METAL AND METALLOID LEVELS IN TOPSOIL AND MUNICIPAL CARDIOVASCULAR MORTALITY IN SPAIN

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Abstract

The role of metals and metalloids beyond arsenic, copper, lead and cadmium in cardiovascular disease is not entirely clear. The aim of this study was to assess the association between 18 metal or metalloid levels in topsoil (upper soil horizon) with all-cause and specific cardiovascular mortality endpoints in Spain. We designed an ecological spatial study, to assess cardiovascular mortality in 7941 Spanish mainland towns from 2010 to 2014. The estimation of metals and metalloids concentration in topsoil came from the Geochemical Atlas of Spain from 13,317 soil samples. We also summarized the joint variability of the metals using principal components analysis (PCA). These components (PCs) were included in a Besag, York, and Mollié model to assess their association with cardiovascular mortality from all causes, coronary heart disease, cerebrovascular, hypertension, and conduction disorders. Our results showed, both in men and women, that at the lowest component scores range, PC2 (mainly reflecting Al, Be, Tl and U) was positively associated with coronary heart disease and cerebrovascular mortality. At medium/highest scores range, PC4 (mainly reflecting Hg) was positively associated with cerebrovascular mortality. For PC3 (reflecting Se), the association with coronary heart disease mortality was positive only in men at the highest PC scores range. For PC1 (partly reflecting metals such as Pb, As, Cu or Cd), we observed a strongly suggestive positive association with all-cause cardiovascular diseases mortality. Our ecological results are consistent with the available evidence supporting a cardiovascular role of excessive exposure to Se, Hg, Pb, As, Cu and Cd, but also identify Al, Be, Tl and U as potentially novel cardiovascular factors. Additional research is needed to confirm the biological relevance of our findings.

Keywords: Cardiovascular mortality, metals, metalloid, topsoil, spatial models, environmental exposure

1. Introduction

Cardiovascular diseases (CVDs) are the main cause of death and disability in the world. It is estimated that around the 30% of the total deaths that occurred in 2017 (55 million deaths) in the world were from CVD (1). In Spain, they are also the first cause of decease (2,3).

Among the major causal risk factors for CVD mortality are high blood pressure, tobacco smoking, obesity, diabetes, and serum cholesterol (3). However, over the past decades, the evidence on the role of the exposure to some metals or metalloids in cardiovascular mortality has rapidly increased. The exposure to As, Pb, Cd, and Cu has been directly associated with an increased risk of CVD incidence and mortality, observing linear-shaped dose-response curves (4–7). Notwithstanding, its relevance at the low levels usually found in general population is still unclear (4,8–10).

Thus, information on the prevalence of exposure to these agents, and on their possible effects in mortality could be important to inform public health strategies aimed to reducing the burden of cardiovascular (CV) mortality. In this sense, studies based on the geographical variability in the risk of death can be useful tools to suggest new etiological hypotheses, to support evidence and/or to assess the effects of ecological exposures to risk factors (11–17). However, this type of approach has not been widely carried out in relation to metal / metalloid exposure, mainly due the complexity of these type of studies and the lack of data on their geographic distribution.

In Spain, the Survey of Spain (IGME) published the Geochemical Atlas of Spain, is the first nation-wide geochemical study of surface materials carried out in the country with low density (18). This study contains, among other things, a comprehensive description of the geochemical composition of the soil at two depth levels (horizons of 0–20 and 20–40 cm) that contains the bioavailable elements.

The presence of chemical elements in soil could be associated with higher population exposure to them through different pathways (i.e. drinking water, air dust, plants or animals…). In this way, López Alonso et al (19) observed that the concentration of heavy metals in soil determines their bioavailability in animal tissue. Therefore, some authors have used topsoil concentrations for some of these agents, such as As, as an indicator of long term exposure to these elements (20).

The information of the metal and metalloid levels in topsoil from the Geochemical Atlas of Spain has been used previously in various ecological studies to evaluate their association with cancer or mental health but not in cardiovascular diseases (21–23). Thus our group (21) observed in Spain an association, in both, men and women, between As topsoil concentration and municipal mortality due to cancers of stomach, pancreas, lung, brain and non-Hodgkin's lymphoma. Also, the trace contents of heavy metals and metalloids in topsoil were associated to a higher probability of having a mental disorder, observing dose-response relationships for Pb, As, and Cd, specifically (23,24).

The aim of this study was to assess the possible association between metal and metalloid levels in topsoil (upper soil horizon) and cardiovascular mortality in mainland Spain for the period 2010-2014.

2. Material and Methods

2.1. Cardiovascular Mortality

Observed municipal mortality data were drawn from the records of the National Statistics Institute of Spain (Instituto Nacional de Estadística, INE) for the study period 2010-2014 and corresponded to deaths due to the following groups of Cardiovascular diseases (CVDs): All-cause Cardiovascular diseases (All-cause CVD) (International Classification of Diseases 10th Revision (ICD-10): I00-I99), Hypertensive Diseases (ICD-10: I10-I14), Coronary Heart Disease/CHD (ICD-10: I20-I25), Conduction Disorders (ICD-10: I44-I49) and Cerebrovascular diseases (ICD-10: I60-I69). Municipal population data, broken down by age group and sex were also drawn from INE records, and person-years were calculated by multiplying the respective populations by 5 (with data for 2012 being taken as the estimator of the population at the midpoint of the study period). Expected deaths in each town were calculated by taking the specific rates for all-cause and cause-specific cardiovascular mortality group in Spain as a whole, broken down by age group (30-34,…, 80–84 years and 85 years and over) and sex, and multiplying them by the corresponding person-years.

2.2. Metals/metalloids topsoil data

The metals/metalloid levels were measured in a total of 21,187 residual soil samples (13,505 from the surface horizon/topsoil and 7682 from the deeper horizon) collected between June 2008 and November 2010. Of the 13,505 total sampling points, 13,317 were from mainland Spain (sample points used in this study) and 188 from the Canary Islands and the Balearic Islands. A detailed description of the sample-collection and the chemical-analysis techniques used can be found in the Geochemical Atlas of Spain (18,21). Briefly, the residual soil samples (from the two horizons mentioned) were sieved to 2-mm fraction and then analysed by instrumental inductively coupled plasma mass spectrometry (ICP-MS) after crushing, pulverizing and subsequent partial digestion (extraction by aqua regia). We selected for our study the partial extraction results yielded by samples from the upper soil horizon (topsoil) because this determination is closest to the bioavailable metal/metalloid content of soil and tends to display the highest association with possible pollution events.

The elements included in this study were Al, As, Cd, Cr, Fe, Mn, Ni, Pb, Zn, Be, Co, Cu, Hg, Mo, Se, Tl, U and V. For the analysis, as mortality data were assigned the town's centroid coordinates, we obtained firstly the corresponding concentration of the metal/metalloid at those points using an interpolation method (21,22).

2.3. Socio-demographic variables

A series of sociodemographic indicators from the 2001 Spanish Census (INE) were included in the analysis to control for possible confounding factors: municipal population size, categorized into four levels: <10,000 inhabitants (rural areas), 10,000 to 50,000 inhabitants (semi-rural areas), 50,000 to 100,000 inhabitants (semi-urban areas) and >100,000 inhabitants (urban areas); unemployment rate (unemployment rate in people aged between 20 and 59 years) and educational level (percentage of people who are studying post-compulsory studies) for each municipality. These variables were chosen for their availability at the municipal level, their ability to explain geographical mortality patterns (25) and their previous association with cardiovascular mortality (26,27).

2.4. Statistical analysis

In this ecological study we conducted sex-stratified analyses, which is divided into three sections: (1) Description of all-cause and cause-specific cardiovascular mortality (rates and municipal spatial distribution). (2) Characterization of the metal and metalloid topsoil levels (descriptive analysis, municipal spatial distribution, correlation analysis, principal component analysis and spatial distribution of principal components). (3) Analysis of association between metal and metalloid topsoil levels (using the type of soil characterized by the principal component analyse) and cardiovascular mortality at a municipal level.

2.4.1. Description of the cardiovascular mortality

CVD mortality rates were calculated across the study period (2010-2014) by sex. We mapped the municipal smoothed standardized mortality ratios (SMRs) for CVD in Spain for the period 2010–2014 and the distributions of posterior probabilities (PP) of having a SMRs >1. The SMRs were calculated using the conditional autoregressive model proposed by Besag, York and Mollié (BYM), based on fitting a Poisson spatial model with observed cases as the dependent variable, expected cases as an offset, and two types of random effect terms, the municipal contiguity and the municipal heterogeneity (28).

2.4.2. Description of metal and metalloid topsoil levels

A descriptive analysis of the metals/metalloid topsoil levels was performed. First, the following estimators were calculated for the whole country and each metal/metalloid: arithmetic and geometric means and their 95% confidence intervals, standard deviation, median, 25th and 75th percentiles and minimum and maximum. Second, we mapped the geographic distribution of estimated metals and metalloids concentrations in topsoil at municipal level using a scale based on the quantiles of the concentration distribution. Some of these metals or metalloids estimations were strongly correlated. We used a principal component analysis (PCA) to reduce this set of highly correlated exposure variables into a smaller set of uncorrelated components. In addition, the distribution of the concentrations sometimes has extreme values. We therefore chose to carry out the PCA on the basis of the log-transformed concentrations to robustify the analysis. We selected those principal components (PC) with percentages of explained variance higher than 5%. Finally, the PC-scores (linear combination of the original variables extracted from the PCA at each spatial location) were mapped in order to visualize the main components of the spatial pattern of the different metals / metalloids.

2.4.3. Association analysis

To evaluate the association between metal/metalloid topsoil levels and cardiovascular mortality at the municipal level, we included the principal component scores obtained from the PCA analysis in the previous BYM model. To take into account possible non-linear associations, a penalized spline (second-order random walk) was used to model the dose-response curve (in percentile scale) associated to each of these principal components, obtaining smoothed standardized mortality ratios (SMRs) by percentiles of the PCs and sex. In addition to these smooth terms, the model includes the sociodemographic variables as fixed effects.

All statistical analyses were performed using R Software. All the models were fitted in a Bayesian framework using the "Integrated nested Laplace approximation" (INLA) (29) implemented in the R-INLA package. The option of a simplified Laplace estimation and the default specification of the hyperparameter distribution were chosen. The criterion of contiguity was the adjacency of the municipal boundaries according to official INE maps.

3. Results

3.1. Cardiovascular Mortality

Between 2010–2014, there were a total of 589,264 deaths due to cardiovascular diseases among people aged 30 years or more (45% men and 55% women) in mainland Spain (7941 towns). The crude mortality rate in women (368.4 deaths per 100,000 habitants) was higher than in men (322.2 deaths per 100,000 habitants) for all cardiovascular diseases studied, excepting coronary heart diseases (CHD) (see **Table 1**).

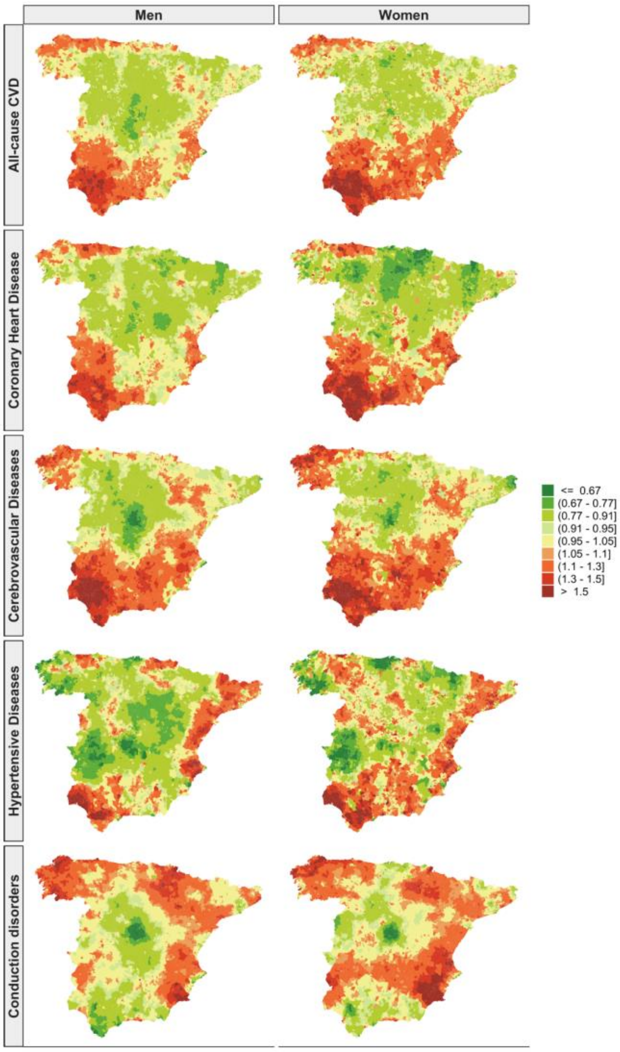
Mortality	ICD_10[a]	Men		Women	
		Deaths	*Crude rate*	*Deaths*	*Crude rate*
All-cause CVD[b]	I00-I99	252241	322.2	306939	368.4
CHD[c]	I20-I25	90602	115.7	67389	80.9
Cerebrovascular	I60-I69	57231	73.1	79869	95.9
Hypertensive Diseases	I10-I14	15839	20.2	33204	39.9
Conduction Disorders	I44-I49	13367	17.1	22586	27.1

a. International Statistical Classification of Diseases and Related Health Problems (ICD) version 10. b. All-cause CVD: all-cause cardiovascular diseases. c. CHD: coronary heart diseases.

Table 1 Crude mortality rates (per 100.000 habitants) and number of deaths among men and women aged 30 years or over for the period 2010-2014 in mainland Spain.

Figure 1 depicts the municipal distribution of cardiovascular diseases mortality in mainland Spain among men and women aged 30 years or more for the period 2010-2014. Municipal SMRs ranked from 0.54 to 1.90 and from 0.49 to 2.38 in men and women respectively for all cardiovascular mortality; from 0.66 to 1.78 and from 0.47 to 3.24 in men and women respectively for CHD ; from 0.39 to 2.65 and from 0.53 to 3.06 in men and women respectively for cerebrovascular disease; from 0.44 to 2.27 and from 0.40 to 3.04 in men and women respectively for hypertensive diseases and from 0.43 to 2.46 and from 0.50 to 2.38 in men and women respectively for conduction disorders.

The distribution of mortality risk shows clear spatial patterns for all the diseases studied, with a quite similar distribution in men and women. The maps for all-cause cardiovascular, CHD and cerebrovascular mortality highlight three high-mortality risk zones for CVD: northwest, southwest and southeast of Spain, and specifically for cerebrovascular mortality, the area located in the east, extends from north to south. For hypertensive diseases, the highest risks were observed in southwest and east of Spain, and finally in conduction disorders, three areas could be considered high-mortality risk zones: northwest, northeast and east of Spain.



All-cause CVD: all-cause cardiovascular diseases

Figure 1. Municipal distribution of the smoothed standardized mortality ratios (SMRs) for cardiovascular diseases in men and women aged 30 years or over for the period 2010-2014 in mainland Spain.

Figure 1 SM of Appendix includes maps representing the probability for each town of having an excess of risk (SMR>1) for causes specific of cardiovascular mortality.

3.2. Metal and Metalloid topsoil levels

The chemical elements analysed in this study included eleven transition metals (Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, V, Zn and Hg), two p-block metals (Pb and Tl), two metalloids (As and Se), one Actinide metal (U), one Alkaline-earth metal (Be) and one Non-ferrous metal (Al) (see **Table 2**). Attending to their possible biological effects, there were 8 toxic elements (As, Cd, Pb, Al, Be, Tl, U and Hg) and 10 essential trace elements (ETE) elements (Co, Cr, Cu, Fe, Mn, Mo, Ni, V, Zn and Se) (30). The municipal median, arithmetic and geometric mean topsoil levels for each metal/metalloid are shown in Table 2 as well as the maximum and minimum levels observed and the values representing the 25% and 75% percentiles.

Name	Caterogy[a]	Type[b]	Aritmetic mean (95%CI)	SD[c]	Geometric mean (95%CI)	Median	P25[d]	P75[e]	Minimun	Maximun
Aluminium (Al)	Non-ferrous metal	T	1.83x10^5 (1.81-1.84)	0.67x10^5	1.72x10^5 (1.71-1.73)	1.69x10^5	1.38x10^5	2.12x10^5	0.42x10^5	5.91x10^5
Arsenic (As)	Metalloid	T	9.32 (9.21-9.42)	4.79	8.20 (8.11-8.29)	8.62	6.07	11.63	0.79	47.39
Beryllium (Be)	Alkaline-earth metal	T	1.09 (1.08-1.10)	0.42	1.02 (1.01-1.03)	1.00	0.79	1.30	0.20	3.53
Cadmium (Cd)	Transition metal	T	0.14 (0.14-0.14)	0.08	0.12 (0.11-0.12)	0.12	0.07	0.18	0.01	1.72
Cobalt (Co)	Transition metal	ETE	7.92 (7.85-7.98)	2.92	7.39 (7.328-7.453)	7.55	6.00	9.38	1.07	37.59
Chromium (Cr)	Transition metal	ETE	22.14 (21.95-22.34)	8.70	20.80 (20.65-20.96)	21.04	16.79	25.38	6.21	169.05
Copper (Cu)	Transition metal	ETE	15.38 (15.23-15.55)	7.42	13.88 (13.74-14.01)	13.97	10.10	18.75	2.49	86.59
Iron (Fe)	Transition metal	ETE	2.15x10^5 (2.13-2.16)	0.70x10^5	2.0x10^5 (2.01-2.04)	2.09x10^5	1.65x10^5	2.59x10^5	0.32x10^5	5.46x10^5
Mercury (Hg)	Transition metal	T	19.38 (18.96-19.78)	18.57	16.65 (16.48-16.83)	15.29	12.02	21.72	5.87	700.15
Manganese (Mn)	Transition metal	ETE	394.72 (391.13-398.31)	16.31	362.51 (359.16-365.91)	371.84	278.37	483.87	60.36	1,453.67
Molybdenum (Mo)	Transition metal	ETE	0.56 (0.56-0.57)	0.28	0.5 (0.49-0.50)	0.52	0.35	0.71	0.08	2.19
Nickel (Ni)	Transition metal	ETE	21.32 (21.10-21.54)	9.97	19.64 (19.47-19.82)	21.11	15.50	25.95	4.92	322.08
Lead (Pb)	p-block metal	T	21.44 (21.22-21.67)	10.32	19.88 (19.72-20.04)	19.51	15.63	24.39	6.57	389.34
Selenium (Se)	Metalloid	ETE	0.596 (0.59-0.60)	0.34	0.503 (0.50-0.51)	0.59	0.31	0.80	0.11	2.63
Thallium (Tl)	p-block metal	T	0.19 (0.19-0.19)	0.12	0.17 (0.16-0.17)	0.16	0.12	0.23	0.03	0.90
Uranium (U)	Actinide metal	T	1.33 (1.30-1.36)	1.36	1.03 (1.01-1.04)	0.88	0.68	1.27	0.29	10.56
Vanadium (V)	Transition metal	ETE	26.96 (26.74-27.19)	10.35	25.02 (24.80-25.24)	25.52	20.25	32.04	3.42	103.02
Zinc (Zn)	Transition metal	ETE	50.79 (50.35-51.22)	19.58	47.27 (46.87-47.67)	47.09	36.33	62.67	10.44	354.32

a Category: Chemical category; b Type: Type of element according to its biological effects (T=toxic, ETE=essential trace element);
c SD: Standard deviation d. P25: 25% percentil; P75: 75% percentil.

Table 2 Descriptive analysis of topsoil levels for each metal/metalloid (mg/kg)

Figure 2 shows the spatial distribution of estimated metals and metalloids concentrations at the municipal level using a scale based on the quantiles of the concentration distribution. In the case of Be, Tl, U and, less clearly, of Al, the highest topsoil levels were registered in the northwest and western areas and at other points in eastern regions of the territory. Moreover, in the case of Se, the highest topsoil levels were mainly observed in the north and in the east. And the highest topsoil levels of Hg were registered in northwest and southwest areas of the country. For the other elements, the areas with the highest topsoil levels are distributed throughout the territory without a clear common geographical pattern.

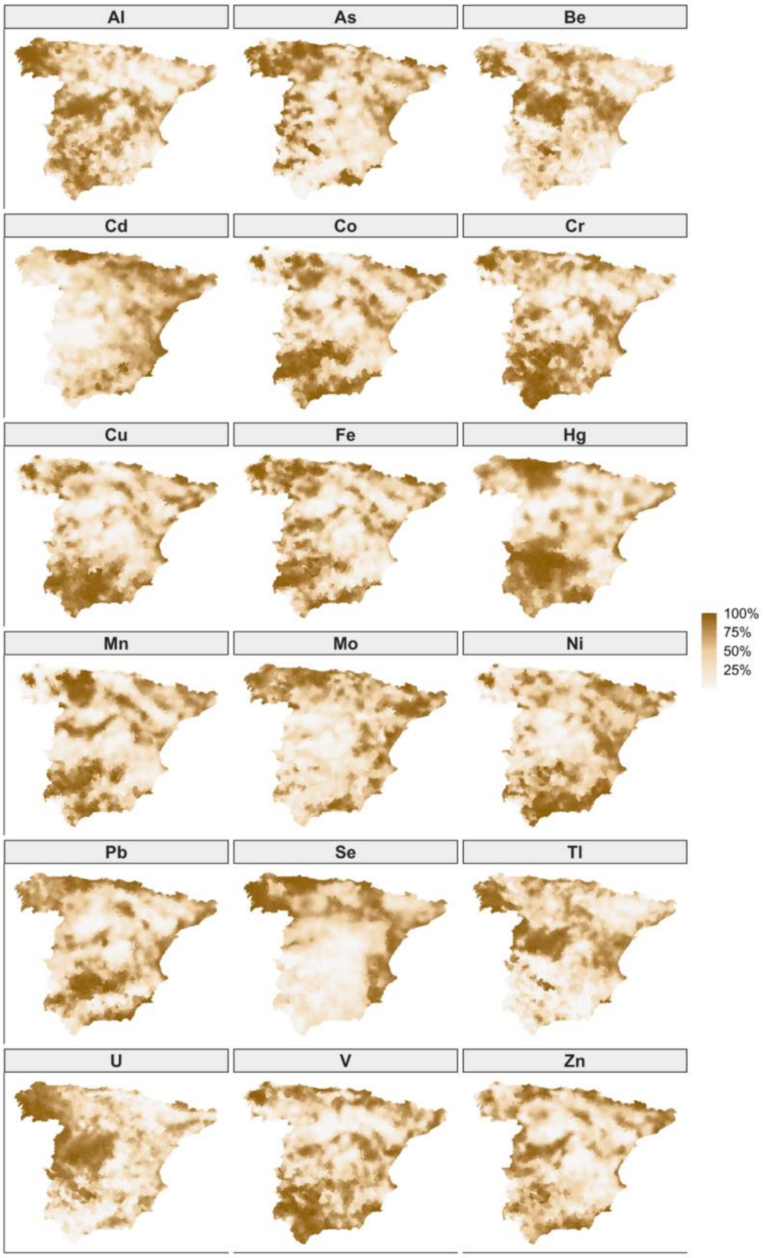


Figure 2. Spatial distribution of estimated metals and metalloids concentrations at the municipal level (the scale is based on the quantiles of the concentration distribution).

3.3. Correlation and Principal Component analysis

There was high correlation among levels of several metal/metalloids topsoil (see **Figure 3 A**), with positive correlation coefficients higher than 0.8 between Mn and Co levels and between Zn and Fe levels, while U had correlation coefficients lower than -0.4 with Cd and Ni.

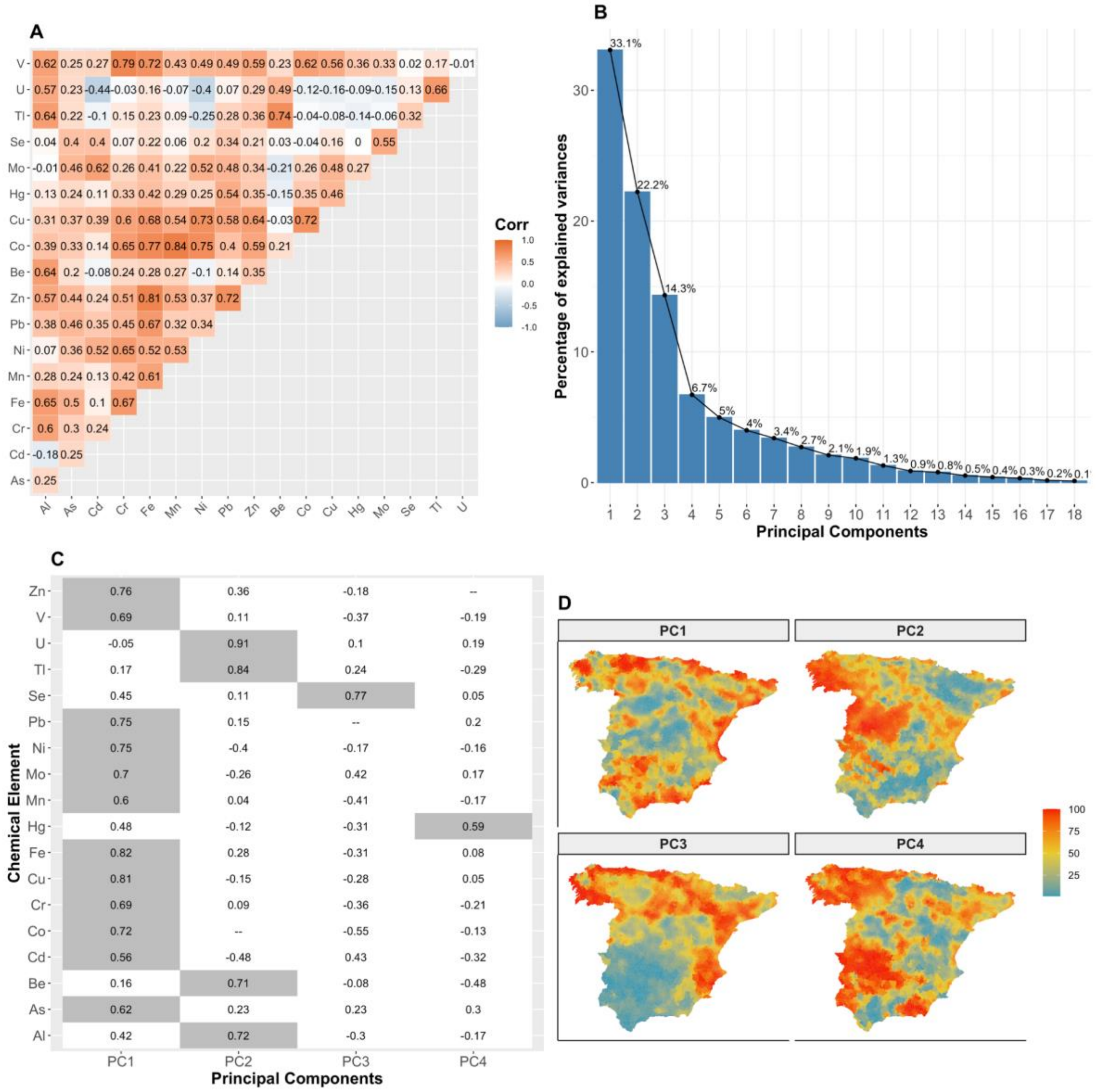


Figure 3. Correlation and Principal Component Analysis of topsoil chemical elements levels. A. Correlation matrix between municipal metal/metalloid topsoil levels. B. Scree plot of the percentage of variations explained by each component principal identified in the analysis. C. Correlation matrix between metals/metalloids in the different PCs (coefficients ≥ 0.5 are highlighted in grey). D. Municipal distribution of PC'scores in percentile scale.

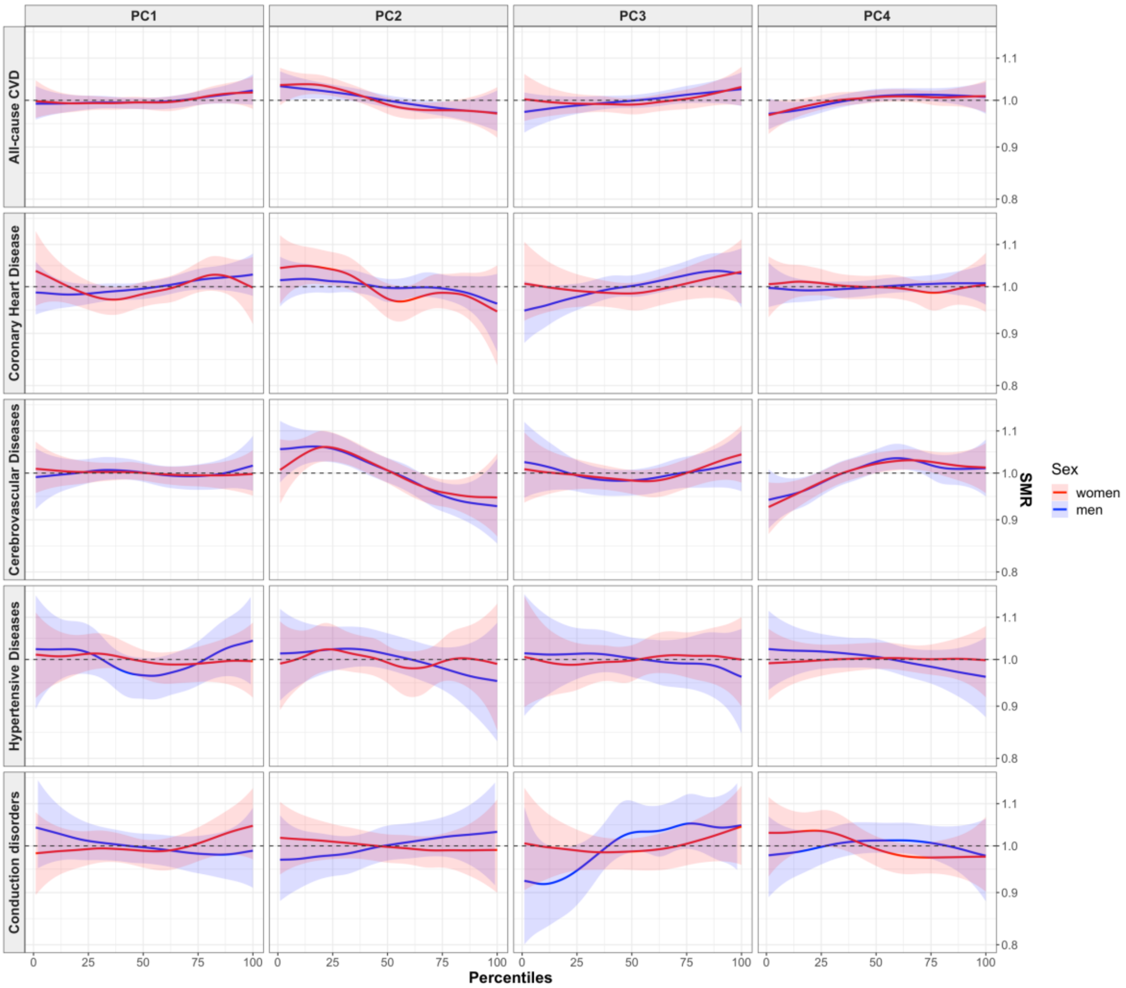
The principal component analysis identified 4 principal components (PCs) accounting for more than 5% of the variance; all together explained 74.3% of the variance (see **Figure 3B**). Each PC is highly correlated (r≥0.5) with a specific subgroup of metals: The first principal component (PC1), reflecting As, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, V and Zn; the second principal component (PC2) reflecting Al, Be, Tl and U; the third principal component (PC3) reflecting Se and the fourth principal component (PC4) reflecting Hg (see **Figure 3C**). In **Figure 2 SM** of Appendix where variable scores in each component are shown, we can observe the aggregations of correlated metals/metalloids in each component described. Supplemental **Table 2 SM** show the PCA loadings that indicate the relative weight of each metal within the corresponding PC.

Table 1 SM of Appendix shows the descriptive analysis of all the metal/metalloids topsoil levels identifying with which component principal they have high correlation (r≥0.5).

Figure 3D shows the municipal distribution of scores for each of the principal components in percentile scale. There are clear geographical patterns for the PC1, PC2, PC3 and PC4. In PC1 the highest values were in the entire coastal strip and southern Spain. In the case of PC2 were located in the northwest and western areas and at other points in eastern regions of the territory. For the PC3, the highest values were mainly observed in the north and in the east. The highest values of PC4 scores were registered in northwest and southwest areas of the country and at other points in eastern regions of the territory.

3.4. Association analysis

The results from the spatial regression models performed to assess the risk of mortality depending on the relative distribution of the levels of metals and metalloids topsoil levels among the towns are shown in **Figure 4 and Table 3.** In general, the associations were quite similar in men and women. For all-cause CVD, we observed a strongly suggestive positive association with PC1 and PC3, and an inverse association with PC2. In sex-specific subgroups, risk of mortality due to CHD was highest in low percentiles (P25) of PC2 (SMR: 1.01, 95%CI (0-99-1.04) in men and SMR: 1.04, 95% CI (1.00-1.08) in women) and high percentiles (P75) of PC3 in men (SMR: 1.03, 95% CI (1.00-1.06)) and in women (SMR:1.01, 95%CI (0.97-1.05)) although in a more marginal way. In regard to cerebrovascular mortality**,** the risk was high at low percentiles (P25) of PC2 (SMR: 1.06, 95%CI (1.02-1.09) in men and SMR: 1.06, 95%CI (1.03-1.10) in women), decreasing afterwards, while the opposite was observed for PC4 (SMR: 1.03, 95% CI (1.00-1.05) in men and SMR: 1.02, 95%CI (1.00-1.05) in women) where the highest risk was at high percentiles (P75). The association between cerebrovascular mortality and PC3 was U shaped in women and men. Only in women an excess mortality from conduction disorders has been found (SMR:1.03, 95%CI (1.00-1.08)) at low percentiles (P25) of PC4. Finally, for Hypertensive diseases and Conduction disorders the patterns were unclear.



All-cause CVD: all-cause cardiovascular diseases

Figure 4. Smooth standardized mortality ratios (SMRs) for cardiovascular diseases by percentiles of the PCs and sex. The purple shaded area corresponds to the overlap of the 95% uncertainty risk bands for men and women.

Mortality	Per	PC1		PC2		PC3		PC4	
		Men	Women	Men	Women	Men	Women	Men	Women
All-cause CVD[a]	P25	0.99(0.98-1.01)	0.99(0.98-1.01)	1.02(1.00-1.04)	1.03(1.01-1.05)	0.99(0.97-1.01)	0.99(0.97-1.01)	0.99(0.97-1.00)	0.99(0.98-1.01)
	P50	1.00(0.98-1.01)	1.00(0.98-1.01)	1.00(0.98-1.01)	0.99(0.97-1.01)	1.00(0.98-1.01)	0.99(0.97-1.00)	1.01(1.00-1.03)	1.01(1.00-1.02)
	P75	1.01(0.99-1.02)	1.01(0.99-1.02)	0.98(0.97-1.00)	0.98(0.96-1.00)	1.01(0.99-1.03)	1.00(0.98-1.02)	1.01(1.00-1.03)	1.01(0.99-1.02)
CHD[b]	P25	0.98(0.96-1.01)	0.98(0.95-1.01)	1.01(0.99-1.04)	1.04(1.00-1.08)	0.98(0.95-1.01)	0.99(0.96-1.03)	0.99(0.97-1.01)	1.01(0.98-1.04)
	P50	1.00(0.97-1.01)	0.98(0.96-1.01)	1.00(0.97-1.02)	0.97(0.93-1.01)	1.00(0.98-1.03)	0.99(0.95-1.01)	1.00(0.98-1.02)	1.00(0.97-1.03)
	P75	1.02(0.99-1.04)	1.02(0.99-1.06)	1.00(0.97-1.03)	0.99(0.95-1.03)	1.03(1.00-1.06)	1.01(0.97-1.05)	1.01(0.99-1.03)	0.99(0.95-1.01)
Cerebrovascular Diseases	P25	1.00(0.98-1.03)	1.00(0.98-1.03)	1.06(1.02-1.09)	1.06(1.03-1.10)	0.99(0.96-1.03)	1.00(0.96-1.03)	0.98(0.95-1.01)	0.98(0.96-1.00)
	P50	1.00(0.98-1.03)	1.00(0.98-1.02)	1.01(0.98-1.03)	1.01(0.98-1.03)	0.98(0.95-1.01)	0.98(0.95-1.01)	1.03(1.00-1.05)	1.02(1.00-1.05)
	P75	0.99(0.96-1.02)	0.99(0.97-1.02)	0.95(0.92-0.98)	0.96(0.93-0.99)	1.00(0.97-1.04)	1.00(0.97-1.03)	1.02(0.99-1.04)	1.03(1.00-1.05)
Hypertensive diseases	P25	1.02(0.97-1.08)	1.01(0.98-1.06)	1.02(0.97-1.08)	1.02(0.98-1.08)	1.01(0.96-1.07)	0.99(0.93-1.04)	1.02(0.98-1.06)	1.00(0.96-1.03)
	P50	0.96(0.91-1.00)	1.00(0.96-1.02)	1.01(0.98-1.06)	0.99(0.95-1.03)	1.00(0.96-1.05)	1.00(0.95-1.03)	1.01(0.98-1.05)	1.00(0.98-1.04)
	P75	0.99(0.94-1.04)	0.99(0.95-1.03)	0.98(0.93-1.03)	1.00(0.95-1.05)	0.99(0.94-1.05)	1.01(0.96-1.06)	0.98(0.95-1.02)	1.00(0.97-1.03)
Conduction disorders	P25	1.01(0.97-1.05)	0.99(0.96-1.03)	0.98(0.93-1.02)	1.01(0.97-1.05)	0.95(0.88-1.00)	0.99(0.95-1.04)	1.00(0.96-1.04)	1.03(1.00-1.08)
	P50	1.00(0.96-1.03)	0.99(0.95-1.01)	1.00(0.97-1.05)	1.00(0.96-1.03)	1.03(0.99-1.11)	0.99(0.95-1.02)	1.01(0.98-1.05)	0.99(0.96-1.02)
	P75	0.98(0.94-1.02)	1.01(0.97-1.04)	1.02(0.98-1.07)	0.99(0.95-1.03)	1.05(0.99-1.12)	1.00(0.96-1.05)	1.01(0.97-1.05)	0.97(0.94-1.01)

a. All-cause CVD: all-cause cardiovascular diseases. b. CHD: coronary heart diseases.

Table 3 Smooth standardized mortality ratios (SMRs) for cardiovascular diseases by percentiles of the PCs and sex. PC1: Zn, V, Pb, Ni, Mo, Mn, Fe, Cu, Cr, Co, Cd, As; PC2: U, Tl, Be, y Al; PC3: Se; PC4: Hg. CHD: Coronary Heart Disease; Per: percentiles.

Because the associations were quite similar in men and women, we have also included a figure in the appendix (**Figure 3 SM)** with the results from the regression models performed to assess the risk of mortality for both sexes. These results showed more clearly the associations found when there are no differences between the sexes. For example, the associations found for CHD or Cerebrovascular mortality and PC2, or Cerebrovascular mortality and PC4.

4. Discussion

CVD mortality present a clear geographical pattern in Spain that suggests the existence of underlying environmental factors. In this ecological analysis we observed that some metal and metalloid levels in topsoil may be playing a role in the distribution of the mortality due to these group of diseases. Our results specifically point towards a positive associations between: (i) principal component scores reflecting Al, Be, Tl and U topsoil levels with mortality due to cerebrovascular disease and CHD at the lowest, but not highest, scores range, in both women and men; (ii) PC scores reflecting Hg topsoil levels with mortality due to cerebrovascular disease among men and women alike; and (iii) PC scores reflecting Se topsoil levels with mortality due to CHD in men at the highest scores range. Our results also show a strongly suggestive positive association between all-cause cardiovascular diseases mortality and PC1 scores partly reflecting metals such as Pb, As, Cu or Cd.

The spatial distribution of each metal in topsoil across the country is not independent of the other metals. Therefore, we opted for defining four “patterns of metals in topsoil”. in a similar way that a-posteriori patterns of diets are defined, and explored their association with the risk of death due to cardiovascular diseases. With this approach, perhaps one of the most striking results is the almost inverse association of CHD and cerebrovascular mortality in municipalities with scores at PC2, mainly reflecting levels of Al, Be, Tl and U in topsoil. These metals have not been previously associated with cardiovascular mortality (31), and this association may seem counterintuitive, as all these metals are toxic, and, in addition, uranium and some isotopes of thallium are radioactive elements. It should be noted that the map of natural gamma radiation in Spain elaborated in the MARNA Project (32) shows a spatial distribution very similar to the one observed for PC2 (see **Figure 3D**). Therefore, what we may be partly assessing is the effect of ionizing radiation emitted by the soil elements above mentioned in cardiovascular mortality.

The association of ionizing radiation and cardiovascular diseases mortality has been previously observed. Epidemiological and clinical studies show that radiation exposure can induce cardiovascular and cerebrovascular mortality (33). High doses of radiation exposure (> 150 mSv) have been associated with cardiovascular diseases among workers (34,35,35,36). The effect on cardiovascular disease of exposure to low doses of radiation has been more controversial. Among workers from the Mayak production association (Russian Federation) was found that the incidence of stroke increased from gamma rays doses greater than 0.1 Sv (Azizova, et al. al, 2014) (37). Loganovsky et al. (2011) proposed considering stroke and some neuronal and mental disorders with high risk of radiation exposure as a stochastic effect of low radiation dose (38). The Shcolbergern study applied to the Mayak cohort of workers (Simonetto et al. 2015)(39) shows a sublinear dose-response for low and medium dose stroke mortality (0-1.4 Gy) and for CHD (0-3Gy). It should also be noted that the excess risk found is only observed at low concentration levels of the metals and that the risk behaviour at the different levels does not seem to be linear. This fact agrees with the results found by Anderson JL et al (40). They observed an association between radiation and stroke and CHD mortality at lower internal doses of radiation using non-linear dose-response models (39).

Another noteworthy result is the excess risk of cerebrovascular mortality observed in municipalities with high percentiles of PC4, mainly reflecting topsoil levels of Hg. These data suggest that the presence of high Hg levels in topsoil might give rise to a population exposure to this metal, and are consistent with the available evidence of the association between exposure to this element and this disease (41–43).

Our results also show a marginal excess of CHD mortality in municipalities at the lowest scores range of PC3 (reflecting Se topsoil levels) mainly in men. The evidence of association between exposure to Se and CHD is still inconclusive. Observational studies showed an inverse association between selenium concentrations and CHD incidence (44). Since our results are not clear, and it is difficult to know the real exposure to selenium that people may have from its presence in the topsoil, the result should be considered with great caution. Nevertheless the U-shape found in the literature when analysing the effect of Se (45) on population´s health can be seen in our study for cerebrovascular mortality although the confidence intervals where wide.

It is of interest to view that, in general, the excess risks observed were found in both sexes which might be indicative of specific environmental exposures. Moreover, the magnitude of risks found is small and in line with the environmental risks shown in other works (11,21,22) and the behaviour of the risk of mortality as a function of the levels of metals or metalloids is not linear in most of the cases.

A strongly suggestive positive association between all-cause cardiovascular diseases mortality and PC1 scores (partly reflecting Zn, V, Pb, Ni, Mo, Fe, Cu, Cr, Co, Cd and As) was also found. This is consistent with available evidence supporting that Pb, As, Cd are cardiovascular risk factors(4) despite the low concentrations of metals in soils and the ecological study design. The biomarker study developed by Domingo-Relloso et al. in the Spanish population observed that Cu, Zn, Sb, Cd, Cr and V in urine, at relatively low levels, were positively associated with all-cause cardiovascular incidence, individually and as mixture (46). Alternatively, in a study conducted in China (47) adjustment for multiple metals attenuated the associations observed in single-metal analysis. This study however, did not evaluate interactions between metals and was challenged by the fact that simultaneously modelling correlated metals can be problematic in the setting of standard linear regression(48).

To the best of our knowledge, no previous studies have assessed the association between metal or metalloid levels in topsoil with cardiovascular mortality, possibly due to the lack of related geographic information. Our study encompasses the whole of mainland Spain, contains an estimate of 18 chemical elements for close on 8.000 towns obtained from a mesh of more than 13.000 sampling points and covered a broad study period over 5 years. Statistical analysis was performed using hierarchical models with spatial components where the risk of falling into the ecological fallacy is minimised by using a very small spatial scale and making no inferences at an individual level (49). We also include principal components in the analysis, instead of assessing the individual effect of each metal on cardiovascular mortality. Given the strong correlation between metals, it is unclear whether or not the individual effect of one metal is a result of the effect of other metals on mortality. Moreover, statistical analysis also took into account possible non-linear associations between mortality risk and topsoil levels and an effort was made to control possible confounders by including a series of sociodemographic components as variables of adjustment in models.

The main limitations of our study are related to the ecological design, and especially relevant is the fact that we had available data grouped by municipality. The study assumed that metal or metalloid topsoil levels determined each town's population exposure, and data on possible other important confounding variables, such as smoking habit, lifestyle factors, diet or other exposures are not taken into account. Other limitation of this type of studies lies in their lack of speciation of the element that determines the potential bioaccessibility and bioavailability of the elements.

5. Conclusions

To conclude, in our data, PC reflecting the presence of Al, Be, Tl and U in topsoil at low, but not high, doses, which might give rise to a population exposure to radiation, was positively associated with the municipal risk of cerebrovascular and CHD mortality. Furthermore, PC reflecting the presence of Hg at medium or high doses in topsoil was associated with cerebrovascular mortality. Our results also show marginal excess of coronary heart disease mortality at low doses of Se in men. Finally, we observed a strongly suggestive positive association between PC partly reflecting Pb, As, Cu or Cd with all-cause cardiovascular diseases mortality. Further studies are needed to verify these results, such as meta-analysis of prospective studies using exposure biomarkers, and also, mechanistic studies to understand the biological implications of our findings.

Contributors

Ana Ayuso Alvarez: Conceptualization, formal analysis and writing original draft, writing review and editing; Olivier Nuñez: Conceptualization, methodology, formal analysis, and writing review and editing. Pablo Fernandez Navarro: Conceptualization, methodology, formal analysis, resources, writing original draft, writing review and editing, Iñaki Galan: Conceptualization, review and editing. Iván Martín Méndez, Alejandro Bel Lan, María Tellez, Beatriz Perez Gómez: review and editing.

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Declaration of interests

All authors declare no competing interests. This article presents independent research. The views expressed are those of the authors and not necessarily those of the Carlos III Institute of Health, Spain. (Instituto de Salud Carlos III (ISCIII)).

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Appendix: Supplementary material

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Graphical abstract

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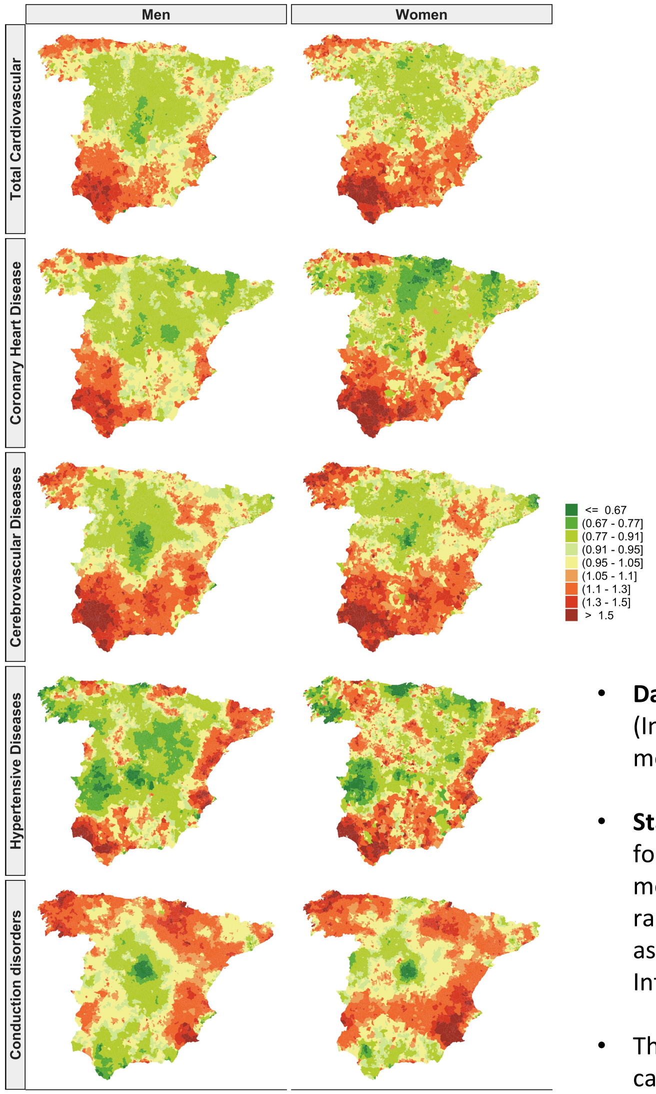
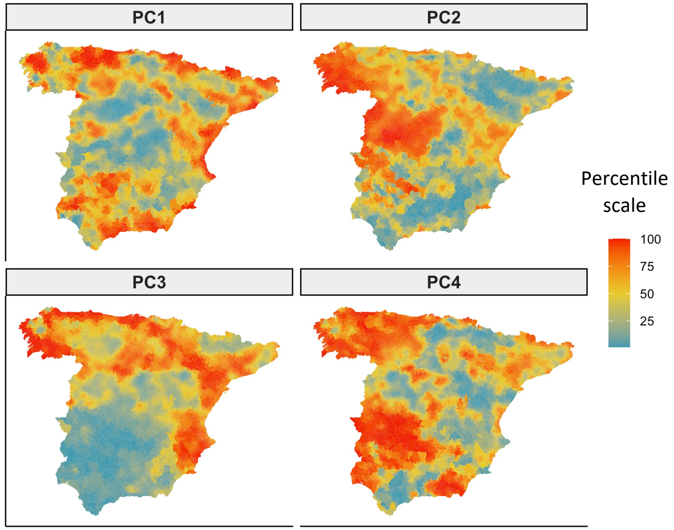
Metal and metalloid levels in topsoil and municipal cardiovascular mortality in Spain

Municipal distribution of the Relative Risks (RRs)



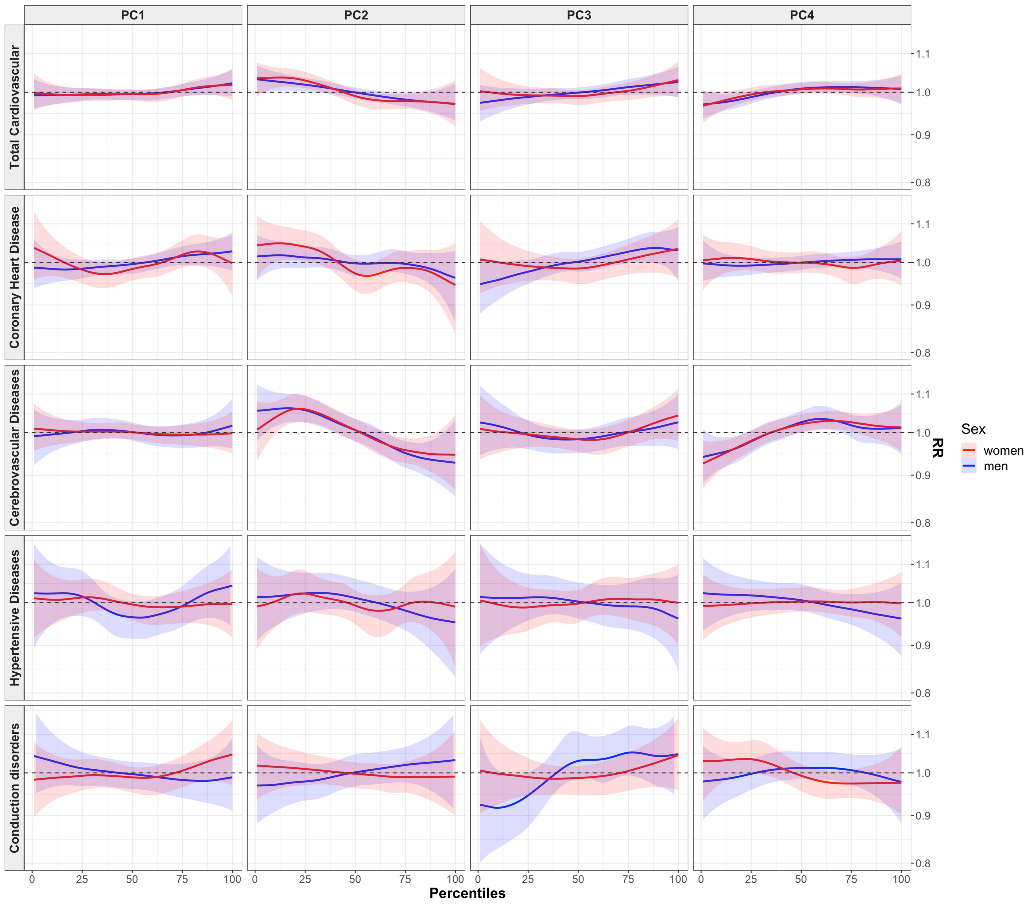
Municipal distribution of principal component scores of metals/metalloid topsoil levels.



PC1= As, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, V and Zn; PC2= Al, Be, Tl and U; PC3= Se; PC4= Hg

- **Data:** Municipal cardiovascular mortality (Spanish Statistical Office (Instituto Nacional de Estadística – INE), 2010-2014). Metals and metalloids concentration in topsoil (Geochemical Atlas of Spain).
- **Statistical Analysis:** Bayesian Hierarchical Poisson Regression Models for mortality maps. Principal component analysis (PCA) of metal/metalloids. Bayesian models with penalized spline (second-order random walk) to model the dose-response curve (in percentile scale) associated to each principal component. Methods of Bayesian Inference: INLA.
- There is a geographical pattern in the distribution of municipal cardiovascular mortality and topsoil metal/metalloid levels.

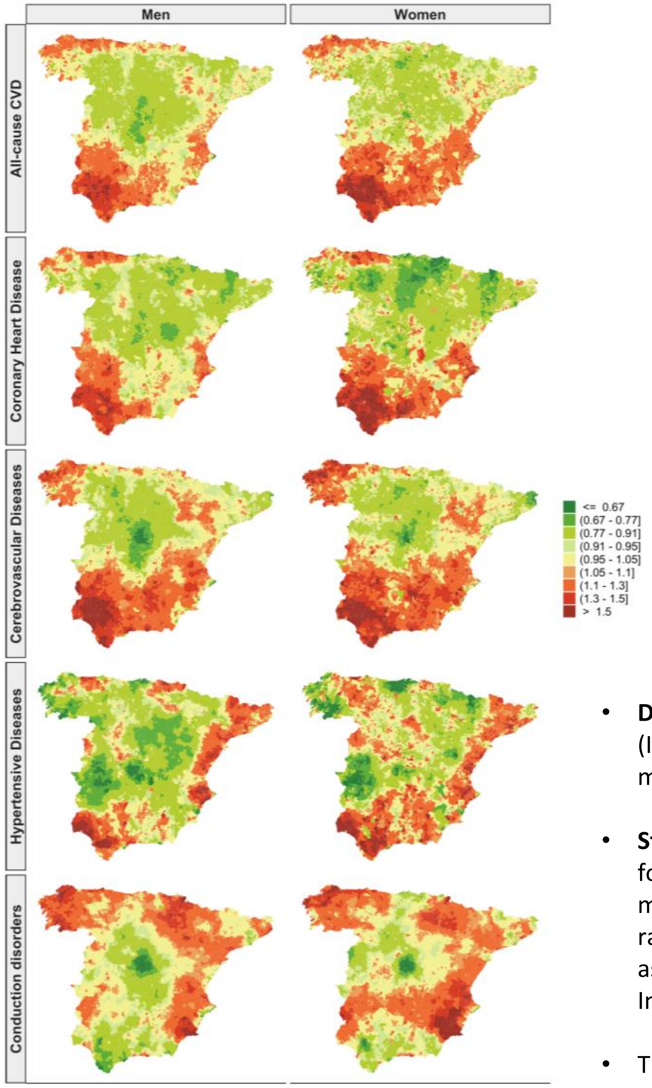
Relative risks of mortality due to cardiovascular diseases by percentiles of the PCs



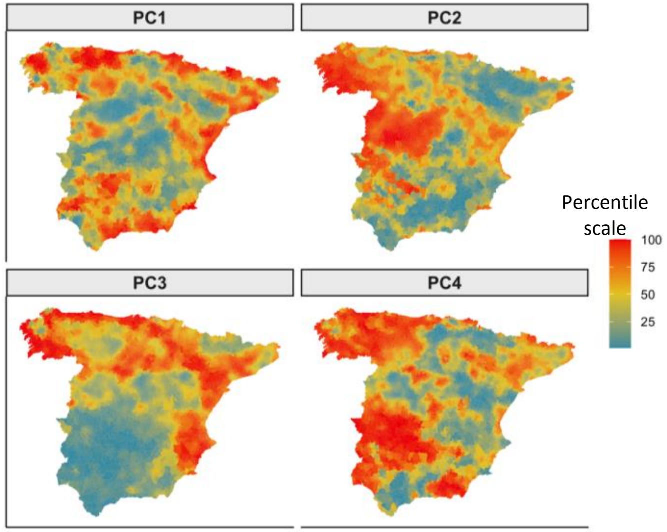
- Al, Be, Tl and U (PC2) in topsoil associated with an excess of Cerebrovascular and CHD mortality in women and men.
- Se (PC3) in topsoil associated with CHD mortality in women and men, and Hg (PC4) in topsoil associated with Cerebrovascular mortality among men and women alike.

Metal and metalloid levels in topsoil and municipal cardiovascular mortality in Spain

Municipal distribution of the smooth standardized mortality ratios (SMRs)



Municipal distribution of principal component scores of metals/metalloids topsoil levels.



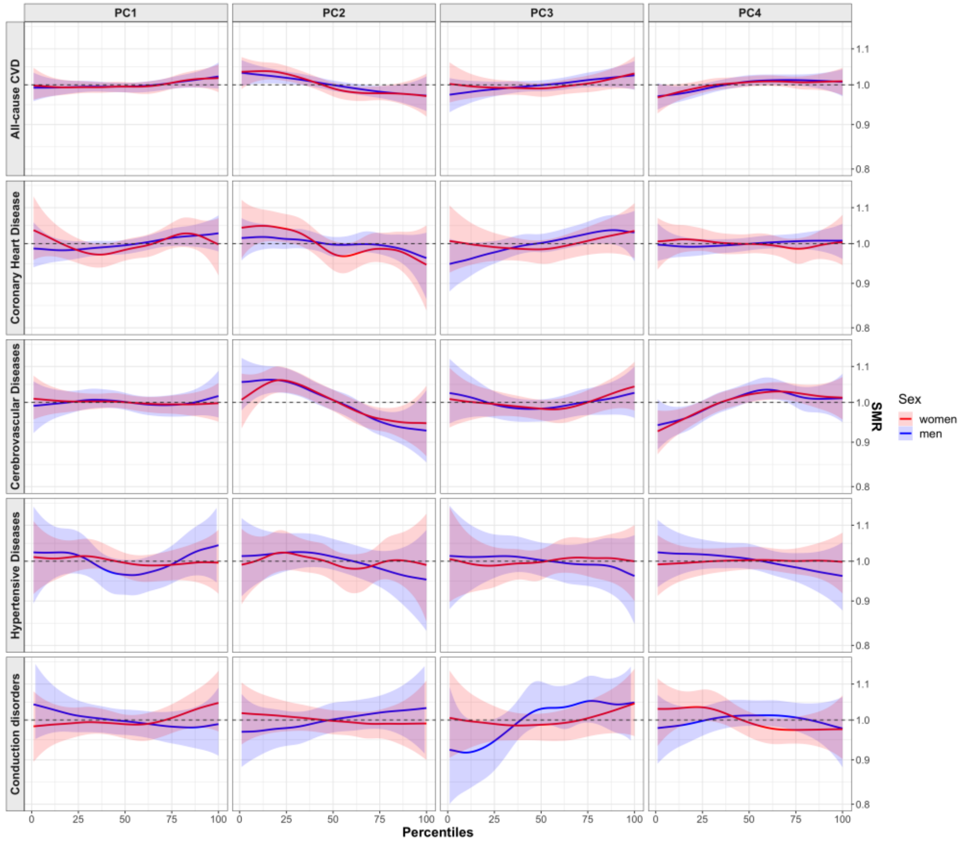
PC1= As, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, V and Zn; PC2= Al, Be, Tl and U; PC3= Se; PC4= Hg

- **Data:** Municipal cardiovascular mortality (Spanish Statistical Office (Instituto Nacional de Estadística – INE), 2010-2014). Metals and metalloids concentration in topsoil (Geochemical Atlas of Spain).

- **Statistical Analysis:** Bayesian Hierarchical Poisson Regression Models for mortality maps. Principal component analysis (PCA) of metal/metalloids. Bayesian models with penalized spline (second-order random walk) to model the dose-response curve (in percentile scale) associated to each principal component. Methods of Bayesian Inference: INLA.

- There is a geographical pattern in the distribution of municipal cardiovascular mortality and topsoil metals/metalloids levels.

Smooth standardized mortality ratios (SMRs) by percentiles of the PCs and sex



- At the lowest component scores range, PC2 (mainly reflecting Al, Be, Tl and U) was positively associated with coronary heart disease and cerebrovascular mortality in women and men.
- At medium/highest scores range, PC4 (mainly reflecting Hg) was positively associated with cerebrovascular mortality in men and women
- At the highest PC scores range, PC3 (reflecting Se), was positive associated with coronary heart disease mortality only in men.
- Strong suggestive positive association between all-cause CVD mortality and PC1 (partly reflecting metals such as Pb, As, Cu or Cd).

Credit Author Statement

Ana Ayuso Alvarez: Conceptualization, formal analysis and writing original draft, writing review and editing; **Olivier Nuñez**: Conceptualization, methodology, formal analysis, and writing review and editing. **Pablo Fernandez Navarro**: Conceptualization, methodology, formal analysis, resources, writing original draft, writing review and editing, **Iñaki Galan:** Conceptualization, review and editing. **Iván Martín Méndez, Alejandro Bel Lan, María Tellez, Beatriz Perez Gómez**: review and editing.