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REVIEW PAPER

Cadmium (Cd) and Lead (Pb) topsoil levels and incidence of childhood leukemias

Santiago Asenjo · Olivier Nuñez · Jordi Segú-Tell · Elena Pardo Romaguera · Adela Cañete Nieto · Iván Martín-Méndez · Alejandro Bel-lan · Javier García-Pérez · Alberto Cárceles-Álvarez · Juan Antonio Ortega-García · Rebeca Ramis

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Abstract There are few well-established risk factors for childhood leukemias. While the frequency of childhood leukemias might be partially attributable to some diseases (accounting for a small fraction of cases) or ionizing radiation, the role of heavy metals has not been assessed. The objective of our study was to assess the potential association between levels of cadmium (Cd) and lead (PB) in soil and childhood leukemias incidence. We conducted a population-based case–control study of childhood leukaemia in Spain, covering 2897 incident cases gathered from the Spanish Registry of Childhood Tumours and including 14 Spanish Regions with a total population of 5,307,433 children (period 1996–2015). Cd and Pb bioavailable levels at every children's home address were estimated using data from the Geochemical Atlas of Spain. We used logistic regression to estimate odds ratios (ORs) and their 95% confidence intervals (95%CIs); we included as covariates: sex, rurality, employment rate and socioeconomic status. Metal levels were analysed according to two definitions: as continuous variable assuming linearity and as categorical variables to explore a potentially nonlinear

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S. Asenjo
C.H.U. Insular-Materno Infantil, Gran Canaria, Spain

O. Nuñez · J. Segú-Tell · J. García-Pérez · R. Ramis (✉)
Cancer and Environmental Epidemiology Unit, National Centre of Epidemiology, Carlos III Institute of Health, Madrid, Spain
e-mail: rramis@isciii.es

O. Nuñez · J. Segú-Tell · J. García-Pérez · R. Ramis
Centre for Biomedical Research in Epidemiology & Public Health (CIBER Epidemiología y Salud Pública - CIBERESP), Madrid, Spain

E. Pardo Romaguera · A. Cañete Nieto
Spanish Registry of Childhood Tumours (RETI-SEHOP), University of Valencia, Valencia, Spain

A. Cañete Nieto
H. Universitario y Politécnico La Fe, Valencia, Spain

I. Martín-Méndez · A. Bel-lan
Instituto Geológico y Minero de España, Madrid, Spain

A. Cárceles-Álvarez · J. A. Ortega-García
Paediatric Environmental Health Speciality Unit, Department of Paediatrics, Institute of Biomedical Research, IMIB-Arrixaca, Clinical University Hospital Virgen de la Arrixaca, Murcia, Spain

A. Cárceles-Álvarez · J. A. Ortega-García · R. Ramis
European and Latin American Environment, Survival and Childhood Cancer Network (ENSUCHICA), Murcia, Spain

association (quantiles). Increases in both Cd and Pb topsoil levels were associated with increased probability of childhood leukemias incidence. The results for the models with the continuous variables showed that a unit increase on the topsoil level was associated with an OR of 1.11 for Cd (95%CI 1.00–1.24) and an OR of 1.10 for Pb (95%CI 0.99–1.21). Our study may point towards a possible link between residential Cd and Pb topsoil levels and the probability of childhood leukemias incidence. Residing in a location with the highest concentrations of these heavy metals compared to those locations with the lowest could increase the risk around a 20%, for both Cd and Pb.

Keywords Childhood cancer · Heavy metals · Topsoil · Environmental exposure

Introduction

Despite low incidence and drastic improvements in survival rates during the last few decades (Marcos-Gragera et al., 2017), cancer remains the most common cause of death among 0–14 year old in Spain ("Defunciones por causas (lista reducida), sexo y edad.," n.d., 2018). It occurs more frequently in boys than in girls, and the largest group of cases consists of childhood leukemias (CL); these account for roughly a third of cases. The most frequent subtypes during the period 1990–2017 were acute lymphoblastic leukaemia (ALL) (79%) and acute myeloid leukaemia (AML) (16%), what is expected and similar to other European countries (Pardo Romaguera E. et al., 2019; Steliarova-Foucher et al., 2017).

The aetiology of childhood leukemias is mostly unknown. Up until now, the risk factors that have been consistently demonstrated are ionizing radiation and certain genetic factors such as Down's Syndrome (Mezei et al., 2014); however, these only explain a small proportion of cases (Schüz & Erdmann, 2016). In the past decades, several international studies have pointed out that abnormal infection patterns to common infections could be risk factors although the evidence is still unclear (Greaves, 2018). Concerning environmental factors there are a number of suspected associations, (McNally et al., 2002), with exposure to tobacco smoke (Chunxia et al., 2019) as well as exposure to environmental factors such as: radon (Tong et al., 2012), electromagnetic radiation (Zhao et al., 2014), benzene (Carlos-Wallace et al., 2016), paints in the home, pesticides (Bailey et al., 2014), air pollution (Filippini et al., 2015), proximity to industrial areas (García-Pérez et al., 2015) and cultivated fields (Gómez-Barroso et al., 2016), as well as proximity to roads (Tamayo-Uria et al., 2018) and socioeconomic conditions (Kroll et al., 2011) among others (Schüz & Erdmann, 2016).

With the aim of filling this gap in childhood cancer aetiology, more hypotheses are generated and one of them is the potential association between the heavy metals exposure, cadmium (Cd) and lead (Pb), and childhood leukemias. This is an emerging hypothesis that could be plausible for several reasons: First, they are considered carcinogenic by the IARC—with cadmium categorised as known and lead as probable ("IARC Monographs—Monographs available in PDF format," n.d., 2011). Their potential association with childhood leukemias, however, has been little studied, although there are studies whose results could provide indications of such an association. These include an ecological study from the University of California (Heck et al., 2014), which found an association between atmospheric lead levels during pregnancy and ALL incidence. Recently, a population-based case–control study carried out in Spain found an association between leukemias incidence in children and proximity to steel industries (García-Pérez et al., 2015). Other studies have measured the lead and cadmium levels in biological samples taken from leukemias patients; for example, a study in Egypt found higher cadmium levels in childhood leukaemia cases than in the controls (Sherief et al., 2015). Another study in Turkey found higher lead and cadmium levels in adult leukaemia patients than in the controls (Demir et al., 2011). An association between leukemias and Cd and Pb exposure has also been found in animal-based studies (Blakley, 1987; Furst et al., 1976; Krugner-Higby et al., 2001; Waalkes & Rehm, 1992).

On the other hand, the population has a generalized exposure to heavy metals due to their ubiquity in the environment, and this exposure is greater among children as a result of their greater capacity to absorb such metals and particular habits that increase oral exposure to soil and dust (hand to mouth activities) (International Agency for Research on Cancer and International Agency for Research on Cancer, 2006;

International Agency for Research on Cancer and Weltgesundheitsorganisation, 2012). Both lead and cadmium are naturally present in the environment, but due to the contamination generated by human activity the levels present increased sharply during the last century. Cd contamination is generated by activities like mining, refining metals, the manufacture and application of fertilizers, the use of fossil fuels and waste incineration (International Agency for Research on Cancer and Weltgesundheitsorganisation, 2012; Rodríguez Eugenio et al., 2018). In the past, Pb was used in a wide variety of products, such as petrol, paint, pipes and canned food, which lead to an increase in the levels found in the general population. This resulted in restrictions in Pb use being introduced, such as the prohibition of leaded petrol in many countries. These measures were effective in reducing the general population's exposure (International Agency for Research on Cancer and International Agency for Research on Cancer, 2006). Soil is the final repository for heavy metals, where it may still come into contact with both air and water. Heavy metal movement from the ground is limited: these metals do not degrade and remain in the soil for long periods—an indicator of an area's prior contamination (Ali et al., 2013). From the soil, Cd and Pb can contaminate humans, principally by passing into the food chain through plants but may also do so through dust produced by erosion or by direct contact (International Agency for Research on Cancer and International Agency for Research on Cancer, 2006; International Agency for Research on Cancer and Weltgesundheitsorganisation, 2012, p. 100; Rodríguez Eugenio et al., 2018).

Investigation into the health effects of these heavy metals has primarily been conducted in cohorts of workers with high-dose exposures or in animal experiments. As a result, less is known about the effects of chronic low-dose exposures (International Agency for Research on Cancer and International Agency for Research on Cancer, 2006; International Agency for Research on Cancer and Weltgesundheitsorganisation, 2012, p. 100). This is the kind of exposure that results from contaminated land. The health effects of this kind of exposure have been investigated through epidemiological studies in contaminated areas, or in those where an excess mortality from cancer has already been identified (Fei et al., 2018). There have also been exploratory ecological studies in Taiwan (Huang et al., 2013), Scotland (McKinley et al., 2013) and, more recently, in Spain (Núñez et al., 2016). These studies were carried out across the whole population, considering different types of heavy metals and all types of cancers.

Spain has two high-quality sources of information for studying this novel hypothesis about potential relationships between soil heavy metals and childhood cancer, e.g. leukemias. The Spanish Registry of Childhood Tumours (Pardo Romaguera E. et al., 2019) is the largest childhood cancer registry in the country, covering the entire country and more than 90% of the incidence of childhood tumours in Spain.

The Geochemical Atlas of Spain (Locutura et al., 2012) provides a precise record of the geochemical characteristics of soils in Spanish territory. Taking advantage of the geospatial data offered by both sources, it is possible to estimate heavy metal levels at places of residence by using interpolation models.

The objective of this study is to evaluate a potential ecological association between Cd and Pb levels in the topsoil and childhood leukemias incidence in various Spanish regions.

Methodology

Study population

This study forms part of a larger research project focused on analysing the effects of environmental risk factors on childhood cancer using cases and controls' geographical locations. More specific details about the project can be found in previous publications (García-Pérez et al., 2019; Gómez-Barroso et al., 2013).

This is a population-based case–control study. We studied the population of 14 autonomous communities in Spain: Andalusia, Asturias, Aragon, Cantabria, Castilla La Mancha, Catalonia, the Valencian Community, Extremadura, Galicia, La Rioja, Madrid, Murcia, Navarre and the Basque Country. All subjects aged 0–14 years old during the period 1996–2015 were included. The autonomous community of Castilla y León and four provinces of Andalusia (Córdoba, Seville, Cádiz and Huelva) were not included in the study.

The cases of childhood leukaemia included are in Group I of the third edition of the "International Classification of Childhood Cancer" (ICCC-3): ALL, AML, Chronic myeloproliferative diseases (l.c), myelodysplastic syndrome and others myeloproliferative syndromes (l.d) and unspecified and other specified leukemias (l.e) (Steliarova-Foucher et al., 2005).

A total of 2897 cases in children 0–14 years old were identified through the Spanish Registry of Childhood Tumours for the period 1996–2016. RETI-SEHOP is a central registry in which all the paediatric onco-haematology units in Spain participate and which collaborates with the regional registries to increase coverage and information. It covers the entire country capturing more than 90% of tumours nationally and close to 100% in Aragon, Catalonia, the Basque Country, Madrid and Navarre (Pardo Romaguera E. et al., 2019).

Population data for the entire at-risk population were obtained from the birth registry of the Spanish Statistical Office, resulting in information for a total of 5,307,443 children ("Instituto Nacional de Estadística. (National Statistics Institute)," n.d., 2017).

Georeferencing of cases and controls

For the cases, the geographical coordinates were obtained from the postal addresses at the time of the diagnosis, which are included in the RETI-SEHOP database. For this, we used the APIs of GoogleMaps and Cartociudad (an application built by the Spanish national cartographic system). The addresses were geocoded twice, once with each API. The coordinates were then validated by calculating the distance between the two points, with the coordinates of the addresses which did not pass this validation completed manually. Finally, the coordinates were plotted in the ETRS89 30 N reference system.

The coordinates of the reference population were provided by the INE, which collects the mother's address at birth of the child. For privacy, these coordinates were altered by introducing a random error of 30 m.

Socioeconomic factors: activity rate and socioeconomic status (SES)

Activity rate measures the level of employment activity. It is calculated as the ratio between the active population (AP) and the population of working age or over 16 years. The SES was obtained from the 2001 Population and Housing Census (the last census where this variable was calculated) using the occupation of the head of the family. The SES is an index that varies between 0.46 and 1.57; lower values are associated with lower SES and higher values with a better socioeconomic situation ("Instituto Nacional de Estadística. (National Statistics Institute)," n.d., 2017). In both cases, since the individual data were not available, each subject was assigned the value of their corresponding census tract.

Region

The region in which each child was resident, at diagnosis for cases and at birth for controls, was included in the model as a random effect to control for the differences between Spain's different autonomous communities.

Type of municipality

To control for the risk factors particular to specific urban areas (Tamayo-Uria et al., 2018), we constructed the variable 'Type of Municipality'. Municipalities with more than 75,000 inhabitants were identified from the 2010 Spanish Statistical Office population data. For each of these areas, we used data from the EU Environment Agency's CORINE land cover inventory ("CORINE land cover 2006," 15AD) in order to get the limits of the inhabited area within the municipality. Finally, we considered the children whose home coordinates were within the selected areas as 'urban', and the children whose home coordinates were outside the selected areas as 'rural'.

Soil heavy metal sampling and analysis

The metals included in this study were Cd and Pb. The data for heavy metal levels in the soil were obtained from the Geochemical Atlas of Spain, produced by Locutura et al. from the Spanish Geological and Mining Institute. Between June 2008 and November 2010, the Institute carried out a geochemical analysis of the topsoils across Spanish territory, producing a geo-referenced geochemical dataset (Geological Survey of Spain). Exposure to heavy metals/metalloids was estimated based on topsoil (top 20 cm) level data from 21,187 samples that were collected from 13,505 sampling points, 13,317 in the peninsula, distributed according to the population density or industrial areas of up to 1 sample/10 km2. The soil samples were analysed using several multielemental techniques in order to get both total and bioavailable content. For the present study, we used the bioavailable content of heavy metals in topsoil. More detail about the sampling and the techniques used in the analysis can be found in the atlas itself and previous publications (Locutura et al., 2012; López-Abente et al., 2018; Núñez et al., 2016).

Exposure coding

We used an interpolation-based methodology to assess the metal concentration levels at the subjects' coordinates. For observations of the cj metal concentrations at the sj sampling points, this logarithmic linear model was employed:

$$Log(cj) = Normal(xj,\ \sigma 2x)$$

xj is the realization of a spatial process at locations sj and $\sigma 2x$ is the variance of the measured error. This spatial process models the variations in metal concentration in the peninsula and was approximated using a grid of Spanish surface territory. This normal distribution was approximated using the stochastic partial differential equation (SPDE). Using this approach, we made a triangulation network from the sampling points across Spain's surface. This model allowed us to estimate exposure at the desired coordinates with the corresponding confidence intervals ("An explicit link between Gaussian fields and Gaussian Markov random fields: the stochastic partial differential equation approach Lindgren - 2011-Journal of the Royal Statistical Society: Series B (Statistical Methodology) - Wiley Online Library," n.d., 2011).

Statistical analysis

The association between the estimation of heavy metal exposure and cancer incidence was estimated by calculating the OR and its 95% confidence interval using logistic regression (Pearce, 2016).

The logistic regression analysis was adjusted for the variables sex, region, socioeconomic level, activity level, type of municipality (rural or urban) and for both Cd and Pb. For this analysis, we used the software package R, Version 3.6.2 (2019-12-12).

Data protection

The protection of confidential data has been carried out in accordance with the provisions of Chapter V of Regulation (EC) No. 223/2009 of the European Parliament and of the Council of 11 March 2009.

Results

Table 1 shows the distribution of cases by histologic subgroup. Of these, ALL was the most common with more than the 80% of the cases, followed by AML with more than 15%. Childhood cancer cases were more frequently in male than female cases overall and all subgroups. The mean age at incidence varied depending on the type, from 3.61 years for myelodysplastic syndrome and other myeloproliferative diseases to 7.48 for AML. The average activity rate of the cases was similar between the subgroups and the overall population, and the same happens with the socioeconomic status. There were slightly more cases in urban areas, than for those residing in rural; although for the total population, there were a slightly greater number living in rural areas. Of the subgroups, myelodysplastic syndrome and other myeloproliferative diseases [I(d)] was the most frequent in rural areas with 26 cases.

Table 2 shows the distribution of the cases by autonomous community and according to histologic subgroup. The autonomous communities with the most cases were Madrid, Catalonia; the Valencian Community and Andalusia (eastern provinces), respectively.

Table 3 describes the average topsoil concentration levels for Cd and Pb in the control group and by histologic subgroup. For both metals, levels range in the general population were wider than in the cases, nevertheless median values were higher for all leukemias subgroups in both metals but for Cd levels in l.c.

Table 4 shows the results of the multivariate logistic regression analysis. For all of the childhood leukemias, we included the results of the model with both Cd and Pb. It shows the results with the variables as continuous, as well as unadjusted and adjusted for the covariates sex, autonomous community, socioeconomic status, activity level and municipality type. It also shows the variables broken into quartiles adjusted

Table 1 Description of the population and cases by subgroup

Population		Cases					
		ALL	AML	I.c	I.d	I.e	Total
Total (%)	5,307,443(100)	2322(80.15)	461(15.91)	33(1.14)	49(1.69)	32(1.10)	2897(100)
Sex (%)							
Male	2,736,998(51.57)	1,293(44.63)	242(8.35)	18(0.62)	25(0.86)	18(0.62)	1,596(55.08)
Female	2,570,445(48.43)	1,028(35.48)	219(7.56)	15(0.52)	24(0.83)	14(0.48)	1,300(44.87)
Mean age at incidence (years) (SD)	–	5.13(3.37)	4.76(4.05)	7.48(4.51)	3.61(3.91)	5.62(4.50)	5.07(3.53)
Activity rate % mean (SD)	75.79(5.57)	76.04(5.6)	76.10(5.3)	76.6(5.8)	76.7(4.7)	76.6(6.0)	76.04(5.54)
Socioeconomic Condition. Mean (SD)	1.02(0.14)	1.03(0.14)	1.02(0.13)	1.01(0.16)	1.04(0.13)	1.02(0.15)	1.03(0.14)
Municipality Type (%)							
Urban (%)	2,570,328(48.42)	1205(51.89)	254(55.10)	19(57.58)	23(46.94)	17(53.12)	1518(52.40)
	2,737,115(51.57)	1,117(48.11)	207(44.90)	14(42.42)	26(53.06)	15(46.88)	1,379(47.60)

Number of individuals, sex, average age at incidence, average activity rate, average socioeconomic status and municipality type

ALL: lymphoid leukemias; AML: acute myeloid leukemias; I.c: chronic myeloproliferative diseases; I.d: myelodysplastic syndrome and other myeloproliferative diseases and I.e: unspecified and other specified leukemias

Table 2 Distribution of cases by autonomous community

Autonomous community	Population	Cases					
		ALL (%)	AML (%)	I.c (%)	I.d (%)	I.e (%)	Total (%)
Andalusia	589,433(11.11)	236 (10.16)	41(8.89)	4(12.12)	5(10.20)	2(6.25)	288(9.94)
Aragon	183,931(3.47)	67 (2.89)	16 (3.47)	0(0.00)	0(0.00)	0(0.00)	83(2.87)
Asturias	110,126 (2.07)	52 (2.24)	13(2.82)	2(6.06)	1(2.04)	2(6.25)	70(2.42)
Cantabria	77,669 (1.46)	9 (0.39)	2(0.43)	0(0.00)	0(0.00)	0(0.00)	11(0.38)
Castilla La Mancha	294,158(5.54)	134 (5.77)	20 (4.34)	2(6.06)	3(6.12)	2(6.25)	161(5.56)
Catalonia	1,114,368(21.0)	516 (22.22)	89(19.31)	4(12.12)	8(16.33)	8(25.00)	625(21.57)
Valencian Community	741,728(13.98)	304 (13.09)	73(15.84)	3(9.09)	6(12.24)	2(6.25)	388(13.39)
Extremadura	153,641(2.89)	86 (3.70)	8(1.74)	1(3.03)	2(4.08)	1(3.13)	98(3.38)
Galicia	302,548 (5.70)	101 (4.35)	25(5.42)	1(3.03)	1(2.04)	0(0.00)	128(4.42)
La Rioja	45,709 (0.86)	18 (0.78)	3(0.65)	0(0.00)	3(6.12)	1(3.13)	25(0.86)
Madrid	1,008,224(19.0)	500 (21.53)	106(22.99)	14(42.42)	14(28.57)	10(31.25)	644(22.23)
Murcia	255,164 (4.81)	114 (4.91)	24(5.21)	1(3.03)	4(8.16)	2(6.25)	145(5.01)
Navarra	98,814 (1.86)	50 (2.15)	6 (1.30)	0 (0.00)	0(0.00)	1(3.13)	57(1.97)
The Basque Country	331,930 (6.25)	135 (5.81)	35 (7.59)	1 (3.03)	2(4.08)	1(3.13)	174(6.01)
Total	5,307,443(100)	2,322 (100)	461 (100)	33 (100)	49(100)	32(100)	2,897(100)

ALL: lymphoid leukemias; AML: acute myeloid leukemias; I.c: Chronic myeloproliferative diseases; I.d: myelodysplastic syndrome and other myeloproliferative diseases and I.e: unspecified and other specified leukemias

by the covariates. In addition, we performed an analysis on the subtypes of ALL and AML, in this case all results are from the model adjusted by the same covariates.

For Cd in the analysis with all childhood leukemias, increases in risk were found in the adjusted model with the continuous variable, with an OR 11% higher when increasing the level of cadmium in the soil measured by the logarithm of the concentration by 1 point (mg/

Table 3 Distribution of heavy metal concentration in topsoil (mg/kg). Interpolated values at residence

		Min	P(5)	P(25)	P(50)	P(75)	P(95)	Max
Population	Cd	0.01	0.05	0.10	0.14	0.22	0.34	1.70
	Pb	6.49	13.01	17.86	26.41	36.40	60.87	629.58
Cases								
ALL	Cd	0.01	0.05	0.10	0.15	0.25	0.36	1.44
	Pb	6.93	13.79	19.39	28.10	39.21	61.00	507.72
AML	Cd	0.02	0.05	0.11	0.16	0.24	0.37	1.06
	Pb	10.47	14.69	20.74	30.49	40.50	71.44	348.64
I.c	Cd	0.04	0.06	0.10	0.15	0.23	0.33	0.37
	Pb	15.60	16.87	23.34	35.61	37.60	58.05	75.51
I.d	Cd	0.05	0.06	0.09	0.13	0.20	0.34	0.56
	Pb	11.66	15.01	18.70	26.49	36.28	53.62	65.44
I.e	Cd	0.04	0.06	0.11	0.16	0.24	0.31	0.48
	Pb	10.84	15.59	21.57	31.08	41.50	54.56	74.38

ALL: lymphoid leukemias; AML: acute myeloid leukemias; I.c: chronic myeloproliferative diseases; I.d: myelodysplastic syndrome and other myeloproliferative diseases and I.e: unspecified and other specified leukemias

kg). In the model broken down by quartiles increase in risks comparing with Q1 were quite constant around 19%. For Pb, we found an increase in risk across all models. For the continuous variable in the adjusted model, a 10% OR increase was found for a 1 point increase in soil lead levels. The model broken down by quartiles found an increase in risk around 9% for Q2 and Q3, and 20% when comparing Q4 with Q1.

In the subgroup analysis (Table 4), for ALL associated with Cd, the fitted model with the continuous variable showed an 11% increase in risk when the metal concentration in the soil increased by one point (on the logarithmic scale). For Pb, 5% more risk was found in the model with the adjusted continuous variable for each 1-point increase in soil metal concentration.

In the adjusted model AML subgroup analysis, the continuous Cd variable presented a 14% risk increase for each 1-point increase in soil Pb concentration on the logarithmic scale. The adjusted model for Pb with the continuous variable presented a 24% risk increase for each 1-point increase in soil lead concentration on the logarithmic scale.

With respect to covariates, females presented a risk of 13% less than men. The categorical variable for the autonomous communities took Andalusia (western provinces) as a reference, and the ORs show the estimated difference in risk in comparison. Cantabria stood out, with 76% lower risk than Andalusia; Extremadura presented 64% higher risk than Andalucía and Madrid was 18% higher. As regards municipality type, urban areas presented 7% more risk than rural. Finally, for socioeconomic level, on the one hand, a 1% increase in the Activity Rate was associated with a 1% decrease in risk; on the other hand, in the Socioeconomic Condition variable, an increase of 1 point on the index, related to a 132% risk increase.

Discussion

This has been the first approach to assess the possible roll of the bioavailable levels of heavy metals in topsoil in the aetiology of childhood leukemias incidence in Spain, as far as we know.

The results of this study suggest that place of residence in relation to soil cadmium and lead bioavailable levels could play a part in the probability of childhood leukaemia incidence, for both ALL and AML subtypes. This potential association would be stronger with AML than ALL.

The carcinogenicity of Cd and PB has already been established by the IARC, which considers Cd as a known carcinogen (group 1A) and inorganic Pb compounds as a probable carcinogen (group 2A) (International Agency for Research on Cancer and International Agency for Research on Cancer, 2006). An association with childhood leukaemia has not been demonstrated for either of these heavy metals, but some studies have still found particular associations that may be in favour of our hypothesis (International Agency for Research on Cancer and International Agency for Research on Cancer, (2006, p. 8);

Table 4 Multivariate analysis results, risk of childhood leukaemia incidence according to soil lead and cadmium levels

	Population	Cases (%)	OR	95%CI	P
Sex					
Male	2,736,998 (51.57)	1596 (55.08)	1	–	–
Female	2,570,445 (48.43)	1,300 (44.87)	**0.87**	**0.80–0.93**	**0.0001**
Autonomous community					
Andalusia	589,433 (11.11)	288 (9.94)	1	–	–
Aragon	183,931 (3.47)	83 (2.87)	0.87	0.66–1.14	0.3214
Asturias	110,126 (2.07)	70 (2.42)	1.01	0.76–1.35	0.9284
Cantabria	77,669 (1.46)	11 (0.38)	**0.24**	**0.13–0.44**	**0.0000**
Castilla La Mancha	294,158 (5.54)	161 (5.56)	1.20	0.98–1.47	0.0781
Catalonia	1,114,368 (21.00)	625 (21.57)	0.93	0.78–1.11	0.4019
Valencian Community	741,728 (13.98)	388 (13.39)	0.91	0.76–1.09	0.3153
Extremadura	153,641 (2.89)	98 (3.38)	**1.64**	**1.28–2.11**	**0.0000**
Galicia	302,548 (5.70)	128 (4.42)	0.85	0.68–1.07	0.1629
La Rioja	45,709 (0.86)	25 (0.86)	1.03	0.67–1.59	0.8765
Madrid	1,008,224 (19.00)	644 (22.23)	**1.18**	**1.00–1.40**	**0.0487**
Murcia	255,164 (4.81)	145 (5.01)	1.09	0.88–1.34	0.4474
Navarre	98,814 (1.86)	57 (1.97)	1.03	0.75–1.41	0.8515
Pais Vasco	331,930 (6.25)	174 (6.01)	0.87	0.70–1.07	0.1855
Total	5,307,443 (100.00)	2,897 (100)	-	-	-
Municipality type					
Rural	2,737,115(51.57)	1,379 (47.60)	1	–	–
Urban	2,570,328(48.42)	1518 (52.40)	1.07	0.99–1.17	0.1024
	Population. Mean (SD)	Cases. Mean (SD)	OR	95%CI	P
Activity Rate	75.79% (5.57)	76.04% (5.54)	**0.99**	**0.98–1.00**	**0.0264**
Socioeconomic condition	1.02 (0.14)	1.03 (0.14)	**2.32**	**1.55–3.49**	**0.0000**
	Population	Cases (%)	OR	95%CI	P
All childhood leukemias					
Cd					
Continuous variable. Unadjusted	5,307,443 (100)	2,897 (100)	0.98	0.91–1.05	0.5996
Continuous variable. Adjusted	5,307,443 (100)	2,897 (100)	1.11	1.00–1.24	0.0587
Categorized variable (Quartiles)					
Q1	1,326,861 (25)	674 (23.27)	1	-	-
Q2 versus Q1	1,326,861 (25)	788 (27.20)	**1.19**	**1.06–1.34**	**0.0039**
Q3 versus Q1	1,326,860 (25)	676 (23.33)	1.16	1.00–1.35	0.0545
Q4 versus Q1	1,326,861 (25)	759 (26.20)	**1.21**	**1.02–1.44**	**0.0334**
Pb					
Continuous variable. Unadjusted	5,307,443 (100)	2,897 (100)	**1.14**	**1.04–1.24**	**0.0030**
Continuous variable. Adjusted	5,307,443 (100)	2,897 (100)	1.10	0.99–1.21	0.0728
Categorized variable (Quartiles)					
Q1	1,326,861 (25)	662 (22.85)	1	-	-
Q2 versus Q1	1,326,861 (25)	710 (24.51)	1.10	0.98–1.24	0.1202
Q3 versus Q1	1,326,860 (25)	752 (25.96)	1.08	0.95–1.23	0.2323
Q4 versus Q1	1,326,861 (25)	773 (26.68)	**1.20**	**1.04–1.39**	**0.0149**

Table 4 continued

	Population	Cases (%)	OR	95%CI	P
l.a (LLA) Subgroup					
Cd					
Continuous variable. Adjusted	5,307,443 (100)	2322 (100)	1.11	0.98–1.26	0.0886
Categorized variable (Quartiles)					
Q1	1,326,861 (25)	554(23.86)	1	-	-
Q2 versus Q1	1,326,861 (25)	625(26.92)	**1.17**	**1.03–1.33**	**0.0192**
Q3 versus Q1	1,326,860 (25)	527(22.70)	1.10	0.93–1.3	0.2814
Q4 versus Q1	1,326,861 (25)	616(26.53)	**1.22**	**1.01–1.48**	**0.0441**
Pb					
Continuous variable. Adjusted	5,307,443 (100)	2322 (100)	1.05	0.94–1.18	0.3497
Categorized variable (Quartiles)					
Q1	1,326,861 (25)	548(23.60)	1	-	-
Q2 versus Q1	1,326,861 (25)	572(24.63)	1.06	0.93–1.21	0.4160
Q3 versus Q1	1,326,860 (25)	588(25.32)	1.03	0.89–1.18	0.7271
Q4 versus Q1	1,326,861 (25)	614(26.44)	1.12	0.95–1.32	0.1782
l.b (AML) Subgroup					
Cd					
Continuous variable. Adjusted	5,307,443 (100)	461(100)	1.14	0.86–1.52	0.3684
Categorized variable (Quartiles)					
Q1	1,326,861 (25)	88(19.09)	1	-	-
Q2 versus Q1	1,326,861 (25)	128(27.77)	**1.42**	**1.05–1.93**	**0.0233**
Q3 versus Q1	1,326,860 (25)	124(26.90)	**1.66**	**1.12–2.45**	**0.0111**
Q4 versus Q1	1,326,861 (25)	121(26.25)	1.40	0.89–2.21	0.1433
Pb					
Continuous variable. Adjusted	5,307,443 (100)	461 (100)	1.24	0.97–1.58	0.0871
Categorized variable (Quartiles)					
Q1	1,326,861 (25)	92(19.96)	1	-	-
Q2 versus Q1	1,326,861 (25)	110(23.86)	1.28	0.94–1.76	0.1193
Q3 versus Q1	1,326,860 (25)	128(27.77)	1.27	0.91–1.77	0.1573
Q4 versus Q1	1,326,861 (25)	131(28.42)	1.45	1.00–2.10	0.0519

Statistically significant ($\alpha = 0.05$) OR in bold figures

Categorized variable (quartiles) and continuous variable, adjusted and unadjusted by the covariates sex, autonomous community, socioeconomic condition, activity rate and type of municipality. Population results (%), cases (%), ORs, 95%CIs and values

CL: childhood leukemias; ALL: acute lymphocytic leukaemia; AML: Acute myeloid leukaemia

International Agency for Research on Cancer and Weltgesundheitsorganisation, 2012, p. 100).

For Cd, studies based on animal experiments and cohorts of exposed workers have established an association with lung cancer, and suspected associations with kidney, bladder, breast and endometrial cancers (International Agency for Research on Cancer and Weltgesundheitsorganisation, 2012; “Toxicological Profile for Cadmium,” n.d., 2012). As regards an association with childhood leukaemia, a prospective study carried out using the NHANES III cohort found an increase in cancer mortality and an association with leukaemia in adult men, and to a lesser degree in women—among other specific associations (Adams et al., 2012). A case–control study in Egypt found greater Cd concentrations in blood, urine, scalp and nail samples from paediatric cancer patients than in the samples from healthy controls (Sherief et al., 2015). In the laboratory, a study conducted on mice administered with cadmium orally showed a clear increase in leukaemia incidence (Waalkes & Rehm, 1992). Finally, genotoxicity studies have shown the presence of chromosome abnormalities in the leukocytes and lymphocytes of humans exposed to cadmium in comparison with the non-exposed population. Such abnormalities have also been observed in animals exposed to Cd ("Toxicological Profile for Cadmium," n.d., 2012).

As regards Pb, epidemiological studies and cohort studies of workers have been limited by the difficulties involved in controlling for exposure to other potentially confounding substances (International Agency for Research on Cancer and International Agency for Research on Cancer, 2006). Of the studies that have found associations with childhood leukemias, one in Sweden found an excess of risk in a population close to a Pb, Cd and other toxic substance-emitting foundry (Wulff et al., 1996). In another retrospective study, in Italy, parental exposure was established via interviews with the parents of 683 children with ALL; it found an association, among other toxic substances, with parental exposure to lead during the pregnancy and post-natal too (Miligi et al., 2013). A case–control-type ecological study carried out by the University of California, analysed exposure to various toxins—measured by air monitoring stations—and found an association with Pb (among other toxins) (Heck et al., 2014). Toxicity studies in animals have demonstrated [a relationship with] the development of various types of cancer (International Agency for Research on Cancer and International Agency for Research on Cancer, 2006). Among them, an association was found with the development of lymphocytic leukaemia in rats administered with powdered Pb orally (Furst et al., 1976)**.** Another study with mice given water with varying Pb concentrations found a higher incidence of murine lymphocytic leukaemia (Blakley, 1987)**.** Finally, a study at the University of Wisconsin-Madison found an association with myeloid leukaemia in monkeys exposed to Pb during the neonatal period (Krugner-Higby et al., 2001).

Cd and Pb exposure in the general population. Heavy metals pass from the ground into plant-based foods and these are the main source of the general population's exposure—via fruits, vegetables, cereals and animal products ("Cadmium in food—Scientific opinion of the Panel on Contaminants in the Food Chain," 2009). On this point, there are two doubts for our study: plants' heavy metal assimilation depends largely on the properties of the soil, such as pH (Rodríguez Eugenio et al., 2018), and the food consumed is not only local, with local consumption varying by region. It is important to understand that this model does not simply explain exposure from soil contamination, rather which the heavy metal concentration is an indirect indicator; we could assume that higher Cd and Pb concentration in the place of residence would indicate higher concentrations in the general environment, thus leading to greater exposure. The ground is metals' final repository, as they remain undegraded, indirectly indicating the area's past contamination, (Ali et al., 2013), and, finally, the population's exposure levels. Various studies have found associations between soil metal concentrations and biomarker levels in the local population (Ikeda et al., 2004; Staessen et al., 1992).

As already noted, children face greater exposure to metals in the environment than adults, in part due to greater absorption capacity, and in part due to habits that bring their hands into more frequent contact with their mouths. Damage to the genetic material during the foetal stage is also suspected in leukaemia genesis; the study of pregnant women's exposure is therefore important (Hernández & Menéndez, 2016). It is also known that Cd and Pb can pass to the foetus through the placental barrier (Espart et al., 2018), and Cd and Pb absorption is higher in pregnant women ("Cadmium in food—Scientific opinion of the Panel on Contaminants in the Food Chain," 2009). Our study design does not allow us to separate pre- and post-natal exposure; however, as Cd and Pb levels are stable, it can be assumed that a reading taken at a specific point in time could cover both pre- and post-natal exposure.

In addition to food, there are other notable sources of exposure. These include tobacco for both metals, which in the case of Pb can result in similar exposure to diet. For Pb, the dust from paint chips and water from Pb pipes in old buildings ("Cadmium in food—Scientific opinion of the Panel on Contaminants in the Food Chain," 2009; International Agency for Research on Cancer and International Agency for Research on Cancer, 2006) mean that past industrial emissions remain important. For this study, it was not possible to take all these factors into account due to the lack of individual-level data.

For that reason, it was not possible to control for potential confounders such as precise socioeconomic status, parents' occupational exposure, diet or changes in residence. However, these limitations have been accounted for as much as possible by adjusting the model for the covariates defined below. For sex, as the risk is higher in males (Schüz & Erdmann, 2016). For region, as there are interregional cultural and epidemiological differences**.** Socioeconomic status has been associated in some studies with a higher incidence of childhood leukaemia (Schüz & Erdmann, 2016), in lieu of individual information, two census tract level variables were used: socioeconomic status—constructed from the head of the family's occupation—and the activity rate, which assumes that higher unemployment is associated with lower social class. Type of municipality and the different activities carried out on rural and urban land suppose different pollution patterns; for example, the highest Pb concentrations are found in areas close to roads, with the highest concentration of traffic (García-Pérez et al., 2015; Tamayo-Uria et al., 2018). Also, we did not have information about the house age that is been associated to blood Pb levels in children (Kim et al., 2002).

Another possible limitation is that cases' addresses were at diagnosis and controls at birth, and as a result, changes of residence may not have been accounted for. Despite this, childhood leukaemia has a relatively short latency period ("Investigating Suspected Cancer Clusters and Responding to Community Concerns," n.d., 2013) and in Spain only 1% of the child population move to another province, according to official data ("Instituto Nacional de Estadística. (National Statistics Institute)," n.d., 2017)**.** For this reason, it seems unlikely that this will have had a notable influence on the results.

As strengths, we consider that the study design is sufficiently robust to permit to explore new hypotheses about the aetiology of childhood leukaemia. It accounts for two of the main problems in the study of childhood leukaemia: the low incidence of the disease, around 300 cases a year in Spain, and the difficulties involved in measuring exposure. These difficulties were addressed using two tools: the RETI-SEHOP database, which records more than 90% of cases, and in some regions 100%. Second, we used the Geochemical and Mining Atlas, which provides detailed geochemical information on the soil (Locutura et al., 2012), despite not reporting temporal changes in concentrations. As both include spatial data, it was possible to estimate heavy metal levels at each subject's place of residence.

Conclusions

The results of the study points toward a possible link between residential Cd and Pb bioavailable topsoil levels and childhood leukaemia. Residing in a location with the highest concentrations of these heavy metals compared to those locations with the lowest could increase the risk around a 20%, for both Cd and Pb. These results may justify carrying out more specific studies that include measures of body metal concentrations of both children and parents.

Authors' contribution Substantial contributions to conception and design, acquisition of data or analysis and interpretation of data: SA, ON, RR. Drafting the article or revising it critically for important intellectual content: ON, JST, JGP, ACÁ, JAOG, RR. Final approval of the version to be submitted for publication: All; SA, ON, JST, EPR, ACN, IMM, ABl, JG-P, ACÁ, JAOG, RR.

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Availability of data and material Data are not available due to confidentiality of the participants.

Code availability Custom code can be shared under request.

Declarations

Conflict of interest There is not conflict of interest.

Human and animal rights Not applicable.

Consent to participate Not applicable for controls. Cases consent of participation in the consent form of the register RETI.

Consent to publish Not applicable for controls. Cases consent of in the publication of results in the consent form of the register RETI.

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