is placed beside the region coefficient if this happens to be significant as well, for a 10% threshold.

In both scenarios, 70% of increasing trends concern women, and no results are observed for "Steel" sites.

In mortality results, as observable in *Table 2*, the highest and positive coefficient is found for "All tumours" on a "Chemical+" site for men; its corresponding trend in the region, however, is negative, decreasing significantly.

In hospitalization results, the group "Lymphatic-hematopoietic system malignant tumours" shows statistically significant increases in 5 sites, whose corresponding regions show decreasing and significant disease trends.

In general, regional trends are much more stable than NPCSs in both scenarios, with slopes ranging between 0 and 1, if positive.

Third phase

Focusing on "General mortality" and "All natural causes" of hospitalization only, graphical analyses for more in-depth comparisons between contaminated sites and regions are provided.

Figures 3a, 3b and *Figures 3c, 3d*, available online as Supplementary material, showing rate-ratios for the two causes, where the rate in each contaminated site, for both mortality and hospitalization, for males and females separately, is divided by the corresponding regional rate, can be observed.

In both scenarios, for both genders, most of the ratios do exceed the threshold 1, highlighting risk excesses in the contaminated sites as compared to the regions where they are located, with higher frequencies in hospitalization results.

Some trends in the hospitalization ratios can be spotted in the *Supplementary Figure 3c*, e.g. in the "Chemical 15" site, with increasing ratios across time, and in "Steel 2" site, with decreasing ratios. Mortality ratios in the study period are extremely variable, with no trends to be detected (*Supplementary Figures 3a, 3b*).

Only a few sites show smaller-than-one ratios for the whole period; most of the "Petrochemical+" sites show risk excesses, especially in hospitalizations.

In addition to the evaluation of the relationship between site and regional rates, the time series of the "General mortality" and "All natural causes" of hospitalization rates were compared using LOESS. Smooth approximations of the series are obtained, helping us to capture their general behavior, and also confidence intervals are calculated around approximations to show the uncertainty surrounding these estimates.

In the following plots, two explicative examples of the LOESS curves are displayed.

Figure 4a shows males have very large mortality rates in the "Petrochemical+ 6" site, with respect to females; however, the two show similar trends in time: the rate in the NCPS has been growing, with respect to the regional one which has been decreasing linearly, and the two have started approaching only in the last years of the observation period.

Figure 4b shows the hospitalization rate for the "Chemical 15" site is always higher than the regional one, and the two do not seem to be approaching one another, even though both of them are decreasing. The ratio between the two rates, as observable in the *Supplementary Figures 3c, 3d*, appears to be increasing.

More explicative examples of LOESS curves can be observed in the Supplementary material.

Supplementary Figure 4c shows males and females present different trends in the mortality rates in the "Chemical 1" site: concerning males, the rate was decreasing at the beginning of the period and then has started increasing in the latest years, diverging from the regional one, while the rate for females appears to be much closer to the regional one, except for a slightly diverging trend in the final years of observation. The regional rate, in both genders, has a linear and decreasing trend.

In *Supplementary Figure 4d*, the regional general mortality rate is almost always larger than the NPCS' one, with wide uncertainty on the estimates, especially for females. This is also observable in *Supplementary Figure 3b*, where rate-ratios in this site are very small throughout the whole period.

In *Supplementary Figure 4e*, the hospitalization rate for the "Petrochemical+ 3" NPCS is always higher than the regional rate, with the difference between the two becoming smaller in the most recent years, and both rates decreasing. This trend between the two rates was observed in most of the cases.

Lastly, *Supplementary Figure 4f* shows one of the few cases where the regional hospitalization rate is higher than the contaminated site rate; this is coherent with what is observable in the *Supplementary Figures 3c, 3d* for this site, "Chemical 14".

DISCUSSION

Results from the three phases of analysis that were run on mortality and hospitalization data in contaminated sites allow multiple considerations on time trends of the rate series.

Findings of the first phase provide awareness on the differences between the two health outcomes in time: more significant trends were observed in hospitalizations than in mortality, and yet, the percentage of increasing trends in the latter was much higher than in the former. This finding shows mortality rates have been growing in time, from 2005 to 2016, due to the long latency of some death causes (the observed high mortality might be associated with exposure to contaminants many years before). In both scenarios, more increasing trends were detected in women than in men, and the gender difference was significant in mortality results, which could be a matter of interest for future work aimed at linking gender-related mortality to specific exposure settings in contaminated areas.

In the second phase, results are provided for the selected group of causes: most of the significant trends in the selected sites were decreasing. Concerning mortality rates, most of the decreasing trends were observed for general mortality and circulatory system diseases in "Chemical" sites; regarding hospitalization, almost all conditions showed high frequencies of decreasing trends in "Petrochemical+" sites. A small percentage of increasing hospitalization trends was observed for lymphatic and hematopoietic system-related diseases, all tumours and trachea and lung tumours, malignant or not, in mortality. The highest frequencies of increasing trends were observed for all respiratory diseases and urinary system diseases. In both scenarios, most of the increasing trends were observed for "Chemical" and "Petrochemical+" sites; for sites with only Steel plants increasing trends were never found.

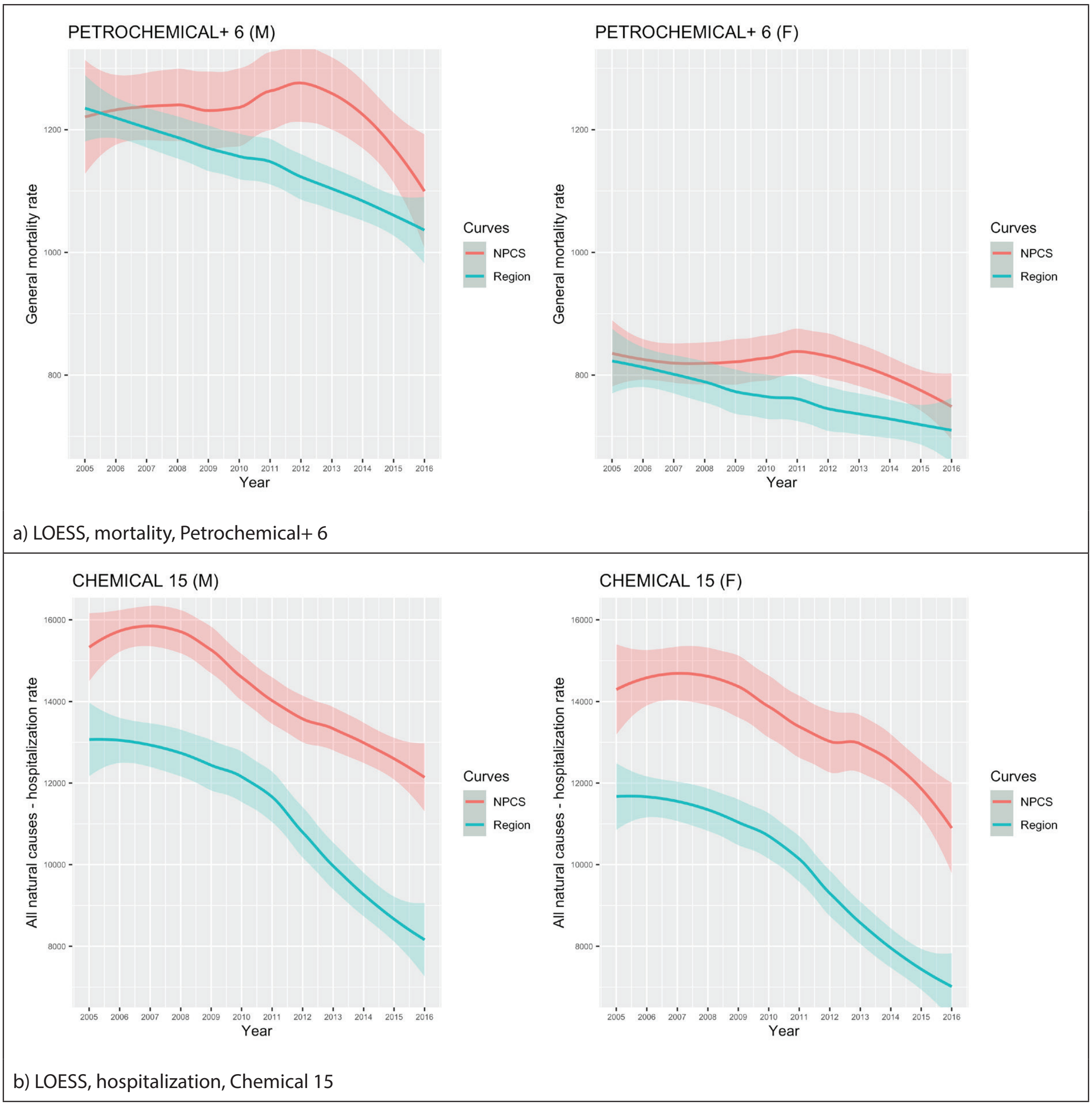

Figure 4
LOESS curves built on mortality and hospitalization rates, for the two selected causes (General mortality, All natural causes of hospitalization). A few explicative examples are shown, for four anonymized NCPSs. In each plot, the red curve is the smooth approximation of the rate series in the NCPS, while the turquoise curve relates to the rate series of the region where the NCPS is located. For each curve, a 95% confidence interval is computed.

In general, what is known from scientific evidence about the association between exposure to petrochemical plants emissions and certain health conditions, such as lymphatic-hematopoietic system-related diseases, lung cancer, and respiratory diseases, has been confirmed with the results of the present study. Also, risk excesses have been detected for the above diseases and also for urinary system diseases, chronic pulmonary diseases, acute respiratory diseases, and all malignant tumours in populations living in sites contaminated by chemical plants.

Through the second phase, comparisons between rates in the contaminated sites and their regions were made: in general, regression coefficients for the linear trends in regions were often negative or small if positive, whereas increasing trends were detected in selected sites.

In the third and final phase, a rate-ratio analysis and a graphical analysis (run via LOESS estimation) helped in capturing the general differences in temporal series when comparing contaminated sites with their regions. As expected, risk excesses for general mortality and all-natural causes of hospitalization have been detected comparing figures of the sites with those of their respective regions, except for a few cases. In most cases, the NPCS rates were higher than the regional ones, with decreasing trends in both and decreasing differences by time between the two. Increasing trends, non-decreasing differences between contaminated sites' rates, and regional rates and regions with higher rates than in the contaminated sites were rarely observed.

STRENGTHS AND LIMITATIONS OF THE STUDY

Information on contaminated sites

The study areas were selected and grouped only based on the main sources of contamination (type of industrial setting). The study does not address the analysis of temporal trends in health outcomes concerning temporal trends regarding direct or indirect estimates of exposure.

The analysis of the associations between exposure and health effects in temporal terms, albeit important in contaminated sites for assessing both the risk associated with past exposure and the health benefit of environmental remediation activities or other public health interventions [13], is beyond the scopes of the present contribution. Nevertheless, the assessment of temporal trends of health outcomes in contaminated sites, especially in terms of comparison with temporal trends of the same outcomes in appropriate reference populations, helps in identifying priorities of interventions from a public health perspective.

A detailed evaluation of temporal trends of health outcomes in association with temporal changes of emissions/contamination, if feasible, strongly depends on the availability of reliable information. Furthermore, industrially contaminated sites are often characterized by mixtures of hazardous toxicants contaminating multiple environmental matrices, while an evaluation of the potential exposures over time in relation to the process of contamination is potentially possible only for air pollutants, whose data are usually monitored with long time-data. This is the case of the Taranto contaminated site, in southern Italy, hosting one of the largest steel factories in Europe, operating since the sixties. A detailed analysis of temporal trends based on available time-series of health and environmental data allowed to estimate a statistically significant increased risk in natural mortality per annual change of industrial PM10 emissions accounting for confounding factors [14].

A simplified approach in analyzing mortality temporal trends in association with potential cumulative exposure was proposed in a site followed-up by SENTIERI contaminated by a petrochemical complex [15]. In this study, an analysis of differential risk over time was performed considering, among the others, a specific age class maximizing the difference, during the time window under study, in terms of share of years of life with potential exposure to the pollutants from the petrochemical complex considering the year of starting operations of the industrial complex [15].

Other studies at ecological-area level analyzed the health risk considering the location of major Spanish industrial sources of contamination [16] or the presence of petrochemical sources of contamination at the regional level in Europe [17]. Such studies estimated the type and amount of pollutants using information available in the European Pollutant Release and Transfer Register (E-PRTR) [16, 17]. Nevertheless, to our knowledge, no study on contaminated sites with a national or international basis analyzed associations between emissions and health risk in temporal terms.

Selection of health outcomes and diseases

Mortality and hospitalization are health outcomes that present differences in terms of use in epidemiological studies.

Mortality is one of the most robust epidemiological outcomes and it is widely used to make geographical and temporal comparisons; it is expected to reflect long term effects of exposure and it is relevant when studying diseases with high lethality; long term effects of exposure showed in the results of the present study, since a large percentage of increasing and significant trends in mortality rates were found.

Regarding hospitalization, the following aspects should be highlighted: temporal changes in this outcome are hardly influenced by regional policies, concerning which diseases are considered to require hospitalization, since those might be different for different regions and they might change over time in the same region as well; this covariate is latent in the present study. Therefore, increasing trends in hospitalization rates might be due to changes in the policies.

These aspects limit the interpretation of results in terms of inferring considerations on the association between temporal trends of mortality and hospitalization and changes in exposure to industrial contamination in the study areas. However, it has to be stressed that the latter is not the objective of this study that aims at identifying new statistical methods in time trend analysis that can be adopted in epidemiological surveillance systems like SENTIERI.

Moreover, the analysis of temporal trends in mortality and hospitalization rate-ratios in the contaminated sites and in the reference regions is likely to identify changes that are, at least, suggestive of a possible impact of the industrial contamination when we can assume that this is one of the most relevant differences between the compared populations.

CONCLUSIONS

This exploratory methodological study proposes a sequence of statistical techniques to analyze temporal trends of mortality and hospitalization rates in industrially contaminated areas.

The obtained results highlighted changes over time in the health status of populations affected by long term exposure to massive pollution sources, compared to other areas in the same region that do not include NPCS.

The adopted methodology indicates some potentially relevant aspects that require further attention in the analysis of temporal trends in epidemiological studies in these areas. The various approaches show that the interpretation of the temporal changes is influenced by multiple factors: mainly by the type of health outcomes (mortality *vs* hospitalization), the type of disease, and its link with the gender and type of emission sources studied.

This work is a first attempt to propose a methodological path for the monitoring of time trends of health profiles in epidemiological surveillance systems like SENTIERI. This approach should be integrated with temporal trends of contamination and/or exposure estimates over time, by also considering drastic temporal changes in potential noxious exposure, such are for example those linked to industrial plants openings and closures.

The ability to detect changes over time in the health profiles attributable to changes in contamination/population exposure in highly contaminated areas is one of the most challenging objectives, as it could be potentially adopted as a measure of the positive impact of remediation activities and the negative impact of contamination processes on local populations.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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REFERENCES

1. Zona A, Pasetto R, Fazzo L, Iavarone I, Bruno C, Pirastu R, Comba P. (Eds). SENTIERI: Studio epidemiologico nazionale dei territori e degli insediamenti esposti a rischio da inquinamento. Quinto Rapporto. Epidemiol Prev. 2019;43(2-3 Suppl 1):1-208. doi:10.19191/EP19.2-3.S1.032
2. Pirastu R, Ancona C, Iavarone I, Mitis F, Zona A, Comba P. (Eds). SENTIERI - Studio Epidemiologico Nazionale dei Territori e Insediamenti Esposti a Rischio da Inquinamento. Valutazione della evidenza epidemiologica. Epidemiol Prev. 2010;34(5-6 Suppl. 3).
3. Pirastu R, Iavarone I, Pasetto R, Zona A, Comba P. (Eds). SENTIERI - Studio Epidemiologico Nazionale dei Territori e Insediamenti Esposti a Rischio da Inquinamento: Risultati. Epidemiol Prev. 2011;35(5-6 Suppl. 4).
4. Comba P, Ricci P, Iavarone I, et al. Cancer incidence in Italian contaminated sites. Ann Ist Super Sanità. 2014;50(2):186-91. doi: 10.4415/ANN_14_02_13
5. Industrial Pollution in Europe. Available fom: www.eea.europa.eu/data-and-maps/indicators/industrial-pollution-in-europe-3.
6. Sorte S, Rodrigues V, Borrego C, Monteiro A. Impact of harbour activities on local air quality: A review. Environ Pollut. 2020;257:113542. doi: 10.1016/j.envpol.2019.113542
7. Lin CK, Hung HY, Christiani DC, Forastiere F, Lin RT. Lung cancer mortality of residents living near petrochemical industrial complexes: a meta-analysis [published correction appears in Environ Health. 2017;16(1):122]. Environ Health. 2017;16(1):101. doi: 10.1186/s12940-017-0309-2
8. Lin CK, Hsu YT, Christiani DC, Hung HY, Lin RT. Risks and burden of lung cancer incidence for residential petrochemical industrial complexes: A meta-analysis and application. Environ Int. 2018;121(Pt 1):404-14. doi: 10.1016/j.envint.2018.09.018
9. Lin CK, Hsu YT, Brown KD, Pokharel B, Wei Y, Chen ST. Residential exposure to petrochemical industrial complexes and the risk of leukemia: A systematic review and exposure-response meta-analysis. Environ Pollut. 2020;258:113476. doi: 10.1016/j.envpol.2019.113476
10. Chang WW, Boonhat H, Lin RT. Incidence of respiratory symptoms for residents living near a petrochemical industrial complex: A meta-analysis. Int J Environ Res Public Health. 2020;17(7):2474. doi: 10.3390/ijerph17072474
11. Jephcote C, Brown D, Verbeek T, Mah A. A systematic review and meta-analysis of haematological malignancies in residents living near petrochemical facilities. Environ Health. 2020;19(1):53. doi: 10.1186/s12940-020-00582-1
12. Revision of the European Standard Population, Report of the Eurostat's task force, 2013. Available from: https://ec.europa.eu/eurostat/documents/3859598/5926869/KS-RA-13-028-EN.PDF/e713fa79-1add-44e8-b23d-5e8fa09b3f8f.
13. Pasetto R, Martin-Olmedo P, Martuzzi M, Iavarone I. Exploring available options in characterising the health impact of industrially contaminated sites. Ann Ist Super Sanità. 2016;52(4):476-82. doi: 10.4415/ANN_16_04_03
14. Leogrande S. et al. Industrial air pollution and mortality in the Taranto area, Southern Italy: A difference-in-differences approach. Environ Int. 2019;132:105030. doi: 10.1016/j.envint.2019.105030
15. De Rocchi D, Zona A, Tumino R, Egidi V, Pasetto R. Mortality temporal trends and cancer incidence profiles of residents in the petrochemical industrially contaminated town of Gela (Sicily). Ann Ist Super Sanità. 2021;57(2):173-81.
16. Fernandez-Navarro P, Garcia-Perez J, Ramis R, Boldo E, Lopez-Abente G. Industrial pollution and cancer in Spain: An important public health issue. Environ Res. 2017;159:555-63. doi: 10.1016/j.envres.2017.08.049
17. Jephcote C, Mah A. Regional inequalities in benzene exposures across the European petrochemical industry: A Bayesian multilevel modelling approach. Environ Int. 2019;132:104812. doi: 10.1016/j.envint.2019.05.006