

A meta-analysis of mortality data in Italian contaminated sites with industrial waste landfills or illegal dumps

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Abstract

Objectives. Adverse effects of waste management represent a public health issue. Mortality meta-analysis in Italian National Priority Contaminated Sites (NPCSs) with industrial waste landfills or illegal dumps is presented.

Methods. 24 NPCSs include industrial waste landfills or illegal dumps. Class 1 (10 NPCSs with industrial waste landfills) and Class 2 (14 NPCSs with illegal dumps) were categorized. Random-effects model meta-analyses of Standardized Mortality Ratios non-adjusted (SMRs) and adjusted for Deprivation (DI-SMRs) computed for each CS (1995-2002) were performed for overall 24 NPCSs and the two classes. The North-Southern gradient was considered.

Results. 24 CSs pooled-SMRs are significantly increased in both genders for cancer of liver (men: SMR = 1.13; women: SMR = 1.18), bladder (men: SMR = 1.06; women: SMR = 1.11), and for cirrhosis (men: SMR = 1.09; women: SMR = 1.13). In Class 2 the increase is confirmed in both genders for liver and bladder cancers and for cirrhosis and in men only for lung cancer. Congenital anomalies and adverse perinatal conditions are not increased.

Conclusion. The results are consistent with the hypothesis of adverse health effects of non-adequately managed hazardous waste. Causal interpretation is not allowed, but the meta-analytic approach provides more confidence in the findings.

Key words

- waste
- contaminated sites
- meta-analysis
- mortality

INTRODUCTION

Adverse health effects associated with waste-management practices represent a potential public-health issue worldwide. The report of the WHO workshop "Population health and waste management: Scientific data and policy options" concluded that the possible health impact of waste management might represent an important issue for public health because of the high number of people living near these sites worldwide [1]. In US as of January 2007, EPA's national priority list (NPL) comprised 1240 hazardous waste sites, with 41 million people living within 4-mile radii of them. Between 1995 and 2004 ATSDR evaluated about 3000 sites containing hazardous substances and defined uncontrolled hazardous waste sites as a major environmental threat to human health [2]. The European Environmental Agency estimated that the industrial and municipal waste treatment and disposal are one of the principal activities causing soil

contamination in Europe, corresponding to 22.5% of the 250,000 contaminated sites requiring clean-up [3]. Illegal movements of waste are a matter of serious concern in Europe, because of their severe consequences, such as the adverse effects on the environment and human health during transport and in receiving countries. The main routes of illegal movements are from South to South-eastern Europe, western Balkans and to West Africa [4]. Low-income countries can be particularly affected because of the lack of appropriate legislation and control systems and the growing illegal transboundary movement of hazardous waste driven by the most industrialized countries [5]. In Asia, recent papers estimated 8,629,750 persons at risk of exposure to pollutants at 373 toxic waste sites in India, Indonesia and Philippines [6] and 245,949 children between the ages of 0 and 4 years at risk of exposure to environmental sources of lead at hazardous waste sites in 7 Asian

countries, at level high enough to cause acute toxicity and to produce chronic effects [7]; the authors of both papers declare that exposure to toxic chemicals from hazardous waste sites is an important and heretofore insufficiently examined global health problem, as contributor to the global burden of disease, and the urgent need to characterize and remediate toxic waste sites around the world and to detect the health of affected populations [6, 7].

The health effects of landfills and incinerators have been object of several reviews. The most recent review of epidemiological studies on health effects of management of solid waste reported as limited the evidence of association of landfills with total birth defects, in particular of neural tube and genitourinary system, and low birth weight; the evidence of association of incinerators was defined limited for overall cancers and specific cancer types, stomach, colorectum, liver, lung, soft tissue sarcomas, non Hodgkin's lymphoma, and specific birth defects, namely orofacial and of genitourinary systems [8].

Regarding the toxic waste sites, two review papers on the available evidence of their health impact and a number of individual studies on specific contaminated sites, have been published. According to both review papers, the available evidence has been considered not adequate to establish causal links between toxic waste exposures and cancer risk, even if one Author lists some cancer types (bladder, lung, stomach cancers and leukemia) as those more consistently associated with the exposure of interest

[9]. Epidemiological monitoring of the population resident in the neighbourhood of toxic waste sites and implementation of multisite studies have also been recommended [10].

Some studies on individual specific sites of toxic waste reported excesses of specific diseases (namely, tumours of kidney and bladder, chronic lymphatic leukemia, total lymphoma, diabete, cirrhosis, asthma and infectious respiratory diseases, adverse reproduction effects and congenital anomalies) in population resident near toxic waste sites [11-22]. In India, Indonesia and the Philippines 828,722 DALYs (disability-adjusted life years) were estimated as a result of chemical exposures at 373 toxic waste sites, identifying lead and hexavalent chromium as the largest contributors [6]. 189,725 children in 7 Asian countries have been estimated to be exposed to levels of lead from unregulated hazardous waste sites sufficiently high to produce losses of intelligence, measured in decreases of IQ scores [7]. In Italy an epidemiological study on population residing in an area characterized by illegal waste dumps showed a significant correlation between an indicator of waste exposure risk and the municipal mortality for tumours of liver, stomach, bladder, kidney and lung and the congenital anomalies of the internal urogenital and central nervous systems [23].

The objective of the present study was to investigate cause-specific mortality in the 24 Italian National Priority List Contaminated Sites (NPLCSs) for remediation with controlled industrial waste landfills or illegal dumps. A meta-analytical approach, based on the Standardized Mortality Ratios (SMRs) computed for each sites in a national causes-specific mortality study (SENTIERI Project), was used to estimate the overall health impact of waste dumping sites.

SENTIERI Project studied cause-specific mortality in 44 contaminated sites included in Italian Priority List for remediation (NPLCSs), because of their environmental impact and the complexity of the required remediation. The potential sources of environmental contamination, listed in Ministry of the Environment Decrees of each Italian Contaminated Site (CS) identification, were retrieved. Each site can include more than one source of environmental contamination. The evaluation of the possible relationship between observed excesses and environmental exposures was based on a review of the epidemiological literature published between 1998 and 2009 [24]. The results of mortality analysis for all 44 CSs, included in the Project, and the SMRs, used in the present meta-analysis, were recently published [25].

MATERIALS AND METHODS

The 24 sites at study include 205 municipalities, with 3,964,425 inhabitants. The sites were categorized into two classes. Class 1 consisted of 10 CSs with controlled industrial waste landfills, 50 municipalities and 771,898 inhabitants; Class 2 consisted of 14 CSs with illegal waste dumps (hazardous or non-hazardous waste, or in most cases both), 155 municipalities and 3,192,527 inhabitants (Figure 1). Class 1 includes nine CSs in North-Central Italian Regions and one in a

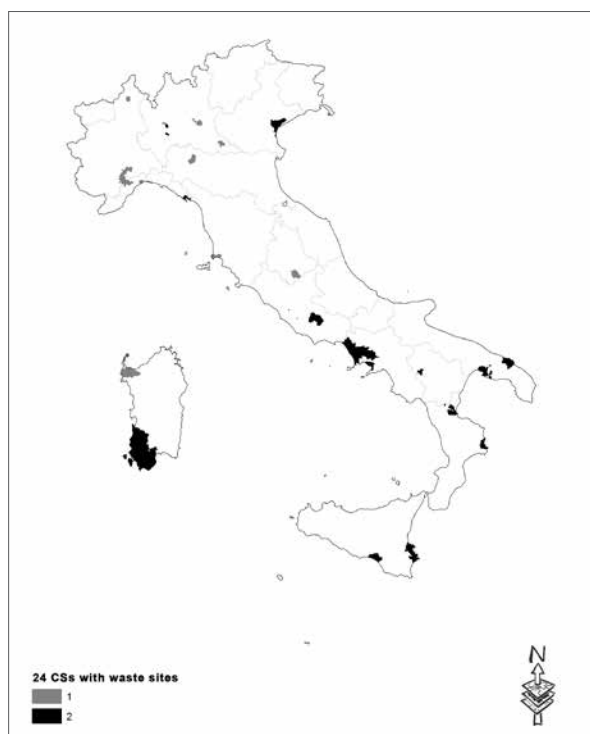


Figure 1

The investigated 24 Italian Contaminated Sites (CSs) with industrial waste landfills or illegal dumping sites. Class 1: 10 CSs with industrial waste landfills; Class 2: 14 CSs with illegal dumping sites.

Southern Region (Sardinia); in Class 2 five CSs are located in North-Central area and nine in Southern Regions (Sicily and Sardinia comprised).

Mortality for 13 causes (Table 1), based on epidemiological evidence of the health status of populations residing near waste dumps available at the starting of the analysis, was considered.

The meta-analysis of the age-specific SMRs and the SMRs adjusted by the Deprivation Index (DI-SMRs), computed for each site (period from 1995 to 2002), was performed using a random-effects model for the 24 sites combined and separately for Class 1 and Class 2 sites. Pooled SMRs and pooled DI-SMRs, with 95% Confidence Intervals, were estimated. The heterogeneity of the SMRs among the sites was

evaluated using Hedges's Q test.

The analysis was performed separately by gender; because of the small number of cases for congenital anomalies and adverse perinatal conditions, mortality for these causes was analysed in total population and not by gender.

In order to evaluate the differences between SMRs and DI-SMRs the correlation between these two estimators was performed, calculating Pearson coefficient.

For 5 of 13 causes of death (stomach and liver cancers, respiratory system diseases, congenital anomalies and conditions originated in prenatal period), the evidence of a causal association with other sources of environmental pollution present in

Table 1
Pooled DI-SMR in Contaminated Sites (CSs) with industrial waste landfills and illegal dumps, overall and two Classes (1995-2002)

		24 CSs overall	Class 1 CSs [§]	Class 2 CSs [^]
MEN				
Causes	ICD-9th Revision	DI-SMR (95% CI)	DI-SMR (95% CI)	DI-SMR (95% CI)
m.n. stomach *	151	1.02 (0.89-1.17)	0.98 (0.72-1.34)	1.05 (0.89-1.24)
m.n. liver	155.0-155.1	1.13 (1.05-1.23)	1.10 (0.91-1.31)	1.14 (1.05-1.23)
m.n. lung *	162	1.06 (0.99-1.13)	0.99 (0.92-1.07)	1.13 (1.04-1.23)
m.n. bladder	188	1.06 (1.00-1.12)	1.07 (0.94-1.22)	1.05 (1.00-1.11)
m.n. kidney	189	1.04 (0.95-1.14)	1.01 (0.84-1.20)	1.05 (0.94-1.16)
m.n. lymphohematopoietic tissue	200-208	0.99 (0.95-1.02)	1.01 (0.95-1.08)	0.98 (0.93-1.03)
leukemia	204-208	0.98 (0.92-1.04)	1.02 (0.93-1.12)	0.96 (0.88-1.04)
diseases of circulatory system	390-459	1.00 (0.97-1.03)	1.01 (0.96-1.06)	0.99 (0.95-1.03)
hypertensive diseases	401-405	0.96 (0.89-1.04)	0.85 (0.70-1.04)	1.01 (0.94-1.09)
diseases of respiratory system *	460-519	0.99 (0.81-1.22)	0.88 (0.72-1.06)	1.03 (0.86-1.24)
cirrhosis and other liver diseases	571	1.09 (1.02-1.15)	1.05 (0.95-1.16)	1.11 (1.03-1.19)
WOMEN				
Causes	ICD-9th Revision	DI-SMR (95% CI)	DI-SMR (95% CI)	DI-SMR (95% CI)
m.n. stomach *	151	1.01 (0.90-1.14)	0.95 (0.67-1.33)	1.06 (0.97-1.16)
m.n. liver	155.0-155.1	1.18 (1.07-1.31)	1.15 (0.92-1.42)	1.22 (1.09-1.36)
m.n. lung *	162	1.01 (0.92-1.10)	1.04 (0.89-1.20)	0.98 (0.90-1.06)
m.n. bladder	188	1.11 (1.03-1.2)	1.07 (0.92-1.24)	1.13 (1.03-1.23)
m.n. kidney	189	1.12 (1.01-1.24)	1.16 (1.00-1.35)	1.09 (0.94-1.26)
m.n. lymphohematopoietic tissue	200-208	0.99 (0.96-1.03)	1.00 (0.94-1.06)	0.98 (0.93-1.04)
leukemia	204-208	0.98 (0.93-1.03)	1.00 (0.91-1.11)	0.97 (0.92-1.03)
diseases of circulatory system	390-459	0.98 (0.94-1.02)	0.97 (0.93-1.02)	0.98 (0.93-1.03)
hypertensive diseases	401-405	0.93 (0.85-1.03)	0.83 (0.67-1.04)	1.00 (0.91-1.11)
diseases of respiratory system *	460-519	1.03 (0.82-1.30)	0.90 (0.72-1.12)	1.04 (0.99-1.09)
cirrhosis and other liver diseases	571	1.13 (1.06-1.22)	1.06 (0.94-1.19)	1.18 (1.09-1.28)
OVERALL				
Causes	ICD-9th Revision	DI-SMR (95% CI)	DI-SMR (95% CI)	DI-SMR (95% CI)
Congenital anomalies	740-759	1.00 (0.93-1.07)	0.97 (0.78-1.22)	0.98 (0.90-1.07)
Adverse cond. orig. prenatal period (0-1year)	760-779	0.89 (0.73-1.08)	0.74 (0.47-1.17)	0.94 (0.71-1.24)

* adjusted for the other pollution sources present in the area; [§] Class1: 10 CSs with industrial waste landfills; [^] Class2: 14 CSs with illegal waste dumps. Legend: DI-SMR: Standardized Mortality Ratio adjusted for Deprivation Index; ICD: International Classification of Diseases; CI: Confidence Interval; m.n.: malignant neoplasms.

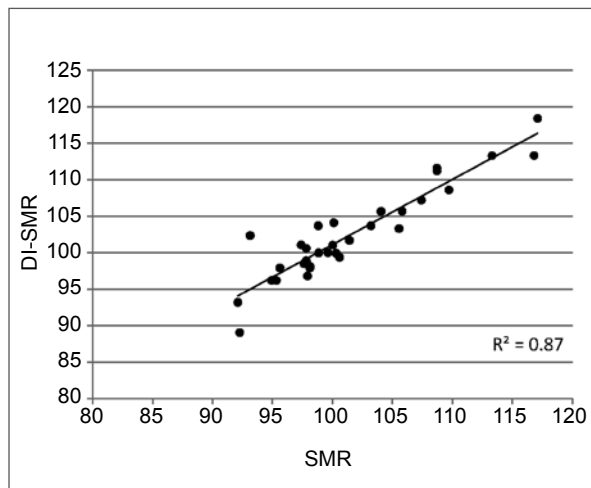


Figure 2
Correlation analysis by Pearson coefficient between DI-SMRs and SMRs for all causes.

the CSs, in addition to waste dumps, was defined as sufficient or limited [24]: in these cases, the pooled SMRs were adjusted for the presence of these sources of pollution. The analyses were performed using STATA 10 software.

Because of the higher number of excesses observed in sites with uncontrolled waste dumps, an additional meta-analysis for the Class 2 was performed, to evaluate the possible role of North-South gradient of the investigated sites in determining the study findings.

In fact, Italian populations of Northern and Southern areas present some significant differences in social and health indicators (social status indicator, cancer prevalence, mortality for all-causes and for specific diseases) [26, 27], with a possible effect on the measured outcomes.

A dichotomous indicator North-South was attributed to each site and the variable was considered in the analysis.

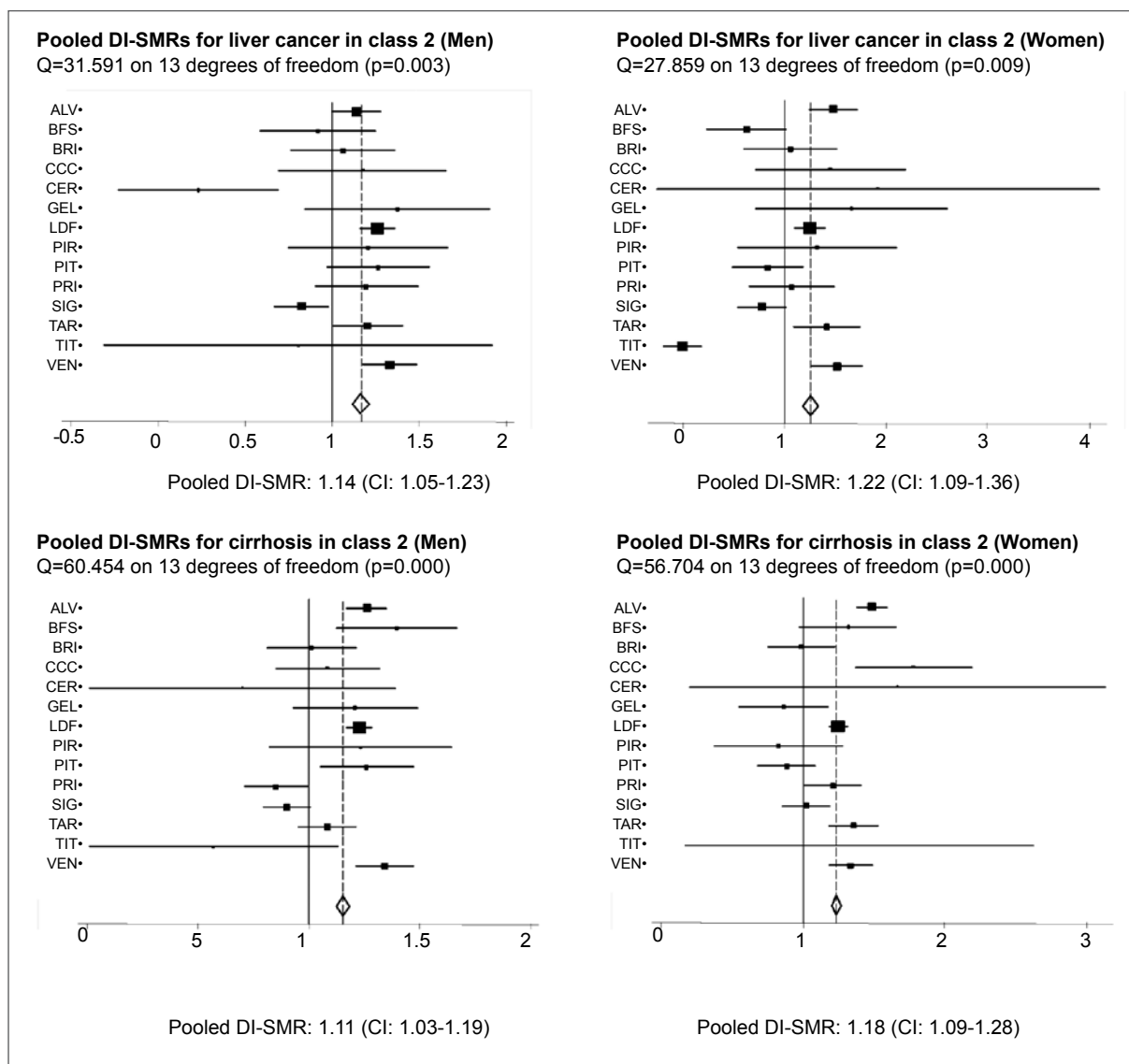


Figure 3
Pooled DI-SMRs for liver cancer and cirrhosis in Class 2 sites.

RESULTS

The Pearson coefficient showed a strong correlation between SMRs and DI-SMRs for all-cause mortality (Pearson coefficient: $R^2 = 0.87$) (i.e., 87% of the variance of the DI-SMRs was explained by variation in the unadjusted SMRs) (Figure 2). In light of this finding, that shows a good overlap between the two estimators, we present the results of the meta-analysis of the DI-SMRs.

The pooled SMRs in the 24 sites combined are shown in Table 1. Significant increases were found in mortality for liver cancer, bladder cancer and liver cirrhosis, in both genders. Kidney cancer mortality was increased only among women.

In Class 1 sites (controlled industrial waste landfills), the mortality for kidney cancer among women was increased (Table 1). In Class 2 sites (illegal dumping sites), there were increases in mortality for liver cancer, liver cirrhosis and bladder cancer in both genders;

lung cancer was increased only in men. Mortality for lymphohematopoietic system cancers and for congenital anomalies and adverse conditions originating in the prenatal period did not show increases (Table 1).

Most of the observed increases were found in Class 2 sites.

Figures 3-4 show forest plots in Class 2 sites for the causes with significantly increased pooled SMRs. The Q test shows the heterogeneity of the results of individual estimates.

In the analysis of illegal waste dumps CSs that took into account the North-South gradient, the increases observed in the previous analysis were confirmed in both geographical area sites, although in some cases they were not statistically significant. The Southern CSs showed significant increases for liver cancer in both genders and for liver cirrhosis among women; cancer of bladder among both genders and liver cirrhosis in men were not significantly increased. In

Table 2
Pooled DI-SMR in CSs Class 2 (illegal dumps), by North-Southern areas

		Northern CSs Class 2 [^]	Southern CSs Class 2 [^]
MEN			
Causes	ICD-9th Revision	DI-SMR (95% CI)	DI-SMR (95% CI)
m.n. stomach *	151	1.01 (0.862-1.19)	1.05 (0.911-1.21)
m.n. liver	155.0-155.1	1.14 (0.961-1.36)	1.13 (1.01-1.27)
m.n. lung *	162	1.02 (0.89-1.17)	1.10 (0.955-1.26)
m.n. bladder	188	1.11 (0.996-1.24)	1.05 (0.991-1.11)
m.n. kidney	189	1.06 (0.867-1.29)	1.04 (0.907-1.20)
m.n. lymphohematopoietic tissue	200-208	0.939 (0.862-1.02)	0.983 (0.938-1.03)
leukemia	204-208	0.921 (0.797-1.06)	0.978 (0.907-1.05)
diseases of circulatory system	390-459	0.973 (0.914-1.03)	1.00 (0.962-1.05)
diseases of respiratory system *	460-519	1.09 (0.852-1.40)	1.21 (0.950-1.53)
cirrhosis and other liver diseases	571	1.21 (1.06-1.37)	1.07 (0.982-1.16)
WOMEN			
Causes	ICD-9th Revision	DI-SMR (95% CI)	DI-SMR (95% CI)
m.n. stomach *	151	0.968 (0.826-1.14)	0.997 (0.862-1.15)
m.n. liver	155.0-155.1	1.23 (1.07-1.42)	1.26 (1.17-1.37)
m.n. lung *	162	1.10 (0.879-1.37)	1.04 (0.807-1.33)
m.n. bladder	188	1.25 (1.06-1.49)	1.06 (0.939-1.21)
m.n. kidney	189	1.11 (0.891-1.38)	1.09 (0.936-1.28)
m.n. lymphohematopoietic tissue	200-208	1.03 (0.948-1.12)	0.969 (0.920-1.02)
leukemia	204-208	1.04 (0.905-1.19)	0.953 (0.881-1.03)
diseases of circulatory system	390-459	0.979 (0.894-1.07)	0.985 (0.923-1.05)
diseases of respiratory system *	460-519	1.00 (0.821-1.22)	1.03 (0.831-1.29)
cirrhosis and other liver diseases	571	1.07 (0.899-1.29)	1.22 (1.09-1.36)
OVERALL			
Causes	ICD-9th Revision	DI-SMR (95% CI)	DI-SMR (95% CI)
Congenital anomalies	740-759	0.995 (0.793-1.25)	1.01 (0.871-1.17)
Adverse cond. Orig. Prenatal period (0-1year)	760-779	0.938 (0.673-1.31)	1.05 (0.85-1.31)

* adjusted for the other pollution sources present in the area; [^] Class 2: 14 CSs with illegal waste dumps.

DI-SMR: Standardized Mortality Ratio adjusted for Deprivation Index; ICD: International Classification of Diseases; CI: Confidence Interval; m.n.: malignant neoplasms.

Northern CSs significant excesses of liver and bladder cancers in women (not significantly increased among men) and of cirrhosis in men (excess not significant in women) were found (Table 2).

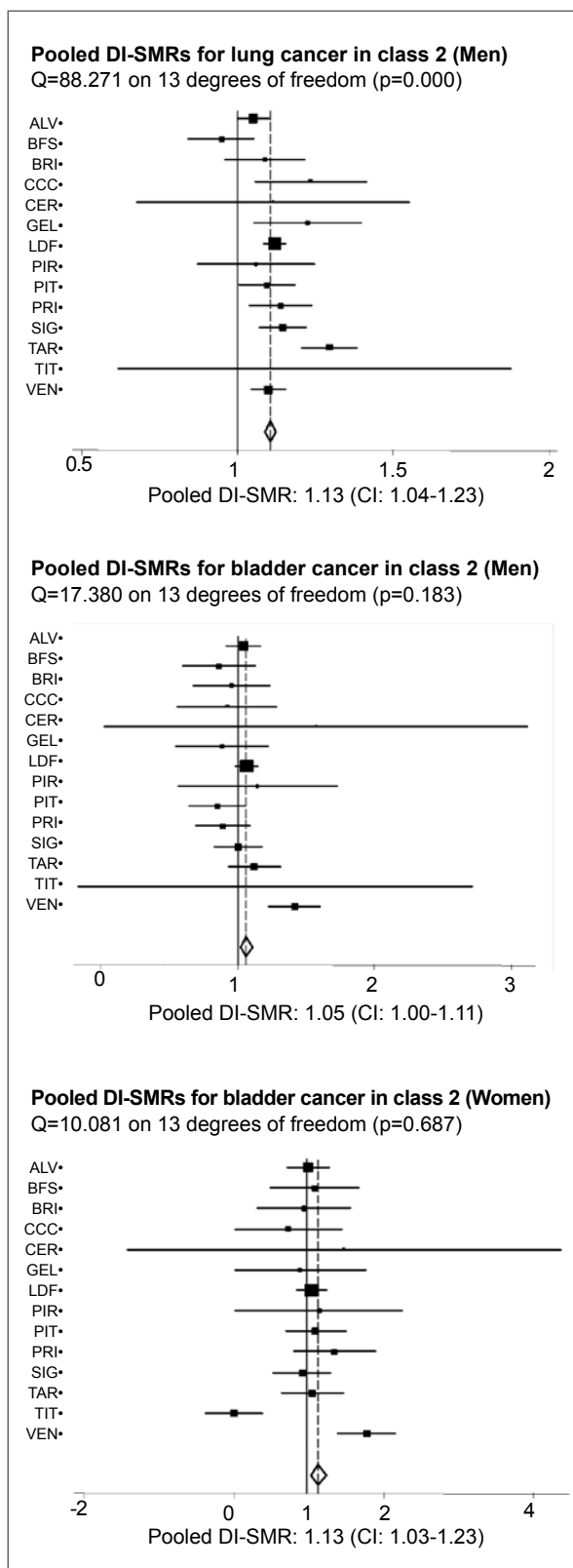


Figure 4
Pooled DI-SMRs for lung and bladder cancer in Class 2 sites.

DISCUSSION

The result that most of the observed increases were found in the illegal waste dumping sites, regardless of the North-South geographical area gradient, supports the hypothesis that uncontrolled waste dumping sites may have adverse health effects on neighbouring populations. The causes of mortality resulted in excess have been reported increased by other authors in similar contexts, characterized by toxic waste dumps or uncontrolled waste handle sites.

Increased mortality for liver cancer and liver cirrhosis, both diseases characterized by a multifactorial etiology with a major role of viral agents and alcohol consumption, might be due, in part, to exposure to hepatotoxic chemicals, such as pesticides, metals, aromatic and halogenated hydrocarbons and chlorinated aromatic compounds, released from waste sites. An interaction between hepatitis viruses and hepatotoxic agents in liver carcinogenesis has also been raised, in particular for chemicals with a fibrogenic action, such as vinyl chloride [28]. Rare instances of liver disease associated with massive environmental contamination have been reported [29]. Furthermore, near Superfund toxic waste sites, one study reported increases in the prevalence of primary biliary cirrhosis (PBC), suggesting that exposure to toxic chemicals, in particular polychloroethylene and benzene, is a possible risk factor [15]. In a review of the studies on the possible risk factors for PBC, it was suggested that the triggering agents of PBC may be ubiquitous, with their presence ranging from water reservoirs and coal mining areas to Superfund waste disposal sites [30]. With regard to the possible relationship between waste exposures and hepatic diseases, the evidence of the association between liver cancer and exposure to incinerators was defined as limited by the review of Porta and colleagues (2009) and in SENTIERI Project [8, 24]. A correlation between liver cancer mortality and the municipal index of environmental pressure due to waste has been shown in illegal waste dumping sites [23] and an increased incidence of liver cancer in same area was observed [31].

As far as the increased mortality for bladder and lung cancer is concerned, a role of illegal waste dumps exposure may be envisaged. For both diseases the main known causes are cigarette smoking and occupational exposure to several chemical agents. Increase of bladder cancer has shown in former residents near Love Canal Superfund site [11]. The increases of respiratory diseases, in particular asthma and infectious respiratory disease, have been reported in population residing near toxic waste sites, and the contribution to respiratory disease of exposure to substances of hazardous waste sites was hypothesized [18]. An increased mortality for bladder and lung cancers in residents in areas close to waste dumps sites has already been reported in one of the areas included in the present investigation [32]. The practice of illegally setting fires, widespread in some contaminated sites, may generate combustion products of both urban and hazardous waste and have a role in the observed excesses.

The mortality for kidney cancer was found increased only in Class 1 CSs among women. Tobacco smoking, diet, and some drugs have been associated with kidney cancer; among occupational risk factors an etiological role has been suggested, but not confirmed, for combustion

products, heavy metals and solvents [33]. Trichlorethylene is a cause of kidney cancer with sufficient evidence [34]. An increased risk of kidney cancer for populations residing near toxic waste sites has been reported [32, 11, 12].

Mortality for cancers of lymphoematopoietic system, leukaemia and lymphomas, reported in excess in similar contexts [13] and associated with exposure to incinerators with limited evidence [8], does not differ from expected rates.

The results of the present study, based on mortality data, are not suitable to support or weaken the hypothesis of an association between exposure to waste dumps and congenital anomalies as well as adverse perinatal outcomes, reported with limited epidemiological evidence by recent reviews [8, 24], because of their high survival rates.

In interpreting the results of the present study, some limitations should be considered. The ecological study design is mainly descriptive and is not intended to allow for causal interpretation [35]. It should be stressed that in the study areas sporadic measurements showed highly polluted spots and that exhaustive environmental data are not available; in some polluted sites environmental monitoring plans are in progress. Uncertainties in exposure estimation do not allow a proper assessment of time-related variables. Nonetheless, environmental contamination has been present in the investigated sites since the 1980s and most of the sites have not yet been cleaned-up, therefore the latency of observed increases is consistent with the hypothesized time window of exposure.

Finally, the presence of multiple environmental exposures and other factors such as socioeconomic status and life style might have played a role in the observed increases, despite the adjustment in statistical models.

Regarding statistical analyses, the greater precision of pooled SMRs, which have a higher statistical power with respect to the individual estimates, increases confidence in study findings [36]. Because of the observed heterogeneity between single estimates, pooled SMRs have to be considered as an overall estimate, that is, they do not imply an underlying homogeneity of effects. The random effects model was used because it incorporates significant

variations between the estimates, as shown by the Q test results. In other words, the random effects model allows for some extent of non-homogeneity between the different estimates [37]. Sensitivity analysis, by testing the stability of the pooled effect estimate [38], allows to determine how much one or more individual estimates may affect the pooled estimate. In the present study the exclusion of two polluted sites with the largest populations, both with illegal dumps, as well as other two small sized sites, did not change the pooled estimate.

Quantification of heterogeneity provides elements for further investigations on sources of differences between areas, which could apply to the sites included in this study.

CONCLUSIONS

The meta-analytical approach in this context may be useful for public health decision making, because of the higher precision of the pooled estimates with respect to individual estimates. The present findings support the notion that inadequately managed, illegal or uncontrolled landfills, in particular of toxic waste, might represent a risk factor for health of populations residing in their neighbourhood. This issue is very important in low-income countries, where environmental legislation is not advanced, and in the areas of more industrialized countries with illegal dumps or old waste landfills, where operations started years before enforcement of national environmental legislation, the plants have not been well controlled, and the related contaminated areas have not yet been cleaned-up.

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Conflict of interest statement

All the authors declare no conflict of interest.

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REFERENCES

1. World Health Organization. *Population health and waste management: scientific data and policy options*. Report of WHO workshop. Rome, Italy 29-30 March 2007. Mitis F, Martuzzi M (Eds.). Copenhagen: WHO, Regional Office for Europe; 2007. p.1-85. DOI: 10.4415/ANN_10_03_12
2. Pohl HR, Tarkowski S, Buczynska A, Fay M, De Rosa CT. Chemical exposure at hazardous waste sites: experiences from the United States and Poland. *Environmental Toxicology and Pharmacology* 2008;25:283-91. DOI: 10.1016/j.etap.2007.12.005
3. European Environment Agency. *Progress in management of contaminated sites (CSI 015)-Assessment published Aug 2007*. Copenhagen: European Environment Agency; 2007. Available from: www.eea.europa.eu/data-and-maps/indicators/progress-in-management-of-contaminated-sites/progress-in-management-of-contaminated-1.
4. European Environment Agency. *Movements of waste across the EU's internal and external borders*. EEA Report n. 7/2012. Copenhagen: European Environment Agency; 2012. DOI: 10.2800/62637.
5. Marsili D, Fazzo L, Comba P. Health risks from hazardous waste disposal: the need for international scientific cooperation. *Eur J Oncol* 2009;4:151-9.
6. Chatham-Stephens K, Caravanos J, Ericson B, Sunga-Amparo J, Susilorini B, Sharma P, Landrigan PJ, Fuller R. Burden of Disease from Toxic Waste Sites in India, Indonesia, and the Philippines in 2010. *Environ Health Perspect* 2013;121:791-6. DOI: 10.1289/ehp.1206127
7. Caravanos J, Chatham-Stephens K, Ericson B, Landrigan PJ, Fuller R. The burden of disease from pediatric lead exposure at hazardous waste sites in 7 Asian countries. *Environmental Research* 2013;120:119-25. DOI: 10.1016/j.envres.2012.06.006
8. Porta D, Milani S, Lazzarino AI, Perucci CA, Forestiere F. Systematic review of epidemiological studies on health effects associated with management of solid waste. *Environ Health* 2009;8:60. DOI:10.1186/1476-069X-8-60
9. Vrijheid M. Health effects of residence near hazardous

- waste landfill sites: a review of epidemiological literature. *Environ Health Perspect* 2000;108(Suppl.1):101-12. DOI: 10.1289/ehp.00108s1101
10. Russi MB, Borak JB, Cullen MR. An examination of cancer epidemiology studies among populations living close to toxic waste sites. *Environ Health* 2008;7:32 DOI: 10.1186/1476-069X-7-32
 11. Gensburg LJ, Pantea C, Kiel C, Fitzgerald E, Stark A, Kim N. Cancer incidence among former Love Canal residents. *Environ Health Perspect* 2009;117:1265-71. DOI: 10.1289/ehp.0800153
 12. Gensburg LJ, Pantea C, Fitzgerald E, Stark A, Kim N. Mortality among Former Love Canal Residents. *Environ. Health Perspect* 2009;117:209-16. DOI: 10.1289/ehp.11350
 13. Boberg E, Lessner L, Carpenter DO. The role of residence near hazardous waste sites containing benzene in the development of hematologic cancers in upstate New York. *Int J Occup Med Environ Health* 2011;24(4):327-38. DOI: 10.2478/s13382-011-0037-8
 14. Kouznetsova M, Huang X, Ma J, Lessner L, Carpenter DO. Increased rate of hospitalization for diabetes and residential proximity of hazardous waste sites. *Environ Health Perspect* 2007;115(1):75-9. DOI: 10.1289/ehp.9223
 15. Ala A, Stanca CM, Bu-Ghanim M, Ahmado I, Branch AD, Schiano TD, Odin JA, Bach N. Increased prevalence of primary biliary cirrhosis near Superfund toxic waste sites. *Hepatology* 2006;43:525-31. DOI: 10.1002/hep.21076
 16. Pukkala E, Antti Pönkä A. Increased incidence of cancer and asthma in houses built on a former dump area. *Environ Health Perspect* 2001;109:1121-5. DOI: 10.2307/3454858
 17. Ma J, Kouznetsova, Lessner L, Carpenter DO. Asthma and infectious respiratory disease in children--correlation to residence near hazardous waste sites. *Paediatr Respir Rev* 2007;8(4):292-8. DOI: 10.1016/j.prrv.2007.07.009
 18. Carpenter DO, Ma J, Lessner L. Asthma and infectious respiratory disease in relation to residence near hazardous waste sites. *Ann NY Acad Sci* 2008;1140:201-8. DOI: 10.1196/annals.1454.000
 19. Dolk H, Vrijheid M, Armstrong B, Abramsky L, Bianchi F, Garne E, Nelen V, Robert E, Scott JE, Stone D, Tenconi R. Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. *Lancet* 1998;352:423-7. DOI: 10.1016/S0140-6736(98)01352-X
 20. Elliott P, Richardson S, Abellan JJ, Thomson A, de Hoogh K, Jarup L, Briggs DJ. Geographic density of landfill sites and risk of congenital anomalies in England. *Occup Environ Med* 2009;66:81-9. DOI: 10.1136/oem.2007.038497
 21. Langlois PH, Brender JD, Suarez L, Zhan FB, Mistry JH, Angela Scheuerle A, Moody K. Maternal residential proximity to waste sites and industrial facilities and conotruncal heart defects in offspring. *Paediatric Perin Epidemiol* 2009;23:321-31. DOI: 10.1111/j.1365-3016.2009.01045.x
 22. Austin AA, Fitzgerald EF, Pantea CI, Gensburg LJ, Kim NK, Stark AD, Hwang SA. Reproductive outcomes among former Love Canal residents, Niagara Falls, New York. *Environmental Research* 2011;111:693-701. DOI: 10.1016/j.envres.2011.04.002
 23. Martuzzi M, Mitis F, Bianchi F, Minichilli F, Comba P, Fazzo L. Cancer mortality and congenital anomalies in a region of Italy with intense environmental pressure due to waste. *Occup Environ Med* 2009;66:725-32. DOI: 10.1136/oem.2008.044115
 24. Pirastu R, Pasetto R, Zona A, Ancona A, Iavarone I, Martuzzi M, Comba P. The health profile of populations living in contaminated sites: Sentieri approach. *J Environm Public Health* 2013. DOI: 10.1155/2013/939267
 25. Pirastu R, Iavarone I, Pasetto R, Zona A, Comba P (Eds.). SENTIERI Project. Mortality study of residents in Italian polluted sites: results. *Epidemiol Prev* 2011;35(Suppl. 4):1-204.
 26. Marinacci C, Sebastiani G, Ferracin E, Grippo F, Pappagallo M, Landriscina T, Gargiulo L, Demaria M, Costa G. Distance among Italian people through geographic and socio-economic inequalities. *Epidemiol Prev* 2011; 35(5-6)Suppl. 2:68-75.
 27. Guzzinati S, Buzzoni C, De Angelis R, Rosso S, Tagliabue G, Vercelli M, Pannozzo F, Mangone L, Piffer S, Fusco M, Giacomini A, Traina A, Capocaccia R, Dal Maso L, Crocetti E, AIRTUM working group. Cancer prevalence in Italy: an analysis of geographic variability. *Cancer Causes Control* 2012;23:1497-510. DOI: 10.1007/s10552-012-0025-8.
 28. Mastrangelo G, Fedeli U, Fadda E, Valentini F, Agnesi R, Magarotto G, Marchi T, Buda A, Pinziani M, Martines D. Increased Risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: synergistic effect of occupational exposure with alcohol intake. *Environ Health Perspect* 2004;112:1188-92. DOI: 10.1289/ehp.6972
 29. Johnson D, Groopman JD. Toxic liver disorders. In: Rom WN, Markowitz SB (Eds.), *Environmental and occupational medicine*, 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2007. p. 789-99.
 30. Smyk D, Mytilinaiou MG, Riopoulou EI, Bogdanos DP. PBC triggers in water reservoirs, coal mining areas and waste disposal sites: from Newcastle to New York. *Disease Markers* 2010;29:337-44. DOI: 10.1155/2010/546926
 31. Fazzo L, De Santis M, Mitis F, Benedetti M, Martuzzi M, Comba P, Fusco M. Ecological studies of cancer incidence in an area interested by dumping waste sites in Campania (Italy). *Ann Ist Super Sanità* 2011;47:181-91. DOI: 10.4415/ANN_11_02_10
 32. Comba P, Bianchi F, Fazzo L, Martina L, Menegozzo M, Minichilli F, Mitis F, Musmeci L, Pizzuti R, Santoro M, Trinca S, Martuzzi M, and "Health impact of waste management in Campania" Working Group. Cancer mortality in an area of Campania (Italy) characterized by multiple toxic dumping sites. *Ann NY Acad Sci* 2006;1076:449-61. DOI: 10.1196/annals.1371.067
 33. McLaughlin JK, Lipworth L, Tarone RE, Blot WJ, 2006. Renal Cancer. In: Shottenfeld D, Fraumeni JF (Eds.). *Cancer epidemiology and prevention*, 3rd ed. New York: Oxford University Press; 2006. p. 1087-100.
 34. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks to humans, Vol. 106. *Some chlorinated solvents and their metabolites*. Lyon: IARC; 2013. Available from: <http://monographs.iarc.fr/ENG/Monographs/vol106/mono106-001.pdf>
 35. Last JM. *A dictionary of public health*. New York: Oxford University Press; 2006.
 36. Rushton L, Elliott P. Evaluating evidence on environmental health risks. *British Medical Bulletin* 2003;68:113-28. DOI: 10.1093/bmb/ldg020
 37. Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional review, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol* 1999;28:1-9. DOI: 10.1093/ije/28.1.1
 38. Ressing M, Blettner M, Klug SJ. Systematic literature reviews and meta-analyses. *Dtsch Arztebl Int* 2009;106:456-63. DOI: 10.3238/arztebl.2009.0456