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Original articles and reviews

Ecological meta-analytic study of kidney disease in Italian contaminated sites

Marta Benedetti[1], **Fabrizio Minichilli**[2], **Maria Eleonora Soggiu**[1], **Valerio Manno**[3] **and Lucia Fazzo**[1]

[1]*Dipartimento Ambiente e Salute, Istituto Superiore di Sanità, Rome, Italy*
[2]*Unità di Ricerca di Epidemiologia Ambientale e Registri di Patologia, Istituto di Fisiologia Clinica, Consiglio Nazionale delle Ricerche (CNR), Pisa, Italy*
[3]*Servizio di Statistica, Istituto Superiore di Sanità, Rome, Italy*

Abstract

Introduction. Environmental heavy metals exposure has been associated with kidney disease. There is also some evidence that exposure to solvents may be a risk factor for kidney disease. We estimated the risk of hospitalization for kidney diseases (ICD-9 580-586) and chronic kidney disease (CDK, ICD-9 585) in residents in thirty-four Italian National Priority Contaminated Sites (NPCSs) polluted by heavy metals.

Methods. Random-effects model meta-analyses of SHR (Standard Hospitalization Ratio) computed for each NPCS was performed for all the NPCSs together, and separately, according to the presence/absence of selected industrial activities (petrochemical/refinery and steel plants), and the presence/absence of solvents contamination.

Results. Pooled SHRs of overall NPCSs were in excess in both genders. Statistically significant excesses were found for CKD in both genders, and for kidney diseases in females, residing in NPCSs with the combined presence of heavy metals and solvents contamination. The pooled SHRs for CKD and kidney diseases were not statistically significant in excess in NPCSs with petrochemical/refinery and steel plants, and only petrochemical/refinery plants.

Conclusions. The results are suggestive of a possible kidney disease risk in population living in the above-mentioned NPCSs. Epidemiological surveillance and remediation actions in these areas are recommended.

Key words
- kidney disease
- heavy metals
- solvents
- environmental exposure
- meta-analysis

INTRODUCTION

The incidence and prevalence of kidney disease, mainly chronic kidney disease (CKD), is rapidly increasing worldwide. Recent estimates suggest that 8-16% of the global population is affected by some form of CKD, with a projection that CKD will become the fifth most common cause of years of life lost globally by 2040. Despite this, kidney disease is missing from the international agenda for global health [1, 2].

The kidney is particularly vulnerable to toxic effects from environmental pollutants. Occupational and environmental exposure to high levels of some heavy metals, such as cadmium (Cd), lead (Pb), mercury (Hg), and arsenic (As), are established risk factors for the development of acute kidney diseases and CKD [3-8]. Cadmium, along with lead, are considered to be the most nephrotoxic heavy metals. At present, there is increasing evidence that chronic environmental exposure to Cd, Pb and Hg at low levels, previously thought to be acceptable, may lead to renal damage [3, 5, 7, 9, 10]. Moreover, there are indications that co-exposure to Cd and As causes more pronounced human renal damage than exposure to each element alone [8, 11, 12].

Humans are exposed to heavy metals via occupational exposure (e.g., mining, petrochemical, refinery, and metallurgical activities), consumption of contaminated food and water, and inhalation of polluted air in areas with heavy traffic [5, 13]. Other exposures can occur with people who live near industrial sites or hazardous dumping sites [5]. In areas with contaminated soil due to heavy metals, house dust is a possible route of exposure even decades after the cessation of the industrial activity [3, 13, 14]. People living in polluted sites are exposed to heavy metals via atmospheric particulate matter (PM) at a level higher than the level allowed [15, 16]. Cigarette smoke is also an important source of Cd and Pb released as CdO and PbO. Inhaled CdO and PbO are more bioavailable than oral Cd and Pb. On average, Cd concentrations in the blood of smokers are four to five times greater, and in the kidney two to three times greater than non-smokers [3, 17].

Once entered the human body, Cd and Pb, due to

Address for correspondence: Marta Benedetti, Dipartimento Ambiente e Salute, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: marta.benedetti@iss.it.

their long half-life, remain in the body for decades. Once adsorbed, Cd is stored mainly in the kidney (approximately 80%) and reaches a biologic half-life of more than 10 to 40 years [18, 19]. The extremely long half-life of Cd in the human body suggests that the majority of Cd that is taken is retained indefinitely in the renal tubular cells [20]. Lead accumulates mainly in bone and teeth (approximately 94%) with a half-life, in bone, of about 30 years. The stored lead may be mobilized from bone under physiological and pathophysiological conditions (e.g., advanced age, hyperthyroidism, broken bones, lactation, menopause, and physiological stress) [19, 21, 22].

Cd levels in men and women appear to differ significantly. In women of reproductive age, the body burden of Cd tends to be greater than in men. This seem to be due to the lower iron stores in women than in men as iron deficiency increases absorption of Cd, rendering women more susceptible to Cd uptake [23]. Moreover, according to Satarug *et al*. (2020) [24], which evaluated kidney dysfunction associated with chronic low-level exposure to Cd and Pb in a population of residents in Bangkok, women may also be more susceptible than men to nephrotoxicity due to exposure to Pb.

There is also evidence that exposure to solvents (mainly via occupational exposure) may be a risk factor for kidney disease [25-28]. Furthermore, recent studies indicate that exposure to some dibenzo-p-dioxins (PCDDs), chlorinated dibenzofuran (PCDFs), and dioxin-like polychlorinated biphenyls (DL-PCBs) might raise the risk of kidney disease [29, 30].

Although it is well established that occupational exposure to high levels of Cd, Pb, Hg, As, and solvents may be a risk factor for kidney disease, few studies have been carried out to evaluate the occurrence of kidney disease in the general population living in proximity to industrial sites contaminated by these elements/chemicals [31-39].

In addition to occupational or environmental exposure to heavy metals and solvents, other factors may also increase the risk of developing kidney disease. Diabetes and hypertension are considered to be the two leading causes of kidney disease. However, hypertension can be either a cause or a consequence of renal failure. Other additional risk factors are obesity, family history of kidney disease, being over age 60, elevated ambient temperature, being affected by lupus erythematosus, and low socioeconomic status [13, 14, 40].

It is important to note that lead has been associated with increased risk for hypertension [5], Cd for type 2 diabetes [41] and hypertension [42], and Cd, Pb and As for obesity [43]. Therefore, exposure to these heavy metals might also indirectly influence development or progression of kidney disease.

The aim of the present study was to assess the risk of hospitalization in the population living in the Italian National Priority Contaminated Sites (NPCSs) with a documented contamination of heavy metals for a set of specific well-defined renal diseases (ICD-9-CM codes 580-586) (hereafter referred as "kidney diseases" for simplicity), and, separately, for CKD (ICD-9-CM code 586), by gender and (*i*) presence or absence of selected type of industrial activities (petrochemical/refinery and steel plants) or other pollution sources (e.g., chemical plants, power plants, waste landfills and dumps, and harbors); (*ii*) combined heavy metals and solvents contamination or heavy metals only contamination. The study is part of the epidemiological surveillance programme (Italian Epidemiological Study of Residents in National Contaminated Sites (SENTIERI Project)) carried out in NPCSs, which are areas identified to be of national concern for environmental remediation due to heavy soil and water pollution [44].

METHODS

Site's description

The thirty-four NPCSs *(Figure 1)* included in this study are, or were in the past, characterized by the presence of one or more polluting sources such as refineries, petrochemical and metallurgic plants, thermoelectric power plants, chemical plants, mines, chemical fertilizer and pharmaceutical plants, controlled and illegal waste dumps, and other industrial facilities. All these activities released into the environment the heavy metals considered of interest in the present study due to their well-recognized nephrotoxic action.

The analysis of the environmental surveys carried out to characterise the contamination in each NPCS, in order to define remediation activities, evidenced Cd, Pb, As, and Hg as the metals most responsible for soil and deep-water contamination. They are present in all selected NPCSs. Other metals that are often detected are nickel (Ni), vanadium (V), chromium (Cr) and cobalt (Co). Other chemicals, such as PCDDs, PCDFs, and PCBs, were also detected in some NPCSs studied. The available data are related to the reporting of the presence of the substances that have exceeded the limit value allowed by current Italian regulations in the various environmental matrices (soil, groundwater, and sea).

Case definition and data source

We considered the hospitalization data included in the last update of SENTIERI Project [44]. We included in the study all the subjects who resided in the thirty-four Italian contaminated Sites in the years 2006-2013, and who, in the same period, had first-time hospitalization with newly diagnosed kidney diseases, defined as a primary diagnosis at discharge of acute glomerulonephritis (code 580), nephrotic syndrome (code 581), chronic glomerulonephritis (code 582), nephritis and nephropathy not specified as acute or chronic (code 583), acute kidney failure (code 584), chronic kidney disease (CKD) (code 585), renal failure and renal failure unspecified (code 586), using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes [45].

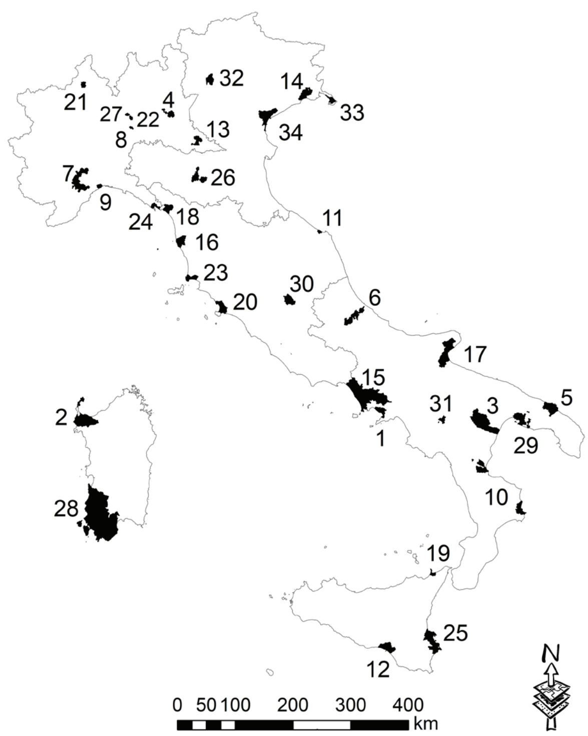
Hospitalization data were extracted from the Italian Hospital Discharge Register (HDR) of the Service of Statistics of the Italian National Health Institute (Istituto Superiore di Sanità), for each calendar year for the period 2006-2013. The HDR is a register of all hospitalization episodes that all public and private hospitals are required to report. The HDR has complete national coverage since 2001. It contains administrative, clinical, and treatment data. The primary and five secondary diagnoses, and treatment data on the HDR are coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) [45]. Data contained in the Hospital Discharge Register are provided anonymously. Each Hospital Discharge Record reports a main diagnosis and up to five secondary diagnoses. We chose to take into consideration only the primary diagnosis as Italian and international studies have shown that measures based only on the primary diagnosis are more specific (less false positives), whereas measures that consider all diagnoses are more sensitive (less false negatives) [46, 47].

Design of analysis

Pooled Standardized hospitalization ratios (SHRs), with their relative 95% confidence intervals, were calculated for all the NPCSs together, and separately according to the presence/absence of specific well-defined industrial activities (see below) and the presence/absence of solvents contamination.

The pooled estimates were obtained through the meta-analysis method using the "metan" routine by Stata statistics software (version 15 for Windows Stata Corporation, 2017) [48]. Heterogeneity in meta-analysis refers to the variation in study outcomes between studies. Between-study heterogeneity was assessed by inspecting the forest plots and the chi-squared test for heterogeneity (I^2). The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance [49, 50]. When the heterogeneity between studies is low, then I^2 will be low and a "fixed effects" model may be appropriate. The main assumption of the fixed effects model is that all studies examined are conducted under similar conditions – the only difference between the studies is their power to detect the outcome of interest. An alternative approach is that of "random effects", which allows to study heterogeneous studies in a valid way. In our study, I^2 statistic with a value above 50% was interpreted as representing high heterogeneity, and therefore, a random-effects model analysis was performed using the model described by DerSimonian and Laird [51], with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Results of the meta-analysis were reported as pooled SHR with 95% confidence intervals (CIs), p-values <0.05 were considered statistically significant.

Among all the Italian NPCSs, we selected those where the chemical characterization of environmental pollution detected a high concentration of heavy metals in soil and/or water. This constituted the main inclusion criteria for the study and led to the selection of thirty-four distinct NPCSs. These NPCSs were divided in 4 classes, as shown in *Table 1*, for the subsequent statistical analysis. The classes identify sites with different industrial patterns: Class 1, NPCSs where petrochemical/refinery and steel plants are located; Class 2, NPCSs where a steel plant is only present; Class 3, NPCSs where petrochemical/refinery plants are only present; and Class 4, NPCSs with presence of other type of industrial facilities, and with the exclusion of petrochemical, refinery and steel plants. The geographi-



Code	Site (abbreviation)
1	Area Litorale Vesuviano (ALV)
2	Aree industriali Porto Torres (APT)
3	Aree industriali Val Basento (AVB)
4	Brescia Caffaro (BRE)
5	Brindisi (BRI)
6	Bussi sul Tirino (BUS)
7	Cengio-Saliceto (CES)
8	Cerro al Lambro (CER)
9	Cogoleto Stoppani (COS)
10	Crotone-Cassano-Cerchiara (CCC)
11	Falconara (FAL)
12	Gela (GEL)
13	Laghi di Mantova (LMN)
14	Laguna di Grado e Marano (LGM)
15	Litorale Domizio Flegreo e Agro Aversano (LDF)
16	Livorno (LIV)
17	Manfredonia (MAN)
18	Massa Carrara (MSC)
19	Milazzo (MIL)
20	Orbetello (ORB)
21	Pieve Vergonte (PIV)
22	Pioltello Rodano (PIR)
23	Piombino (PIO)
24	Pitelli (PIT)
25	Priolo (PRI)
26	Sassuolo-Scandiano (SAS)
27	Sesto San Giovanni (SES)
28	Sulcis-Iglesiente-Guspinese (SIG)
29	Taranto (TAR)
30	Terni-Papigno (TER)
31	Tito (TIT)
32	Trento Nord (TRE)
33	Trieste (TRI)
34	Venezia Porto Marghera (VEN)

Figure 1
Italian National Priority Contaminated Sites (NPCSs).

Table 1
National Priority Contaminated Sites (NPCSs) information on pollution sources

Class	Presence/absence of selected industrial activities or presence of other pollution sources*	Number of sites	NPCSs abbreviation
1	Presence of petrochemical/refinery and steel plants	4	MSC, MIL, TAR, TRI
2	Presence of only steel plants	4	PIO, SES, TER,TIT
3	Presence of only petrochemical/refinery plants	8	APT, BRI, FAL, GEL, LMN, LIV, PRI, VEN
4	Presence of other pollution sources*, with absence of petrochemical/refinery and steel plants	18	ALV, AVB, BRE, BUS, CES, CER, COS, CCC, LGM, LDF, MAN, ORB, PIV, PIR, PIT, SAS, SIG,TRE
Class	**Presence/absence of solvents contamination**	**Number of sites**	**NPCSs abbreviation**
5	Presence heavy metals and solvents	25	APT, AVB, BRI, BUS, CES, CCC,FAL, GEL,LMN, LDF, LGM, LIV, MAN, MIL, PIV, PIR, PIO, PIT, PRI, SES, SIG, TAR, TIT,TRI, VEN
6	Presence of heavy metals and absence of solvents	9	ALV, BRE, CER, COS, MSC, ORB, SAS, TER, TRE

ALV: Area Litorale Vesuviano; APT:Aree industriali Porto Torres; AVB:Aree industriali Val Basento; BRE: Brescia Caffaro; BRI: Brindisi; BUS: Bussi sul Tirino; CES: Cengio-Saliceto; CER: Cerro al Lambro; COS: Cogoleto Stoppani; CCC: Crotone-Cassano-Cerchiara; FAL: Falconara; GEL: Gela; LMN: Laghi di Mantova; LGM: Laguna di Grado e Marano; LDF: Litorale Domizio Flegreo e Agro Aversano; LIV: Livorno; MAN: Manfredonia; MSC: Massa Carrara; MIL: Milazzo; ORB: Orbetello; PIV: Pieve Vergonte; PIR: Pioltello Rodano; PIO: Piombino; PIT: Pitelli; PRI: Priolo; SAS: Sassuolo-Scandiano; SES: Sesto San Giovanni; SIG: Sulcis-Iglesiente-Guspinese; TAR: Taranto; TER: Terni-Papigno; TIT: Tito; TRE: Trento Nord; TRI: Trieste; VEN: Venezia Porto Marghera.
*This indicates the presence of one or more of the following pollution sources: chemical plants, power plants, waste landfills and dumps, and harbors.

cal distribution shows fourteen plants in the North of Italy, thirteen in the South and seven in Central Italy. Petrochemical and refinery plants are more numerous in the South, while steel plants are equally distributed among geographical regions.

In addition, to investigate the population health effects due to the combined exposure to heavy metals and solvents, the abovementioned thirty-four NPCSs studied were classified and analysed according to the presence or absence of solvents. Twenty-five NPCSs were classified with solvent contamination, while nine NPCSs were classified without (Class 5 and 6 in *Table 1*). The chemical characterization showed that the benzene, toluene and xylene (BTX) mixtures are the most present solvents in fourteen sites. The other solvents occasionally detected are trichloroethylene, tetrachloroethylene, and chlorobenzene. All NPCSs with refineries and/or petrochemical plants are included in Class 5 since the production cycle and the raw materials processed cause the emission of solvents.

Data on the presence of heavy metals and solvents in the NPCSs were derived from the legislative national decrees where the NPCSs are defined, in addition to data from surveys carried out by regional environmental agencies [52, 53].

RESULTS

Thirty-four NPCSs, included in the SENTIERI Project, were considered eligible for the study due to the presence of heavy metals or the combined presence of heavy metals and solvents considered to be risk factors for kidney disease.

The number of observed and expected cases, and of the population residing in the thirty-four NPCSs, by gender and type of kidney disease are shown in *Table 2*. Results of pooled SHRs, with their 95% confidence intervals (95% CIs), by gender, typology of industrial facilities, presence or absence of solvents, and for the thirty-four NPCSs overall are shown in *Table 3*.

The pooled SHRs for all thirty-four NPCSs together showed a statistically significant excess of hospitalization for CKD (ICD-9-CM code 585) in both genders, while for "kidney diseases" (ICD-9-CM codes 580-585), a statistically significant excess was found in females.

In the analysis by typology of industrial facilities present in the NPCSs, the pooled SHRs for CKD showed in males a non-significant excess risk of 16% in Class 1 (presence of petrochemical, refinery and steel plants), of 12% in Class 3 (presence of only petrochemical and refinery plants), and of 4% in Class 4 (presence of other pollution sources, with absence of petrochemical/refinery and steel plants). In females, the pooled SHRs for CKD showed a non-significant excess risk of 12% in Class 1, of 9% in Class 3, and of 10% in Class 4 (presence of other pollution sources, with absence of petrochemical/refinery and steel plants).

In the analysis by heavy metals contamination and presence/absence of solvents contamination (Class 5 and 6), the pooled SHR for CKD showed a significant excess risk of 9% in males and of 11% in females in Class 5 (presence of heavy metal and solvents), while for "kidney diseases" a significant excess risk of 8% was found in females. In the NPCSs in Class 6 (presence of heavy metals and absence of solvents) non-statistically significant excesses for "kidney diseases" were observed in both genders.

The excesses observed for "kidney diseases" might be due to the inclusion of CKD cases in this group of kidney diseases.

Considering that CKD has been recognized as a leading public health problem worldwide [1, 2], in the present paper the only forest plots of CKD meta-analyses are shown *(Figures 2* and *3)*. In each analysis, the test of heterogeneity showed a high value of I squared, highlighting the heterogeneity of individual estimates. The *Figures* showed a high variability of the estimates for some NPCSs (TIT, PIR, PIV, ORB, CER), due to a low number of cases. In these NPCSs, the observed excesses were not statistically significant. In the analyses

Table 2
Number of observed and expected cases, and of the population residing in the thirty-four NPCSs, by gender and type of kidney disease, 2006-2013

NPCS (abbreviation)	Kidney diseases (ICD-9-CM codes 580-586)				Chronic kidney disease (CKD) (ICD-9-CM code 585)				Annual resident population*	
	Males		Females		Males		Female		Males	Females
	Observed cases	Expected cases	Observed cases	Expected cases	Observed cases	Expected cases	Observed cases	Expected cases		
Area Litorale Vesuviano (ALV)	1,738	2,153.46	1,336	1,714.80	1,304	1,568.44	983	1,198.38	213,870	230,534
Aree industriali Porto Torres (APT)	749	625.18	582	551.27	406	391.57	276	331.76	70,026	75,889
Aree industriali Val Basento (AVB)	142	162.60	132	133.38	77	88.86	63	69.12	19,001	19,724
Brescia Caffaro (BRE)	1,126	899.22	921	763.46	588	464.70	338	327.62	96,097	107,696
Brindisi (BRI)	590	470.16	486	420.19	465	319.42	386	275.36	42,354	46,207
Bussi sul Tirino (BUS)	561	431.24	468	345.94	339	270.83	245	192.29	41,227	44,568
Cengio e Saliceto (CES)	218	681.06	137	164.54	132	126.65	85	78.40	18,417	19,309
Cerro al Lambro (CER)	28	29.72	32	19.97	12	15.85	11	9.09	4,461	4,514
Cogoleto Stoppani (COS)	127	155.43	103	121.07	80	90.11	62	60.79	9,864	10,828
Crotone-Cassano-Cerchiara (CCC)	496	365.46	393	275.10	380	259.44	293	184.6	38,459	40,615
Falconara (FAL)	170	140.96	119	109.26	112	81.82	72	57.38	13,012	14,088
Gela (GEL)	371	413.29	314	292.85	292	303.79	238	210.08	36,813	38,204
Laghi di Mantova (LMN)	290	295.03	217	255.87	179	151.82	124	108.89	28,546	32,566
Laguna di Grado e Marano (LGM)	79	128.42	69	86.56	48	70.20	35	39.96	15,485	16,108
Litorale Domizio Flegreo e Agro Aversano (LDF)	5,110	5,880.21	3,952	4,507.07	3,661	4,263.11	2,640	3,141.69	680,318	714,171
Livorno (LIV)	1,017	944.96	911	759.81	471	532.84	311	380.51	82,819	90,634
Manfredonia (MAN)	405	393.48	342	324.78	301	265.89	214	212.06	34,500	35,174
Massa Carrara (MSC)	628	654.06	454	567.86	329	375.74	228	285.58	63,843	69,435
Milazzo (MIL)	399	297.85	279	239.45	334	220.94	222	172.05	22,124	23,470
Orbetello (ORB)	124	79.07	110	64.96	51	45.07	43	32.72	6,933	7,745
Pieve Vergonte (PIV)	26	25.06	15	17.95	16	13.52	10	8.58	2,928	3,049
Pioltello Rodano (PIR)	146	131.98	113	89.17	59	69.75	46	40.49	19,208	19,321
Piombino (PIO)	155	208.36	134	165.94	80	117.73	63	83.03	16,300	17,943
Pitelli (PIT)	931	754.31	930	678.21	554	433.91	468	334.23	48,077	54,677
Priolo (PRI)	1,059	1,101.23	889	868.30	773	815.70	637	624.66	88,576	91,909
Sassuolo – Scandiano (SAS)	484	465.50	389	361.87	220	241.07	141	157.84	56,706	58,091
Sesto San Giovanni (SES)	565	543.97	439	405.58	284	285.37	169	178.91	59,415	64,219
Sulcis-Iglesiente-Guspinese (SIG)	1,356	1,213.97	1,254	989.26	916	756.69	823	592.34	130,414	133,681
Taranto (TAR)	1,245	1,175.13	1,205	1,078.00	980	798.20	909	707.95	102,992	112,349
Terni – Papigno (TER)	505	419.86	368	314.99	340	251.93	229	173.00	51,119	57,466
Tito (TIT)	23	24.46	20	19.38	12	13.49	9	10.03	3,520	3,522
Trento Nord (TRE)	355	402.10	297	340.09	175	160.45	146	131.97	53,760	58,978
Trieste (TRI)	920	893.85	696	694.66	520	484.47	347	312.20	95,250	107,955
Venezia Porto Marghera (VEN)	1,159	1,120.08	922	937.64	676	541.26	474	390.26	123,300	138,667

NPCSs: National Priority Contaminated Sites; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification [45].
*Data refer to the annual average of resident population for 2006-2013.

Table 3
Pooled Standardized Hospitalization Ratios (SHRs) for kidney diseases, by gender and NPCS class

	NPCS	Kidney diseases (ICD-9-CM codes 580-586) Males	Kidney diseases (ICD-9-CM codes 580-586) Females	Chronic kidney disease (CKD) (ICD-9-CM code 585) Males	Chronic kidney disease (CKD) (ICD-9-CM code 585) Females
		SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
	34 NPCSs overall	1.03 (0.97-1.09)	1.07 (1.00-1.13)	1.07 (1.00-1.15)	1.09 (1.01-1.17)
Classes by presence/absence of specific industrial activities or presence of other pollution sources*					
1	Presence of petrochemical/refinery, and steel plants	1.08 (0.96-1.20)	1.02 (0.85-1.18)	1.16 (0.95-1.38)	1.12 (0.88-1.36)
2	Presence of only steel plants	0.99 (0.77-1.21)	1.03 (0.85-1.20)	0.99 (0.68-1.30)	0.99 (0.72-1.27)
3	Presence of only Petrochemical and refinery plants	1.06 (0.98-1.15)	1.06 (0.99-1.13)	1.12 (0.99-1.26)	1.09 (0.94-1.24)
4	Presence of other pollution sources*, with absence of petrochemical/refinery and steel plants	1.00 (0.90-1.11)	1.10 (0.99-1.2)	1.04 (0.94-1.14)	1.10 (0.99-1.22)
Classes by presence/absence of solvents contamination					
5	Presence of heavy metals and solvents	1.03 (0.96-1.10)	1.08 (1.01-1.16)	1.09 (1.01-1.18)	1.11 (1.01-1.21)
6	Presence of heavy metals and absence of solvents	1.04 (0.89-1.19)	1.04 (0.88-1.20)	1.02 (0.87-1.16)	1.01 (0.89-1.14)

NPCS: National Priority Contaminated Site; CI: Confidence Interval; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification [45].
*This indicates the presence of one or more of the following pollution sources: chemical plants, power plants, waste landfills/dumps, and harbors.

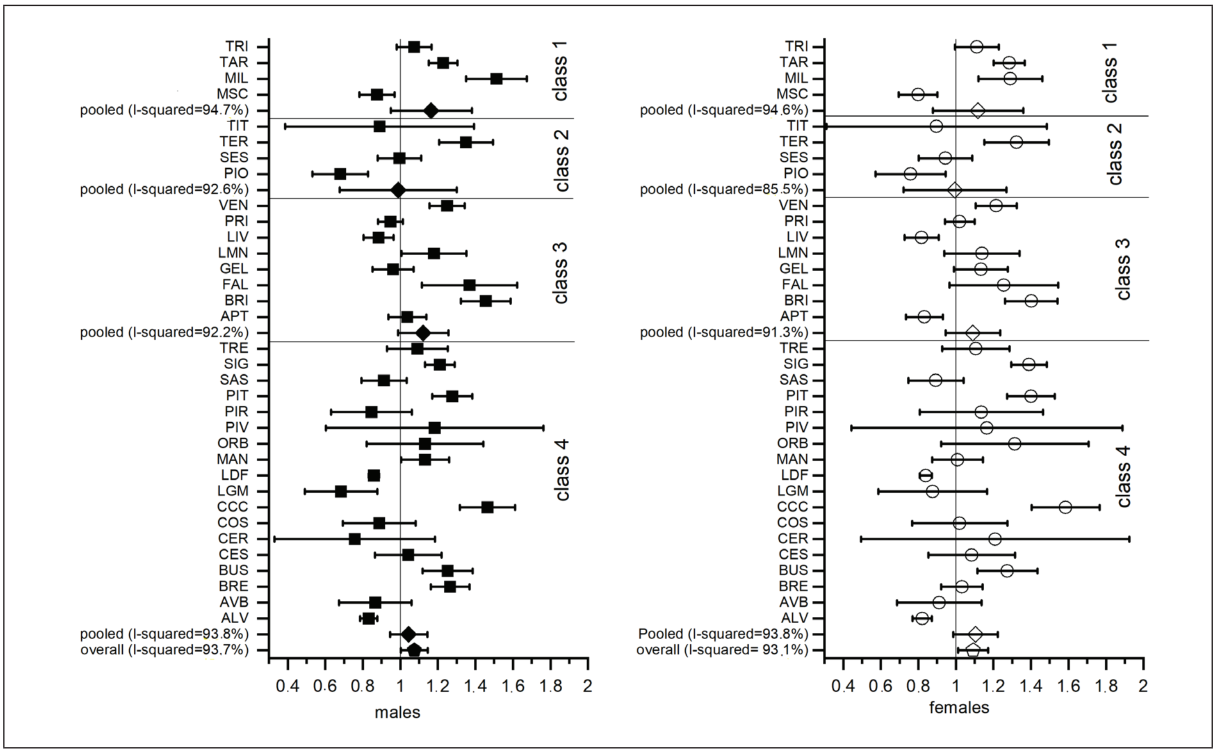


Figure 2
Forest plots of pooled Standardized hospitalization ratios (SHRs) for chronic kidney disease (CKD) in classes 1-4, by gender. Class 1 = presence of petrochemical/refinery and steel plants; Class 2 =p resence of only steel plants; Class 3 = presence of only petrochemical and refinery plants; Class 4 = presence of other pollution sources (e.g., chemical plants, power plants, waste landfills/dumps, and harbors), and absence of petrochemical/refinery and steel plants.

shown in *Figure 2* and *3*, excesses of hospitalization for CKD were more frequent than deficits.

The pooled excess of CKD, highlighted in females in the analysis of Class 4 (presence of other industrial facilities and absence of petrochemical/refinery and steel plants *(Figure 2)*), seems to be more influenced by the risk excesses of the BUS, PIT, SIG and CCC NPCSs. The pooled excess of CKD, highlighted in both gender in the analysis of Class 5, seems to be more influenced by the risk excesses of VEN, TAR, SIG, PIT, MIL, FAL, CCC, BUS and BRI sites *(Figure 3)*.

DISCUSSION

In the meta-analysis of ecological studies, the heterogeneity between studies is often high, so the most appropriate method to reduce the bias on the results

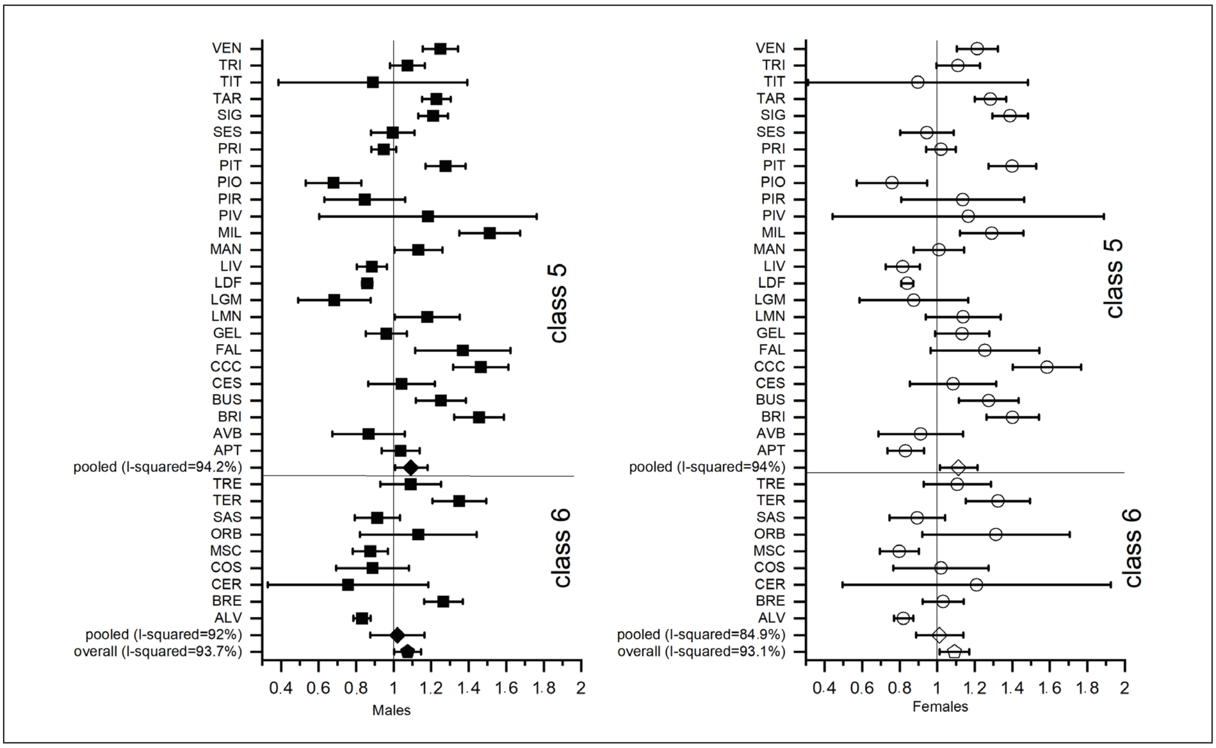


Figure 3
Forest plots of pooled Standardized hospitalization ratios (SHRs) for chronic kidney disease (CDK) in classes 5-6, by gender. Class 5 = presence of heavy metals and solvents; Class 6 = presence of heavy metals and absence of solvents.

is that of random effects which under such conditions provides more accurate results than those provided by the fixed effects model.

In the present study, the meta-analysis of the combined thirty-four NPCSs, selected on the basis of the presence of heavy metals contamination, showed a statistically significant excess of hospitalization for CKD (ICD-9-CM code 585) in both genders, and for kidney diseases (ICD-9-CM codes 580-586) in females; the excess of kidney diseases among men was non-statistically significant.

In the analyses by classes of NPCSs, statistically significant excesses were found for CKD in males and females, and for kidney diseases in females, residing in the twenty-five NPCSs characterized by the combined presence of heavy metals and solvents (Class 5). The NPCSs that seem to mainly contribute to the excesses observed in Class 5 are characterized by the "presence of other pollution sources, and absence of petrochemical/refinery and steel plants" (SIG, PIT, CCC, BUS), and by "the presence of only petrochemical/refinery plants" (VEN, FAL, BRI).

Several non-significant excesses for CKD and kidney diseases were found in residents (both gender) in the four NPCSs characterized by the presence of petrochemical/refinery and steel plant (Class 1) and in the eight NPCSs with presence of only petrochemical/refinery plants (Class 3). No excesses were observed in resident in NPCSs characterized by the presence of only steel plant (Class 2).

The excesses observed for CKD and kidney diseases in Class 5 (presence of heavy metals and solvents), mainly in females, are suggestive of a possible adverse effect associated to the combined exposure to heavy metals and solvents. It is worth noting that excesses for CKD and kidney diseases have also been observed in the NPCSs with presence of petrochemical/refinery and steel plants or only petrochemical/refinery plants (Classes 1 and 4), where the exposure to solvents, as well as to heavy metals, is likely to occur. However, the effect of other factors (e.g., random variability, confounding) cannot be excluded, due to the adoption of an ecological study design.

The results obtained for all the thirty-four NPCSs are strongly influenced by the fact that the twenty-five NPCSs in Class 5 (characterized by the combined presence of heavy metals and solvents) represent 74% of all NPCSs, as it is highlighted by the substantial overlapping of the corresponding SHR pooled values.

To the best of our knowledge, this is the first study describing hospitalization risk for selected kidney diseases in residents near contaminated sites according to the presence/absence of some type of industrial facilities releasing heavy metals in the environment, and to the presence/absence of solvents contamination.

There are some limitations to our study, mainly due to the ecological study design. The most important is the lack of a quantitative indicator of residential exposure to heavy metals and solvents. However, this study restricted the analyses only to NPCSs where the environmental contamination by heavy metals, and in some cases solvents, possibly related to renal disease was a priori documented, thus reducing the possibility to observe spurious association only due to chance. Another limitation is that we could not exclude the possibility of residual confounding factors (e.g., diabetes, hypertension, obesity, age), and of the action or co-exposure to other chemicals (e.g., dioxins, furans, and PCB), recently related to renal dysfunction. Moreover, as most patients with kidney disorders, even chronic kidney disorders are often asymptomatic or may never have been hospitalized, there may have been an underestimation of the cases of the kidney diseases studied.

CONCLUSIONS

According to the results of our study, living in proximity of petrochemical, refinery and steel plants, and particularly, in proximity of contaminated sites with a combined presence of heavy metals and solvents contamination might be considered a potential risk factor for the kidney diseases studied.

This study results support the need for further analytical epidemiological studies to be performed. Future analytical studies should attempt to collect information on occupational and residential history, diabetes, hypertension, obesity, tobacco smoking, and family history of kidney disease. Moreover, the analysis should be performed by specific age-classes as aging is characterized by a progressive decline in renal function [54].

In addition, considering that: (*i*) cadmium and lead nephrotoxic effects may progress even after exposure reduction; (*ii*) CKD can progress into end stage kidney disease, a condition associated with significant mortality; (*iii*) patients with CKD have an increased risk of cardiovascular disease and death; and (*iiii*) the healthcare costs of renal replacement therapy dialysis and/or kidney transplants needed for survival, consume 2-3% of the annual health-care budget in high income countries [55], efforts should be made in development of remediation plans in the NPCSs in order to reduce exposure to heavy metals and solvents.

Due to the findings of several excesses of hospitalization for kidney diseases observed in the present study, an epidemiological surveillance of residents in the NPCSs studied is warranted. Moreover, as kidney disease causes no symptoms until its later stages and the onset and progression of kidney disease is often preventable, for the residents in the NPCSs studied it should be considered to incorporate early detection into current screening protocols, using biomarkers of early effects [56, 57], capable of detecting renal effects at a relatively early stage when they are still reversible, and consequently, preventing the progression to complete renal failure. In future surveillance studies, it is also recommended to use biomonitoring of heavy metals and solvents (particularly of lead and cadmium due to their ability to accumulate in the body and their long half-life) in selected subpopulations residing in the NPCSs studied, in order to validate present and/or past exposure to these chemicals/elements. Besides, biomonitoring can provide a more precise exposure assessment than estimating exposure only based on concentrations in environmental matrices.

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Authorship contributions

MB collected and reviewed the scientific literature, MB, FM, MES, LF contributed to study design and wrote the article. FM performed meta-analysis. VM collected cases and computed standardized hospitalization ratios. MB, FM, MES, LF reviewed the manuscript and approved the final version of the manuscript.

Conflict of interest statement

The Authors declare no conflicts of interest.

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