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Levels and determinants of urinary cadmium in general population in Spain: Metal-MCC-Spain study

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ABSTRACT

Background: Cadmium is a ubiquitous and persistent metal, associated with different harmful health effects and with increased morbidity and mortality. Understanding the main sources of exposure is essential to identify at risk populations and to design public health interventions.
Objective: To evaluate cadmium exposure in a random-sample of general adult population from three regions of Spain, assessed by the urinary cadmium (U–Cd) concentration, and to identify its potential determinants and sex-specific differences, including sociodemographic, lifestyle and dietary factors.
Materials and methods: We measured U–Cd (μg/g creatinine) in single urine spot samples from 1282 controls enrolled in the multicase-control study in common tumors in Spain (MCC-Spain) with inductively coupling plasma-mass spectrometry equipped with an octopole reaction systems (ICP-ORS-MS). The association between sociodemographic, lifestyle, and dietary characteristics and U–Cd concentrations was evaluated using geometric mean ratios (GMR) estimated by multiple log-linear regression models.
Results: Overall, geometric mean U–Cd concentration was 0.40 (95%CI: 0.38, 0.41) μg/g creatinine. Levels were higher in women than in men (GMR]: 1.19; 95%CI: 1.07, 1.32), and increased with age in males ($p_{trend}< 0.001$). Cigarette smoking was clearly associated to U–Cd levels ($GMR_{former\ vs\ non\text{-}smokers}$: 1.16; 95%CI: 1.05, 1.29; $GMR_{current\ vs\ non\text{-}smokers}$: 1.42; 95%CI: 1.26, 1.60); the relationship with secondhand tobacco exposure in non-smokers, was restricted to women ($p_{interaction} = 0.02$). Sampling season and region also seemed to influence U–Cd concentrations, with lower levels in summer ($GMR_{summer\ vs\ average}$: 0.79; 95%CI: 0.71, 0.88), and higher levels in North-Spain Asturias ($GMR_{Asturias\ vs\ average}$: 1.13; 95%CI: 1.04, 1.23). Regarding diet, higher U–Cd concentration was associated with eggs consumption only in men ($p_{interaction} = 0.04$), just as rice intake was associated in women ($p_{interaction} = 0.03$). *Conclusion*: These results confirmed that tobacco exposure is the main

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modifiable predictor of U–Cd concentrations, and remark that the role of dietary/sociodemographic factors on U–Cd levels may differ by sex.

1. Introduction

Cadmium (Cd) is a highly persistent toxic metal with no known function in human physiology. It is naturally present in the earth's crust associated with other metals; however, the main sources of Cd contamination are anthropogenic: production of rechargeable nickel-cadmium batteries, fossil fuel combustion, waste combustion, mining activities, iron and steel production, and use of Cd-containing fertilizers, among others. Cd exhibits high rates of soil-to-plant transfer, making it a food-chain contaminant of great concern (ATSDR, 2012).

Diet and tobacco smoke are considered the major sources of Cd exposure in non-occupationally exposed human population. As tobacco leaves concentrate this metal, tobacco is the main source of exposure among smokers; Cd oxide, a highly bioavailable form of Cd, is present in tobacco smoke and is absorbed in the lung, contributing to elevated Cd concentrations in blood, urine, and tissues of smokers, compared with non-smokers of similar age and gender (Satarug, 2018). In non-smokers, diet is usually the primary source of Cd exposure (EFSA, 2012; Satarug, 2018). High concentrations of Cd have been found in leafy vegetables, as well as in tubers and roots, grains, pulses, nuts, mushroom, shellfish and organ meats (IARC, 2012). Dietary intake of zinc and iron may modify Cd absorption, since individuals with lower intake of these micronutrients exhibit increased Cd uptake (Kim et al., 2019; Kippler et al., 2009). Women generally have higher internal Cd levels than men, since iron deficiency is common among women of childbearing age, increasing the intestinal absorption of Cd (Gunier et al., 2013; Vahter et al., 2002). Once absorbed, Cd is distributed throughout the body and accumulates in human tissues, mainly in the liver and kidney. It's excreted mostly via urine, making urinary Cd concentration (U–Cd) a valid biomarker of long-term exposure in epidemiological studies (Satarug, 2018; Vacchi-Suzzi et al., 2016).

Chronic Cd exposure is associated with potential toxic effects in the kidney, causing tubular damage and renal dysfunction (Satarug, 2018), in the bone (Engström et al., 2011), in the liver(Hyder et al., 2013), in the cardiovascular system (Tellez-Plaza et al., 2013), and in testicular function (Siu et al., 2009). Moreover, Cd and Cd compounds are considered as a Group 1 human carcinogens due to their association with lung cancer and, potentially, with other types of cancer (kidney and prostate) (IARC, 2012).

Because of its wide distribution in the environment, its long biological half-life (10–30 years) (Järup and Akesson, 2009), and the adverse health effects associated with its exposure, Cd is usually one of the focus of human biomonitoring surveys in order to establish baseline reference values, to identify vulnerable and/or highly exposed population groups, and to orientate environmental and public health policies aimed to reduce the exposure to this metal. However, information about Cd exposure and reference values for general population in Europe is only available in a few countries (López-Herranz et al., 2016).

In the Spanish population, little is known about the distribution of Cd levels. Most of the studies have been carried out in occupationally exposed groups (Gil et al., 2011; Schuhmacher et al., 2002) or in so-called "hot-spots", i.e people living close to zones with industrial or mining activities (Aguilera et al., 2008; Alonso et al., 2001; Gil et al., 2006; Gonzalez et al., 2000; Zubero Oleagoitia et al., 2008). Some exceptions include a study where Cd exposure was evaluated in a population-based survey among adults (18–85 years) residing in Valladolid (Spain) in 1997–2003 (Domingo-Relloso et al., 2019). More recently, a cross-sectional nationwide survey provided reference levels for selected heavy metals, including Cd, in a representative sample of the Spanish workforce, but the study population did not include unemployed or age groups over 65 years (López-Herranz et al., 2016).

Therefore, the goal of this study was to evaluate Cd exposure, assessed by U–Cd concentration, in a random-sample-of general adult population from three regions of Spain, as well as to identify sociodemographic, lifestyle and dietary determinants of this exposure, taking into account sex-specific differences.

2. Materials and methods

2.1. Study population

The study population used to address the objective of this analysis was formed by the population-based controls from the MCC-Spain study, conducted between September 2008 and December 2013, in Spain. The study was designed to evaluate the association between environmental exposures and five frequent cancers (prostate, breast, gastric, colorectal, and chronic lymphocytic leukemia), as well as the interaction with genetic factors. Studying exposure to trace metals and its effects were one of its aims (metal-MCC-Spain). A detailed description of its methodology has been previously published (Castaño-Vinyals et al., 2015). Briefly, subjects aged 20–85 years, resident in the study regions for at least six months prior to the interview and with a histologically-confirmed newly-diagnosed cancer were recruited. Population-based controls, frequency-matched to cases by age (±5 years), sex and region, were randomly selected from the listings of primary health care centers within hospitals' reference areas where the cases were recruited. Even though MCC-Spain covered 12 Spanish provinces, only three of them (Asturias (Oviedo), and Cantabria (Santander) –North of Spain-, and Madrid-centre of Spain), collected urine samples (Fig. 1). These three regions included a total of 1342 controls, in whom we measured U–Cd levels; in a second step, controls exhibiting urinary creatinine lower than 30 or higher than 300 mg/dL were excluded (8 participants), as recommended by WHO (WHO, 1996), finally obtaining a total of 1282 controls available for analyses.

2.2. Ethics

The protocol of MCC-Spain was approved by the Ethics committees of the participating institutions. All participants were informed about the study objectives and signed an informed consent. Confidentiality of data was ensured by removing personal identifiers in the datasets.

2.3. Data collection

At enrollment into the study, participants answered a multi-purpose structured questionnaire applied face-to-face by trained interviewers. It collected data on socio-demographic and anthropometric characteristics; personal and family background; occupational and residential history; reproductive history (in women) and lifestyle factors, including smoking, alcohol consumption, physical activity, and self-reported weight and height, which were used to estimate body mass index (BMI).

2.4. Dietary information

To measure usual food intake during the year prior to recruitment, a self-administered, semi-quantitative, validated Food Frequency Questionnaire (FFQ) was used (Martin-Moreno et al., 1993). All participants received the paper FFQ to be completed at home, and interviewers gave them instructions to fill it out correctly. To facilitate the understanding of some items, portion sizes were specified, and photographs were used as visual aids. The FFQ was returned to the interviewer in person or by mail.

This FFQ collects information about 140 different foods, distributed in 12 general groups (eggs; white and red meats; fish and seafood; vegetables and legumes; fruits and nuts; dairy products and derivatives; bread and cereals; sauces and condiments; fats and oils; sweets and snacks; vitamin and mineral supplements, and beverages). Each food item had a predetermined portion size and 8 consumption frequency options, ranging from never to two or more times a day. Reported frequencies of consumption were converted into grams or ml per day. Nutritional composition of foods was compiled from the Spanish CESNID food composition tables (Farrán et al., 2003), and was used to estimate average daily energy and minerals (iron and zinc) intake for each study participant.

2.5. Sampling and Cd analysis

Participants provided spot urine samples (60 ml) that were collected specifically for trace metal determination the day of the interview or the following day, using urine collection containers as well as white capped polypropylene aliquot tubes which had been previously washed with nitric acid. Aliquots were stored in freezers at −80 °C, until they were processed and analyzed. U–Cd analysis was performed after diluting the sample five times with a 5% (v/v) solution of ultrapure nitric acid in ultrapure water. This extract was analyzed by ICP-ORS-MS using the conditions previously described (García-Sevillano et al., 2014). Quality control of the analysis was based on the following operations: (a) analysis of two reference materials, *Clincheck (RECIPE) Urine Control for trace elements -Level I* and *Standard Reference Material (2670a) –Toxic Elements in Freeze dried urine (LGC) – high level,* in each sample batch, with a mean accuracy of 90% maintained along the time ±5%; (b) monitoring of the ICP-MS response along the time by measurement of control concentrations of Cd at a point on the calibration curve (2 ng ml^{-1}), every 20 samples analyzed, based on a previous study we performed with *Clincheck (RECIPE) Urine Control* instrument, which showed that this interval guaranteed a good evaluation of the instrument response; (c) instrumental drift correction by addition of Rh (100 ng ml^{-1}), as internal standard, to all the samples and calibrants used, the samples whose response differed ± 10% with respect to the internal standard were measured again; (d) Analysis every 5 samples of reagents blanks containing 5% (v/v) HNO_3 (Suprapur quality), 1% (v/v) HCl and Rh 100 ng ml^{-1} in Milli-Q water; (e) Analysis of duplicate samples every 2.5 h of the sequence; (f) Spike sample analysis, spiking the reference materials with the analytes under study (50 ng ml^{-1}). Finally, potential interferences from molybdenum and tin, frequently present in urine, were removed operating the ICP-MS system in helium collision mode (He flow: 4 ml min^{-1}).

The creatinine concentration in urine was determined by the classical Jaffé method (Peake and Whiting, 2006; Weber and van Zanten, 1991), based on the photometric measurement of the kinetics of creatinine reaction with picric acid at 37 °C. For this purpose, a kit of reagents was supplied by Biosystems (Barcelona, Spain). Similar quality control tests to those previously described were used in creatinine analysis. Creatinine-adjusted U–Cd levels (μg/g creatinine) were calculated by dividing the U–Cd concentrations (in μg/liter) by the creatinine concentrations.

2.6. Description of variables

Controls were grouped by registered sex, age at the time of recruitment (<45, 45–54, 55–64, and >64), education (less than primary school, primary, secondary, and ≥ university); season (winter, spring, summer, fall); BMI[kg/m^2] (less or equal to normal weight: <25; overweight: 25–29.9; obese: ≥30); region (Madrid, Asturias, Cantabria); physical activity performed between 6 years and one year prior to recruitment and transformed to metabolic equivalents hours per week (MET-h/week) (none, <median and ≥median); and occupational exposure to Cd (yes or no), derived from reported job titles and classified as exposed according to the Spanish Job-Exposure Matrix (MatEmESp) (García et al., 2013).

Based on the smoking status at interview, participants were classified as non-smokers, former or current smokers. Non-smokers were those participants who reported that they had never smoked or had smoked less than 100 cigarettes in their whole life. Former smokers were defined as those who had smoked at least 100 cigarettes in their lifetime, but had quitted smoking at least one year before the interview. Current smokers

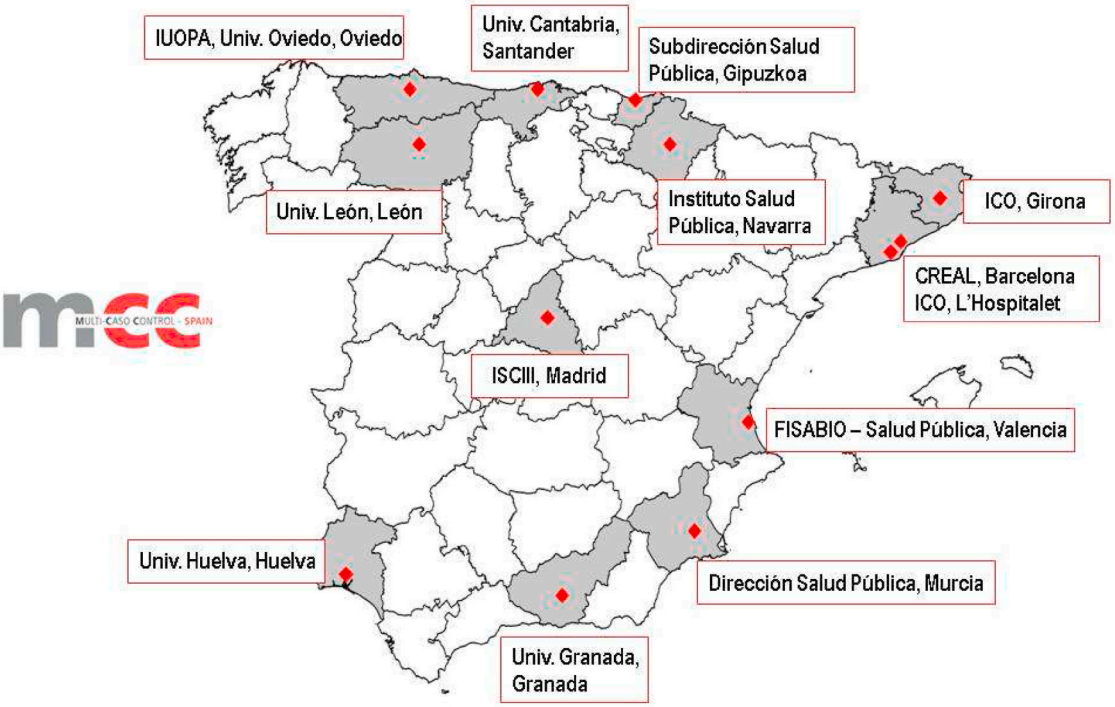

Fig. 1. Study regions included in the analysis: Asturias (**Oviedo**), and Cantabria (**Santander**) –North of Spain-, and Madrid-centre of Spain.

were active smokers at that time or during the year preceding the interview. Passive smokers (yes or no) were those reporting having inhaled the smoke from others' cigarettes on a regular basis either at work, at home or during leisure time throughout their lives.

Women were classified as postmenopausal if natural menopause (no menstrual periods for at least one year) or an oophorectomy were reported at recruitment. Women who reported hysterectomy without oophorectomy were classified as premenopausal if they were less than 50 years old, and as postmenopausal if they were 50 years old or older.

Food items included in the analyses were selected a priori, taking into account their Cd content reported in previous studies (Supplemental TableS1). Foods, food groups and alcohol intakes were categorized using as thresholds the tertiles of daily consumption in the whole study population. Due to the low reported consumption of nuts and processed meat, they were categorized as "no consumption", ≤median and >median, and organ meats intake was dichotomized ("yes" vs "no"). Egg consumption was also dichotomized (≤median and >median) because there were no women in the intermediate consumption category.

The intake of zinc (Zn) and iron (Fe) were classified as meeting or not meeting the dietary recommendations. The recommended zinc intake is 13 mg/day and 8 mg/day for adult men and women, respectively (Gibson et al., 2016), and the recommended daily iron intake is 11 mg/day for men and postmenopausal women, and 16 mg/day for premenopausal women (EFSA, 2009; López-Herranz et al., 2016).

2.7. Statistical analyses

Unadjusted and creatinine-adjusted U–Cd concentrations were initially described by calculating crude arithmetic and geometric means (GM), and by providing range and selected percentiles of their distribution, overall, by sex and by smoking habit.

Sociodemographic, lifestyle and dietary categorical variables were described by frequencies and percentages. The Chi-square test was used to estimate statistically significant differences in the distributions of these variables between sexes. Geometric means and medians of unadjusted and creatinine adjusted U–Cd levels were also calculated across sociodemographic, lifestyle and dietary variables.

Creatinine-adjusted U–Cd was log-transformed to improve fitting to the normal distribution and was entered as dependent variable in linear regression models. To assess its association with the variables of interest, geometric mean ratios (GMRs) and their 95% confidence intervals were estimated. Dietary variables were examined categorically using the lowest category (tertile) as reference. The analyses were done for the whole population and stratified by sex. First, the association of U–Cd levels with each variable was evaluated in a basic model, which included age, registered sex, tobacco - and total caloric intake in the case of dietary variables-as potential confounding factors. Afterwards, a complete model was fitted, including other relevant variables, such as education, geographical region, occupational exposure to Cd, and those variables that were associated with U–Cd in the previous analysis ($p \leq 0.10$), in both men and women. Menopausal status was excluded from the multivariable models because of its strong correlation with age. Potential interactions between variables of interest and sex were explored by including the corresponding interaction term in the models. In addition, we replicated the previous analysis restricting the study population to non-smokers.

We also conducted a sensitivity analysis, using U–Cd levels (μg/L) as dependent variable instead of creatinine-adjusted U–Cd, and including log-transformed urinary creatinine concentration as an independent variable.

Additionally, given that we included multiple dietary variables in the multivariate models, we have performed an analysis using the Benjamini & Hochberg method to correct p values for multiple comparisons.

Statistical analyses were performed using Stata/MP 15.0 statistical software.

3. Results

Globally, the GM of unadjusted and creatinine adjusted U–Cd were 0.35 (95%CI: 0.33, 0.36) μg/L and 0.40 (95% CI: 0.38, 0.41) μg/g, respectively, whereas the medians were 0.36 μg/L and 0.40 μg/g. The highest U–Cd levels were found in past or current smokers (Table 1). Around 7.7% of the participants had U–Cd levels greater than 1 μg/L, the proposed Human Biomonitoring (HBM) value for cadmium, defined as the concentration below which no adverse health effects are expected (Schulz et al., 2011), a percentage that rose to 12.9% in currently smokers.

Of the total studied population, 46.6% were over 64 years old. Overall, 56.1% were former or current smokers, and 74.1% were exposed to secondhand smoke. Only a small proportion of participants, mostly men, reported to be employed in occupations involving Cd exposure. Significant differences ($p < 0.001$) between men and women were observed in the distribution of age, BMI, smoking habits, Cd related occupation and physical activity, as well as in total energy intake, alcohol consumption, dairy products, processed and cured meat, seafood, vegetables, legumes, tubers, zinc and iron (data not shown in tables).

For GMR estimations we used creatinine adjusted U–Cd. GMRs adjusted for sex, age and tobacco, and stratified by sex showed that U–Cd increased with age, and that women had significantly higher U–Cd concentrations than men, across all age groups. Premenopausal women had lower levels than postmenopausal participants. People with primary education had higher U–Cd concentration than that observed in the entire sample. Participants from Cantabria and those whose urine samples were taken in summer show lower U–Cd concentrations than the average. Among possible sources of Cd, tobacco had the clearest association with U–Cd levels: the highest concentrations were found in current smokers, medium levels in former smokers and the lowest in non-smokers. (Table 2).

For diet, once adjusted for age, sex, tobacco consumption, and caloric intake, marginally positive associations of U–Cd levels were found with higher daily intake of leafy vegetables, vegetable fruits, tubers, and rice. In the sex-stratified analysis, marginally positive associations with eggs and negative with nut consumption were found in men; in women, U–Cd levels were positively associated with intake of leafy vegetables, vegetable fruits, non-citrus fruits, tubers and rice, and inversely with eggs consumption. Unexpectedly, women who met the recommended levels of zinc and iron intake had higher U–Cd levels than those who didn't. No significant associations were observed with the reported consumption of other foods or food groups, such as organ/processed meat or seafood, which have been considered sources of Cd (EFSA, 2012) (Table 3).

Multivariate analyses (Table 4) confirmed most of the previous results. Women had higher U–Cd concentrations than men, but the positive association of age with U–Cd was only observed in men (p for trend<0.001). Again, we observed differences in U–Cd levels by attained education, region of residence, and sampling season, with higher levels among participants with primary school education, and lower levels among those from Cantabria and in samples taken in summer. Smoking remained positively associated with U–Cd in both men and women (current smokers > former smokers > non-smokers). When restricting the analysis to non-smokers, women exposed to secondhand smoke showed higher U–Cd concentrations than those non exposed, whereas this association was not found in men (p for interaction = 0.02); the U–Cd differences previously found among regions and among seasons became somehow stronger (Table 5).

Regarding diet, there were not clear associations of specific foods with U–Cd levels in the whole population. By sex, egg consumption remained positively associated with U–Cd in men, but not in women (p for interaction = 0.044), while the positive association with rice consumption was now only suggested in women (p for interaction = 0.032). Also in women, higher tubers consumption marginally increased U–Cd

Table 1
Unadjusted and creatinine adjusted U-Cd levels in metal-MCC-Spain participants.

	Cadmium (μg/L)									Max[d]	-	Cadmium (μg/g creatinine)									Max[d]
	AM[a]	GM[b]	Min[c]	P5	P10	P25	P50	P75	P90	P95			AM[a]	GM[b]	Min[c]	P5	P10	P25	P50	P75	P90	P95	
All	0.47	0.35	0.03	0.10	0.11	0.20	0.36	0.61	0.90	1.17	5.72		0.53	0.40	0.03	0.11	0.15	0.24	0.40	0.64	1.00	1.36	10.25
Men	0.51	0.38	0.05	0.11	0.13	0.22	0.39	0.68	0.95	1.26	5.72		0.51	0.39	0.04	0.11	0.15	0.24	0.39	0.61	0.97	1.28	4.71
Women	0.43	0.32	0.03	0.08	0.11	0.18	0.34	0.55	0.86	1.13	4.19		0.56	0.41	0.03	0.12	0.15	0.24	0.41	0.68	1.07	1.41	10.25
Non-smoker	0.40	0.29	0.03	0.08	0.11	0.17	0.31	0.50	0.74	1.01	3.43		0.48	0.35	0.04	0.11	0.14	0.21	0.34	0.56	0.88	1.30	7.19
Ex-smoker	0.48	0.36	0.03	0.09	0.12	0.21	0.37	0.65	0.91	1.19	4.19		0.54	0.41	0.03	0.11	0.15	0.25	0.43	0.67	0.99	1.31	10.25
Smoker[e]	0.59	0.46	0.07	0.12	0.16	0.28	0.49	0.77	1.09	1.25	5.72		0.63	0.49	0.08	0.14	0.20	0.31	0.52	0.78	1.11	1.42	4.71

[a] Arithmetic mean.
[b] Geometric mean.
[c] Minimum value.
[d] Maximum value.
[e] Current smoker.

concentration, whereas higher cured meat consumption decreased it. Again, we found that those female participants with iron intake within the recommended levels had higher levels of U–Cd, although the association became marginally significant. No significant associations were found with other food items or groups considered (Table 4). These results were quite similar in the non-smokers, but in this group, a higher consumption of cured meat decreases significantly U–Cd, both in men and women (Table 5). Dietary variables explained about 1.3% of the variation in U–Cd levels in the entire sample, 2.9% in men, and 5.1% in women. These percentages were higher in non-smokers (4.4% in the all the participants, 9.4% in men and 7.3% in women).

In the sensitivity analysis, using unadjusted U–Cd levels (μg/L) as the dependent variable and including log-transformed urinary creatinine concentration as an independent variable, results did no differ substantially from those obtained in the main analyses (Supplemental TableS2).

When we corrected for multiple comparison in the multivariate analysis, none of the dietary variables were significantly associated with cadmium concentrations, but interactions between sex and some foods, like rice (p for interaction = 0.04) and eggs (p for interaction = 0.03) are still significant (data not shown in tables).

4. Discussion

We studied the levels and determinants of U–Cd in men and women from a population-based sample of controls participating in the MCC-Spain study. This is one of the few studies carried out in Spain that analyzes a sample of the general adult population from several regions, with a wide age range, including age groups over 65, and unemployed population. It, therefore, expands the knowledge provided by previous studies carried out in general population in Spain, which have been restricted to an specific geographical area (Domingo-Relloso et al., 2019) or to working people (López-Herranz et al., 2016).

Table 6 shows a summary of the levels reported in other studies from Spain and other countries. In our study population, with a low frequency of occupational exposure to Cd and a high prevalence of tobacco exposure, U–Cd concentrations were similar to those reported in Spanish people of a similar age range (Domingo-Relloso et al., 2019). Because Cd bioaccumulates in human tissues and the body burden increases with age, we found relatively higher U–Cd levels than in other studies that included younger population in Spain (López-Herranz et al., 2016), and in other European countries (Fréry et al., 2011; Pirard et el. 2014; Berglund et al., 2015). We also found higher levels than those found in US general population, where there is a lower frequency of current smokers (Kim et al., 2019). On the other hand, our levels were lower than those reported by some Asian studies (Zeng et al., 2013; Lim et al., 2016; La Up et al., 2017), where rice is the main staple food. The higher Cd accumulation ability of rice, compared to other cereals, makes it a major source of dietary Cd intake in Asian populations (Hu et al., 2016), but its importance as a source of Cd in Spanish population has not been stablished. Although in our study women who consume more rice show higher U–Cd levels, these levels are far from those observed in Asian populations.

In this study, 7.7% of the participants had U–Cd levels above the HBM value 1 μg/L (Schulz et al., 2011). This percentage is slightly higher than the 4.9% reported by López-Herranz et al. (2016) in samples obtained in 2009 from active workers not occupationally exposed to Cd. However, since Cadmium is a toxic metal with not known function in the human physiology, this reference value should be taken with caution. In fact, U–Cd levels ≥0.37 μg/g creatinine have been associated with higher risk of harmful health effects, such as female breast cancer (Gallagher et al., 2010), and even low levels of Cd have been related to all-cause and cardiovascular mortality (Tellez-Plaza et al., 2012). In our population, half of the participants had levels higher than 0.40 μg/g creatinine, a figure that may be a cause for concern.

As in most biomonitoring studies, women in our population have

Table 2
U-Cd (μg/g creatinine) in metal-MCC-Spain participants by sociodemographic characteristics: sex, age and tobacco use adjusted geometric means and geometric mean ratios.

	ALL					MEN					WOMEN				
	n (%)	GM	GMR[a]	95%CI	P-val	n (%)	GM	GMR[b]	95%CI	P-val	n (%)	GM	GMR[b]	95%CI	P-val
Sex															
Male	620 (48.4)	0.39	1.00												
Female	662 (51.6)	0.41	1.18	(1.08–1.30)	<0.001										
Age															
<45	161 (12.6)	0.36	1.00			23 (3.7)	0.28	1.00			138 (20.8)	0.38	1.00		
45–54	225 (17.6)	0.40	1.10	(0.94–1.27)	0.233	45 (7.3)	0.36	1.27	(0.89–1.82)	0.187	180 (27.2)	0.41	1.07	(0.91–1.27)	0.403
55–64	298 (23.2)	0.41	1.23	(1.06–1.43)	0.005	169 (27.3)	0.38	1.35	(0.99–1.85)	0.058	129 (19.5)	0.45	1.24	(1.03–1.48)	0.022
>64	598 (46.6)	0.40	1.26	(1.10–1.44)	0.001	383 (61.8)	0.40	1.43	(1.06–1.94)	0.020	215 (32.5)	0.41	1.18	(1.00–1.40)	0.048
Educational level[c]															
Incomplete primary school	162 (12.6)	0.37	0.93	(0.85–1.03)	0.162	73 (11.8)	0.38	0.98	(0.86–1.12)	0.769	89 (13.4)	0.36	0.89	(0.77–1.02)	0.099
Primary school	416 (32.4)	0.44	1.11	(1.04–1.19)	0.002	207 (33.4)	0.43	1.11	(1.01–1.21)	0.033	209 (31.6)	0.45	1.11	(1.01–1.22)	0.036
Secondary school	402 (31.4)	0.39	0.99	(0.92–1.06)	0.691	186 (30.0)	0.36	0.93	(0.84–1.02)	0.127	216 (32.6)	0.42	1.04	(0.95–1.16)	0.389
University graduate	302 (23.6)	0.38	0.98	(0.91–1.05)	0.564	154 (24.8)	0.38	1.00	(0.90–1.10)	0.929	148 (22.4)	0.38	0.97	(0.87–1.09)	0.623
Smoking habit															
Non-smoker	562 (43.8)	0.35	1.00			187 (30.2)	0.31	1.00			375 (56.6)	0.38	1.00		
Former smoker	440 (34.3)	0.41	1.20	(1.09–1.32)	<0.001	300 (48.4)	0.41	1.31	(1.15–1.49)	<0.001	140 (21.1)	0.40	1.07	(0.92–1.25)	0.366
Current smoker	280 (21.8)	0.49	1.46	(1.31–1.63)	<0.001	133 (21.5)	0.47	1.54	(1.31–1.80)	<0.001	147 (22.2)	0.51	1.41	(1.21–1.64)	<0.001
Body mass index (Kg/m^2)															
<25	494 (39.5)	0.40	1.00			165 (27.1)	0.37	1.00			329 (51.3)	0.42	1.00		
25–29	521 (41.7)	0.40	0.98	(0.89–1.08)	0.693	324 (53.2)	0.41	1.07	(0.93–1.22)	0.358	197 (30.7)	0.39	0.91	(0.79–1.04)	0.158
>29	235 (18.8)	0.38	0.96	(0.86–1.08)	0.523	120 (19.7)	0.37	1.01	(0.85–1.20)	0.917	115 (17.9)	0.40	0.94	(0.80–1.11)	0.446
Physical activity (MET-hours/week) [d]															
None	583 (45.5)	0.40	1.00			252 (40.6)	0.38	1.00			331 (50.0)	0.41	1.00		
<21	361 (28.2)	0.42	1.05	(0.96–1.16)	0.290	150 (24.2)	0.40	1.05	(0.91–1.22)	0.481	211 (31.9)	0.43	1.05	(0.92–1.19)	0.513
>21	338 (26.4)	0.38	0.98	(0.89–1.09)	0.762	218 (35.2)	0.39	1.04	(0.91–1.18)	0.587	120 (18.1)	0.37	0.91	(0.77–1.06)	0.226
Menopausal status															
Postmenopausal											429 (64.8)	0.44	1.00		
Premenopausal											233 (35.2)	0.36	0.74	(0.61–0.91)	0.003
Cd related occupation															
No	1229 (95.9)	0.40	1.00			570 (91.9)	0.39	1.00			659 (99.5)	0.41	1.00		
Yes	53 (4.1)	0.36	0.96	(0.78–1.18)	0.673	50 (8.1)	0.36	0.92	(0.75–1.13)	0.438	3 (0.5)	0.56	1.52	(0.64–3.59)	0.344
Season[c]															
Winter	582 (46.1)	0.43	1.15	(1.08–1.22)	<0.001	265 (43.5)	0.42	1.15	(1.05–1.25)	0.002	317 (48.5)	0.43	1.15	(1.05–1.26)	0.002
Spring	343 (27.2)	0.41	1.11	(1.03–1.20)	0.004	163 (26.8)	0.40	1.11	(1.00–1.22)	0.050	180 (27.5)	0.42	1.13	(1.01–1.25)	0.031
Summer	155 (12.3)	0.29	0.73	(0.67–0.81)	<0.001	83 (13.6)	0.29	0.77	(0.68–0.87)	<0.001	72 (11.0)	0.29	0.70	(0.60–0.81)	<0.001
Autumn	183 (14.5)	0.39	1.07	(0.98–1.16)	0.151	98 (16.1)	0.37	1.03	(0.91–1.16)	0.669	85 (13.0)	0.42	1.11	(0.97–1.26)	0.136
Geographical region[c]															
Madrid	704 (54.9)	0.44	1.12	(1.06–1.18)	<0.001	338 (54.5)	0.43	1.13	(1.04–1.22)	0.002	366 (55.3)	0.45	1.12	(1.04–1.21)	0.003
Asturias	223 (17.4)	0.43	1.11	(1.03–1.19)	0.006	101 (16.3)	0.38	1.00	(0.91–1.11)	0.952	122 (18.4)	0.48	1.20	(1.09–1.32)	<0.001
Cantabria	355 (27.7)	0.31	0.81	(0.76–0.86)	<0.001	181 (29.2)	0.33	0.88	(0.81–0.97)	0.006	174 (26.3)	0.30	0.75	(0.68–0.81)	<0.001

[a] Adjusted for age, sex and tobacco exposure.
[b] Adjusted for age and tobacco exposure.
[c] GMR using as reference the global geometric mean.
[d] None (no physical activity); ≤median; >median.

Table 3
U-Cd (μg/g creatinine) in metal-MCC-Spain participants for selected dietary variables: sex, age, tobacco use and total energy intake adjusted geometric means and geometric mean ratios.

	ALL					MEN					WOMEN				
	n (%)	GM	GMR[a]	95%CI	P-val	n (%)	GM	GMR[b]	95%CI	P-val	n (%)	GM	GMR[b]	95%CI	P-val
Total energy intake (kcals)[c]															
<1612.59	382 (33.3)	0.38	1.00			140 (24.6)	0.36	1.00			242 (41.9)	0.40	1.00		
1612.59–2083.05	382 (33.3)	0.38	1.01	(0.91–1.13)	0.830	191 (33.6)	0.36	1.01	(0.87–1.18)	0.870	191 (33.1)	0.41	1.01	(0.87–1.17)	0.864
>2083.05	382 (33.3)	0.40	1.06	(0.95–1.18)	0.319	238 (41.8)	0.41	1.13	(0.97–1.31)	0.110	144 (25.0)	0.39	0.97	(0.83–1.14)	0.720
Alcohol consumption (g/day)[c]															
<1.28	382 (33.3)	0.40	1.00			102 (17.9)	0.35	1.00			280 (48.5)	0.41	1.00		
1.28–10.41	382 (33.3)	0.38	0.96	(0.87–1.07)	0.507	169 (29.7)	0.36	1.02	(0.86–1.22)	0.799	213 (36.9)	0.39	0.96	(0.83–1.11)	0.569
>10.41	382 (33.3)	0.40	0.99	(0.88–1.11)	0.842	298 (52.4)	0.40	1.05	(0.90–1.24)	0.520	84 (14.6)	0.40	0.93	(0.76–1.13)	0.448
Dairy products (g/day)[c]															
<273.20	382 (33.3)	0.39	1.00			216 (38.0)	0.38	1.00			166 (28.8)	0.41	1.00		
273.20–454.92	382 (33.3)	0.38	0.96	(0.86–1.07)	0.481	193 (33.9)	0.36	0.93	(0.81–1.08)	0.345	189 (32.8)	0.39	0.99	(0.84–1.17)	0.910
>454.92	382 (33.3)	0.40	1.01	(0.90–1.13)	0.902	160 (28.1)	0.40	1.02	(0.87–1.20)	0.784	222 (38.5)	0.41	1.02	(0.86–1.21)	0.808
Eggs (g/day)															
<10.72	827 (72.2)	0.39	1.00			413 (72.6)	0.36	1.00			414 (71.8)	0.42	1.00		
>10.72	319 (27.8)	0.39	0.98	(0.89–1.08)	0.643	156 (27.4)	0.43	1.12	(0.98–1.28)	0.092	163 (28.2)	0.35	0.86	(0.74–0.99)	0.035
Organ meat															
No	848 (74.0)	0.39	1.00			409 (71.9)	0.37	1.00			439 (76.1)	0.40	1.00		
Yes	298 (26.0)	0.40	1.01	(0.92–1.12)	0.806	160 (28.1)	0.39	1.02	(0.89–1.16)	0.766	138 (23.9)	0.40	0.99	(0.85–1.15)	0.886
Processed meat (g/day)[d]															
No	394 (34.4)	0.39	1.00			178 (31.3)	0.37	1.00			216 (37.4)	0.41	1.00		
<5.02	376 (32.8)	0.40	1.01	(0.90–1.12)	0.916	174 (30.6)	0.39	1.05	(0.91–1.22)	0.512	202 (35.0)	0.40	0.97	(0.84–1.13)	0.708
>5.02	376 (32.8)	0.38	1.00	(0.89–1.12)	0.953	217 (38.1)	0.38	1.01	(0.87–1.17)	0.892	159 (27.6)	0.39	0.99	(0.83–1.18)	0.898
Cured meat (g/day)[c]															
<8.23	382 (33.3)	0.39	1.00			165 (29.0)	0.36	1.00			217 (37.6)	0.41	1.00		
8.23–16.21	382 (33.3)	0.39	1.00	(0.90–1.11)	0.942	182 (32.0)	0.36	1.01	(0.87–1.18)	0.851	200 (34.7)	0.41	1.00	(0.86–1.16)	0.979
>16.21	382 (33.3)	0.39	1.01	(0.91–1.13)	0.797	222 (39.0)	0.41	1.12	(0.97–1.30)	0.124	160 (27.7)	0.38	0.91	(0.77–1.08)	0.267
Seafood (g/day)[c]															
<7.07	382 (33.3)	0.38	1.00			177 (31.1)	0.35	1.00			205 (35.5)	0.40	1.00		
7.07–17.14	384 (33.5)	0.39	1.02	(0.92–1.13)	0.733	186 (32.7)	0.39	1.06	(0.92–1.23)	0.412	198 (34.3)	0.39	0.98	(0.84–1.14)	0.781
>17.14	380 (33.2)	0.40	1.05	(0.94–1.17)	0.388	206 (36.2)	0.40	1.06	(0.92–1.23)	0.423	174 (30.2)	0.41	1.03	(0.87–1.21)	0.745
Leafy vegetables (g/day)[c]															
<14.39	382 (33.3)	0.37	1.00			218 (38.3)	0.37	1.00			164 (28.4)	0.37	1.00		
14.39–33.56	382 (33.3)	0.39	1.07	(0.96–1.18)	0.244	182 (32.0)	0.38	1.03	(0.89–1.18)	0.713	200 (34.7)	0.40	1.11	(0.95–1.30)	0.194
>33.56	382 (33.3)	0.41	1.11	(0.99–1.23)	0.070	169 (29.7)	0.38	1.02	(0.88–1.18)	0.839	213 (36.9)	0.43	1.21	(1.03–1.42)	0.019
Root vegetables (g/day)[c]															
<3.45	382 (33.3)	0.40	1.00			224 (39.4)	0.39	1.00			158 (27.4)	0.41	1.00		
3.45–8.62	382 (33.3)	0.40	1.00	(0.90–1.11)	0.929	189 (33.2)	0.38	0.97	(0.84–1.11)	0.613	193 (33.4)	0.42	1.04	(0.88–1.23)	0.625
>8.62	382 (33.3)	0.38	0.95	(0.85–1.05)	0.310	156 (27.4)	0.37	0.97	(0.83–1.13)	0.696	226 (39.2)	0.38	0.95	(0.81–1.12)	0.560
Vegetable fruits (g/day)[c]															
<37.26	382 (33.3)	0.37	1.00			221 (38.8)	0.38	1.00			161 (27.9)	0.36	1.00		
37.26–71.74	382 (33.3)	0.40	1.08	(0.97–1.20)	0.171	182 (32.0)	0.37	0.97	(0.85–1.12)	0.720	200 (34.7)	0.42	1.21	(1.03–1.42)	0.023
>71.74	382 (33.3)	0.41	1.10	(0.98–1.23)	0.098	166 (29.2)	0.39	1.02	(0.88–1.19)	0.751	216 (37.4)	0.42	1.20	(1.02–1.41)	0.030
Non-citrus fruits (g/day)[c]															
<113.87	382 (33.3)	0.38	1.00			195 (34.3)	0.39	1.00			187 (32.4)	0.37	1.00		
113.87–214.02	382 (33.3)	0.40	1.06	(0.95–1.18)	0.281	194 (34.1)	0.38	0.96	(0.83–1.11)	0.608	188 (32.6)	0.42	1.17	(1.00–1.37)	0.052
>214.02	382 (33.3)	0.39	1.03	(0.92–1.15)	0.658	180 (31.6)	0.37	0.92	(0.79–1.07)	0.266	202 (35.0)	0.41	1.16	(0.98–1.37)	0.085
Legumes (g/day)[c]															
<37.21	382 (33.3)	0.38	1.00			133 (23.4)	0.37	1.00			249 (43.2)	0.39	1.00		
37.21–52.70	382 (33.3)	0.40	1.07	(0.96–1.19)	0.243	223 (39.2)	0.38	1.00	(0.86–1.17)	0.963	159 (27.6)	0.44	1.13	(0.96–1.32)	0.132
>52.70	382 (33.3)	0.39	1.00	(0.90–1.12)	0.942	213 (37.4)	0.38	0.97	(0.83–1.14)	0.731	169 (29.3)	0.39	1.00	(0.86–1.17)	0.982
Tubers (g/day)[c]															
<25.01	382 (33.3)	0.37	1.00			168 (29.5)	0.37	1.00			214 (37.1)	0.36	1.00		
25.01–54.96	382 (33.3)	0.40	1.09	(0.98–1.21)	0.124	178 (31.3)	0.38	0.99	(0.85–1.15)	0.909	204 (35.4)	0.42	1.18	(1.02–1.37)	0.027

(*continued on next page*)

Table 3 (*continued*)

	ALL					MEN				WOMEN				
	n (%)	GM	GMR[a]	95%CI	P-val	n (%)	GM	GMR[b]	95%CI	P-val	n (%)	GM	GMR[b]	95%CI	P-val
>54.96	382 (33.3)	0.41	1.11	(0.99–1.24)	0.078	223 (39.2)	0.39	1.01	(0.87–1.18)	0.898	159 (27.6)	0.43	1.22	(1.03–1.44)	0.023
Rice (g/day)[c]															
<8.75	382 (33.3)	0.37	1.00			187 (32.9)	0.38	1.00			195 (33.8)	0.37	1.00		
8.75–14.82	382 (33.3)	0.41	1.11	(1.00–1.23)	0.061	185 (32.5)	0.42	1.08	(0.94–1.25)	0.270	197 (34.1)	0.41	1.11	(0.95–1.30)	0.172
>14.82	382 (33.3)	0.39	1.07	(0.96–1.19)	0.239	197 (34.6)	0.35	0.94	(0.82–1.09)	0.429	185 (32.1)	0.44	1.19	(1.02–1.40)	0.031
Nuts (g/day) [d]															
No	343 (29.9)	0.41	1.00			168 (29.5)	0.41	1.00			175 (30.3)	0.40	1.00		
<6.42	345 (30.1)	0.39	0.95	(0.85–1.06)	0.392	164 (28.8)	0.37	0.93	(0.80–1.09)	0.358	181 (31.4)	0.40	0.99	(0.84–1.17)	0.938
≥6.42	458 (40.0)	0.38	0.92	(0.82–1.02)	0.110	237 (41.7)	0.36	0.88	(0.76–1.02)	0.098	221 (38.3)	0.40	0.99	(0.84–1.17)	0.897
Dietary zinc (mg/day) [e]															
Below cut-off point	602 (52.5)	0.38	1.00			397 (69.8)	0.37	1.00			205 (35.5)	0.39	1.00		
Above cut-off point	544 (47.5)	0.40	1.06	(0.95–1.19)	0.285	172 (30.2)	0.39	0.97	(0.83–1.13)	0.687	372 (64.5)	0.41	1.18	(1.00–1.40)	0.047
Dietary iron (mg/day) [f]															
Below cut-off point	500 (43.6)	0.37	1.00			159 (27.9)	0.35	1.00			341 (59.1)	0.38	1.00		
Above cut-off point	646 (56.4)	0.40	1.09	(0.98–1.22)	0.109	410 (72.1)	0.39	1.01	(0.87–1.18)	0.903	236 (40.9)	0.43	1.22	(1.04–1.44)	0.015

[a] Adjusted for age, sex, **energy intake (Kcals)** and tobacco exposure.
[b] Adjusted for age, energy intake (Kcals) and tobacco exposure.
[c] In tertiles.
[d] No (no consumption); ≤median; >median.
[e] cut-off point: 13 mg/day for men and 18 mg/day for women.
[f] cut-off point 11 mg/day for men and postmenopausal women, and 16 mg/day for premenopausal women.

significantly higher concentrations of U–Cd than men; this divergence has been attributed to a higher gastrointestinal absorption (Diamond et al., 2003), probably associated to depletion of iron stores due to menstruation, which leads to increased Cd uptake and accumulation (Vahter et al., 2002). However, this is not the only difference between men and women, since we observed a sex-specific association of U–Cd levels with relevant factors such as age or diet. In this sense, in our study, the increase of U–Cd concentration with age, consistent with the current understanding of long-term Cd storage in the kidneys, was only clearly observed in men. Previous studies conducted in the U.S. (Gunier et al., 2013; McElroy et al., 2007), Japan (Moriguchi et al., 2005), or Sweden (Olsson et al., 2002) have found an increase of U–Cd levels in both sexes; however, several authors have described a peak in urinary Cd levels in females around 60 years, followed by a decrease (Belgium, Sartor et al., 1992); NHANES III (Paschal et al., 2000). It might be possible that the lower gastrointestinal Cd absorption after menopause due to improved iron stores (Jian et al., 2009) could explain the lack of increase in Cd levels at advanced ages in women.

Tobacco exposure seems to be the main predictor of U–Cd in both men and women. Thus, current smokers exhibit the highest levels, followed by former smokers, which is largely in agreement with previous studies (Caini et al., 2018; Echeverría et al., 2019; López-Herranz et al., 2016; Torres-Sánchez et al., 2018). However, the positive association with secondhand smoke among non-smokers was sex-specific and restricted to women. In Korean general non-smoking populations, Lee et al. (2017) found a significant association between blood cadmium and passive tobacco exposure measured through urinary cotinine levels, both in males and females. However, they also observed that women had higher blood cadmium level according to urine cotinine level than men. This suggests that women could be more vulnerable than men to secondhand tobacco exposure even with the same exposure level. The different approaches used to measure current or lifetime secondhand smoke exposure, as well as the biological matrix used, limit the comparison between these two studies.

Regarding educational level, we did not observe any clear trend, although those with primary education had higher U–Cd levels. Freire et al. (2015) found that people with secondary or superior educational level had 40% lower U–Cd levels than those with primary education or less, but these results have not been confirmed by other studies (Caini et al., 2018; López-Herranz et al., 2016).

We also observed seasonal and geographical variation in U–Cd levels. The highest concentrations were found in winter/spring and the lowest in summer. López-Herranz et al. (2016) also reported differences in U–Cd concentration by season in Spain, but in this case, the lowest U–Cd concentrations corresponded to winter. We did not find any physiological reason for the lower U–Cd levels found in summer, which is also seen in both men and women, and in the non-smokers sub--analysis. U–Cd is usually considered an indicator of long-term exposure, but its seasonal variations suggest that there are short term characteristics that also module its levels. Even though seasonal changes in the diet of individuals could be a plausible explanation for the differences observed, our data indicate that dietary variables explained only a small percentage of the observed U–Cd variation.

By region, participants from Asturias showed the highest values, whereas those from Cantabria showed the lowest ones. The reasons behind the differences between these neighbor regions, both in the North of Spain, are unknown. Cd intake and food Cd content can vary between and within regions, due to dietary patterns, to growing conditions, such as crop rotation or the use of phosphate fertilizers –which contain Cd-that may affect soil levels, to pollutant emissions from industrial facilities, or to levels of Cd contamination in different food environments (Kim et al., 2018; Quraishi et al., 2016). In this sense, Asturias is a region with an important mining activity and with Cd concentration in soil over the mean of the country (Ballester and Rupérez, 2012); additionally, the largest electrolytic zinc production installation in the world, where Cd is obtained as a co-product (IGME,

Table 4
U-Cd(μg/g creatinine) in all metal-MCC-Spain participants: Geometric mean ratios adjusted for all the variables included in the table.

	ALL				MEN				WOMEN				Pint
	n (%)	GMR	95%CI	P-val	n (%)	GMR	95%CI	P-val	n (%)	GMR	95%CI	P-val	
Sex													
Male	561	1.00											
Female	570	1.19	(1.07–1.32)	0.002									
Age													
<45	136	1.00			22	1.00			114	1.00			
45–54	193	0.99	(0.84–1.17)	0.922	38	1.10	(0.76–1.61)	0.607	155	0.95	(0.79–1.16)	0.624	
55–64	256	1.14	(0.96–1.35)	0.123	149	1.27	(0.91–1.76)	0.162	107	1.07	(0.86–1.34)	0.532	
>64	546	1.23	(1.04–1.45)	0.016	352	1.44	(1.05–1.99)	0.024	194	1.06	(0.84–1.34)	0.604	0.701
Educational level[a]													
Incomplete primary school	139	0.98	(0.88–1.09)	0.703	63	1.05	(0.91–1.22)	0.513	76	0.95	(0.81–1.12)	0.550	
Primary school	372	1.10	(1.03–1.18)	0.006	195	1.10	(1.00–1.21)	0.041	177	1.09	(0.98–1.21)	0.126	
Secondary school	357	0.97	(0.90–1.04)	0.405	168	0.92	(0.83–1.02)	0.124	189	1.01	(0.91–1.13)	0.860	
University graduate	263	0.95	(0.88–1.04)	0.263	135	0.93	(0.84–1.04)	0.226	128	0.96	(0.84–1.09)	0.499	0.699
Smoking habit													
Non-exmoker	501	1.00			171	1.00			330	1.00			
Ex-smoker	406	1.16	(1.05–1.29)	0.004	280	1.24	(1.08–1.42)	0.002	126	1.08	(0.92–1.27)	0.362	
Current Smoker	224	1.42	(1.26–1.60)	<0.001	110	1.45	(1.22–1.73)	<0.001	114	1.35	(1.14–1.60)	0.001	0.333
Cd related occupation													
No	1084	1.00			516	1.00			568	1.00			
Yes	47	0.98	(0.79–1.22)	0.866	45	0.97	(0.77–1.21)	0.768	2	1.54	(0.54–4.43)	0.419	0.408
Season[a]													
Winter	516	1.11	(1.02–1.20)	0.010	244	1.14	(1.03–1.27)	0.015	272	1.04	(0.92–1.17)	0.569	
Spring	301	1.11	(1.02–1.20)	0.012	148	1.10	(0.98–1.23)	0.109	153	1.08	(0.96–1.22)	0.198	
Summer	150	0.79	(0.71–0.88)	<0.001	81	0.79	(0.69–0.91)	0.001	69	0.83	(0.69–1.00)	0.046	
Autumn	164	1.03	(0.93–1.14)	0.580	88	1.00	(0.87–1.15)	0.950	76	1.07	(0.92–1.25)	0.364	0.664
Geographical region[a]													
Madrid	620	1.05	(0.97–1.13)	0.218	305	1.06	(0.95–1.18)	0.284	315	1.07	(0.96–1.20)	0.229	
Asturias	200	1.13	(1.04–1.23)	0.004	96	1.05	(0.93–1.20)	0.416	104	1.18	(1.04–1.32)	0.007	
Cantabria	311	0.84	(0.78–0.91)	<0.001	160	0.89	(0.81–0.99)	0.028	151	0.79	(0.71–0.89)	<0.001	0.096
Total energy intake (kcals)[b]													
<1612.59	376	1.00			136	1.00			240	1.00			
1612.59–2083.05	378	0.95	(0.84–1.07)	0.399	190	1.01	(0.85–1.20)	0.915	188	0.93	(0.79–1.10)	0.412	
>2083.05	377	0.97	(0.84–1.12)	0.717	235	1.07	(0.87–1.32)	0.524	142	0.87	(0.71–1.07)	0.177	0.438
Eggs (g/day)[b]													
<=10.72	818	1.00			407	1.00			411	1.00			
>10.72	313	1.02	(0.92–1.13)	0.687	154	1.17	(1.02–1.35)	0.022	159	0.90	(0.78–1.04)	0.165	0.044
Cured meat (g/day)[b]													
<8.23	378	1.00			162	1.00			216	1.00			
8.23–16.21	373	0.94	(0.84–1.04)	0.235	178	0.99	(0.85–1.16)	0.927	195	0.91	(0.78–1.06)	0.211	
>16.21	380	0.95	(0.85–1.06)	0.372	221	1.06	(0.91–1.24)	0.423	159	0.86	(0.73–1.01)	0.070	0.209
Leafy vegetables (g/day)[b]													
<14.39	376	1.00			214	1.00			162	1.00			
14.39–33.56	376	1.00	(0.89–1.12)	0.979	178	0.99	(0.84–1.16)	0.896	198	1.02	(0.86–1.20)	0.825	
>33.56	379	1.00	(0.88–1.13)	0.954	169	0.93	(0.78–1.11)	0.433	210	1.04	(0.87–1.24)	0.661	0.260
Vegetables fruits (g/day)[b]													
<37.26	377	1.00			218	1.00			159	1.00			
37.26–71.74	377	1.01	(0.90–1.13)	0.890	178	0.94	(0.81–1.10)	0.450	199	1.08	(0.92–1.28)	0.344	
>71.74	377	1.01	(0.90–1.14)	0.836	165	1.02	(0.86–1.22)	0.817	212	1.05	(0.88–1.25)	0.612	0.168
Non–citrus fruits (g/day)[b]													
<113.87	378	1.00			193	1.00			185	1.00			
113.87–214.02	377	1.03	(0.92–1.14)	0.613	190	0.95	(0.82–1.1)	0.530	187	1.13	(0.97–1.33)	0.125	
>214.02	376	0.98	(0.87–1.10)	0.712	178	0.88	(0.75–1.03)	0.119	198	1.09	(0.92–1.29)	0.321	0.162
Tubers (g/day)[b]													
<25.01	376	1.00			165	1.00			211	1.00			
25.01–54.96	379	1.06	(0.95–1.18)	0.297	176	0.96	(0.82–1.13)	0.653	203	1.11	(0.96–1.29)	0.157	
>54.96	376	1.07	(0.95–1.20)	0.269	220	0.97	(0.82–1.14)	0.692	156	1.16	(0.98–1.37)	0.085	0.433
Rice (g/day)[b]													
<8.75	377	1.00			183	1.00			194	1.00			
8.75–14.82	380	1.07	(0.97–1.19)	0.183	184	1.08	(0.93–1.26)	0.294	196	1.07	(0.91–1.25)	0.395	
>14.82	374	1.02	(0.92–1.14)	0.689	194	0.93	(0.8–1.08)	0.334	180	1.13	(0.96–1.33)	0.147	0.032
Dietary iron (mg/day)[c]													
Below cut-off point	495	1.00			157	1.00			338	1.00			
Above cut-off point	636	1.09	(0.97–1.22)	0.155	404	1.02	(0.86–1.21)	0.820	232	1.16	(0.98–1.38)	0.075	0.559

[a] GMR using as reference the global geometric mean.
[b] In tertiles.
[c] Cut-off point: 11 mg/day for men and postmenopausal women, and 16 mg/day for premenopausal women.

Table 5
U-Cd (μg/g creatinine) in metal-MCC-Spain in non-smokers participants: Geometric mean ratios adjusted for all the variables included in the table.

	ALL				MEN				WOMEN				Pint
	n (%)	GMR	95%CI	P-val	n (%)	GMR	95%CI	P-val	n (%)	GMR	95%CI	P-val	
Sex													
Male	171												
Female	330	1.20	(1.03–1.40)	0.022									
Age													
<45	68				10				58				
45–54	79	0.76	(0.60–0.97)	0.030	13	1.29	(0.73–2.29)	0.372	66	0.71	(0.53–0.94)	0.018	
55–64	100	0.89	(0.69–1.14)	0.355	43	1.25	(0.77–2.04)	0.364	57	0.80	(0.58–1.11)	0.179	
>64	254	0.97	(0.76–1.23)	0.810	105	1.27	(0.80–2.02)	0.303	149	0.88	(0.65–1.20)	0.407	0.208
Educational level[a]													
Incomplete primary school	88	0.98	(0.84–1.13)	0.733	24	1.02	(0.80–1.30)	0.885	64	0.94	(0.78–1.13)	0.508	
Primary school	169	1.12	(1.01–1.25)	0.028	55	1.27	(1.06–1.52)	0.009	114	1.10	(0.96–1.27)	0.156	
Secondary school	140	1.00	(0.89–1.12)	0.983	46	0.89	(0.74–1.06)	0.195	94	1.06	(0.92–1.23)	0.413	
University graduate	104	0.91	(0.80–1.04)	0.160	46	0.87	(0.72–1.05)	0.155	58	0.91	(0.75–1.09)	0.309	0.619
Passive smoker													
No	103				36				67				
Yes	398	1.01	(0.83–1.22)	0.925	135	0.89	(0.66–1.19)	0.419	263	1.21	(0.93–1.57)	0.161	0.018
Cd related occupation													
No	483				155				328				
Yes	18	0.95	(0.67–1.35)	0.773	16	0.92	(0.64–1.34)	0.669	2	1.93	(0.67–5.60)	0.225	0.256
Season[a]													
Winter	242	1.15	(1.02–1.30)	0.024	73	1.22	(1.01–1.48)	0.040	169	1.09	(0.92–1.29)	0.306	
Spring	116	1.13	(1.00–1.29)	0.054	47	1.23	(1.01–1.51)	0.042	69	1.06	(0.90–1.26)	0.484	
Summer	76	0.79	(0.67–0.93)	0.005	28	0.77	(0.61–0.99)	0.038	48	0.79	(0.63–0.99)	0.045	
Autumn	67	0.97	(0.83–1.13)	0.694	23	0.86	(0.67–1.11)	0.238	44	1.09	(0.89–1.34)	0.405	0.739
Geographical region[a]													
Madrid	263	0.95	(0.84–1.07)	0.379	82	0.86	(0.71–1.05)	0.144	181	0.97	(0.82–1.15)	0.740	
Asturias	86	1.30	(1.14–1.49)	<0.001	29	1.47	(1.15–1.87)	0.002	57	1.23	(1.04–1.46)	0.017	
Cantabria	152	0.81	(0.72–0.92)	0.001	60	0.79	(0.66–0.94)	0.010	92	0.84	(0.70–1.00)	0.048	0.457
Total energy intake (kcals)[b]													
<1612.59	184				43				141				
1612.59–2083.05	175	1.00	(0.84–1.19)	0.977	61	1.20	(0.89–1.62)	0.234	114	0.95	(0.76–1.18)	0.616	
>2083.05	142	0.99	(0.80–1.22)	0.914	67	1.31	(0.92–1.87)	0.140	75	0.83	(0.63–1.08)	0.170	0.139
Eggs (g/day)[b]													
<=10.72	367				129				238				
>10.72	134	0.98	(0.84–1.14)	0.765	42	1.32	(1.03–1.69)	0.031	92	0.85	(0.70–1.03)	0.094	0.016
Cured meat (g/day)[b]													
<8.23	184				49				135				
8.23–16.21	174	0.85	(0.72–0.99)	0.039	60	0.86	(0.66–1.13)	0.271	114	0.80	(0.66–0.98)	0.030	
>16.21	143	0.81	(0.69–0.96)	0.015	62	0.80	(0.61–1.05)	0.114	81	0.79	(0.64–0.98)	0.034	0.901
Leafy vegetables (g/day)[b]													
<14.39	152				56				96				
14.39–33.56	173	1.01	(0.85–1.19)	0.928	61	0.84	(0.63–1.12)	0.222	112	1.13	(0.91–1.40)	0.272	
>33.56	176	1.03	(0.86–1.24)	0.739	54	1.07	(0.79–1.43)	0.673	122	1.03	(0.81–1.30)	0.811	0.078
Vegetable fruits (g/day)[b]													
<37.26	147				58				89				
37.26–71.74	178	1.15	(0.97–1.36)	0.118	57	1.04	(0.79–1.36)	0.794	121	1.19	(0.96–1.49)	0.119	
>71.74	176	1.15	(0.96–1.38)	0.123	56	1.15	(0.86–1.53)	0.345	120	1.14	(0.90–1.43)	0.288	0.338
Non-citrus fruits (g/day)[b]													
<113.87	141				49				92				
113.87–214.02	165	1.06	(0.90–1.25)	0.479	57	0.98	(0.75–1.28)	0.885	108	1.14	(0.92–1.42)	0.224	
>214.02	195	1.05	(0.88–1.24)	0.605	65	1.03	(0.78–1.35)	0.847	130	1.10	(0.88–1.37)	0.424	0.735
Tubers (g/day)[b]													
<25.01	178				52				126				
25.01–54.96	175	1.03	(0.88–1.21)	0.680	57	0.89	(0.67–1.18)	0.417	118	1.06	(0.87–1.29)	0.545	
>54.96	148	1.04	(0.87–1.23)	0.672	62	0.81	(0.60–1.08)	0.143	86	1.14	(0.92–1.42)	0.235	0.506
Rice (g/day)[b]													
<8.75	171				65				106				
8.75–14.82	160	1.08	(0.92–1.27)	0.360	49	1.05	(0.80–1.37)	0.745	111	1.13	(0.91–1.40)	0.274	
>14.82	170	1.11	(0.94–1.31)	0.218	57	1.00	(0.77–1.31)	0.996	113	1.13	(0.91–1.40)	0.267	0.442
Dietary iron (mg/day)[c]													
Below cut-off point	232				48				184				
Above cut-off point	269	1.08	(0.91–1.29)	0.390	123	1.09	(0.81–1.47)	0.556	146	1.14	(0.91–1.43)	0.263	0.322

[a] GMR using as reference the global geometric mean.
[b] In tertiles.
[c] Cut-off point: 11 mg/day for men and postmenopausal women, and 16 mg/day for premenopausal women.

Table 6
Urinary cadmium levels in selected biomonitoring studies.

Author/year publication	Country	N	Sampling Year	Age	Urinary Cadmium concentrations (μg/g creatinine)		
					Total	Men	Women
Present Study	Spain	1282	2008–2013	20–85	0.40 [a]	0.39 [a]	0.41 [a]
MCC-Spain Study					0.40 [b]	0.39 [b]	0.41 [b]
Domingo –Relloso (2019)	Spain	1440	1997-2003	18–85	0.39 [b]	0.41 [b]	0.37 [b]
The Hortega Study							
López-Herranz et al., 2016	Spain	1770	2009	16–65	0.19 [a]	0.17 [a]	0.24 [a]
Bioambient 2016							
Berglund (2015)	16 European countries	1632 (women)	2011–2012	24–52			0.20 [a]
COPHES/DEMOCOPHES							
Pirard (2014)	Belgium	125 (women)	2011–2012	18-45			0.18[a]
COPHES/DEMOCOPHES							
Fréry et al., 2011	France	1930	2006–2007	18–74	0.29 [a]	0.25 [a]	0.33 [a]
Olmedo (2017)	United States	1725	2002	≥15	0.44 [b]	0.31 [b]	0.56 [b]
The Strong Heart Family Study							
Kim (2019)	United States	3900	2007–2012	≥20	0.30 [c]	0.30 [c]	0.40 [c]
NHANES 2007–2012							
Zeng et al., 2013	China	118 (men)	2012	22–47		0.78 [a]	
Lim (2016)	Korea	1953	2010–2012	>18	1.08 [a]		
Korean Research Project on the Integrated Exposure Assessment to Hazardous Materials for Food Safety							
La-Up (2017)	Thailand	288[d]	No data	≥18		1.10 [a]	1.59 [a]
		279[e]				0.36 [a]	0.60 [a]

[a] Geometric Mean
[b] Median.
[c] Arithmetic Mean.
[d] Polluted area.
[e] Non polluted area.

2002), is located there, which could explain the higher U–Cd concentrations found in this region. In contrast, according to data from the Spanish Fertilizer Commercial Society (ACEFER, 2017), in 2017 Asturias was one of the regions with lowest use of phosphate fertilizers within Spain, and the amount of these products consumed in Asturias was half of that consumed in Cantabria (2.5 and 4.9 thousand tonnes, respectively). Of note, recruitment periods in our study were quite different among study regions; region estimates are adjusted by sampling season, but there could be residual confounding due to this factor.

Diet is usually considered as the main source of Cd exposure in non-smoking population. According to the European Food Safety Authority (EFSA), the greatest impact on Cd dietary exposure comes from foods consumed in larger quantities, including the broad food categories of grains and grain products, vegetables and vegetable products, and starchy roots and tubers (EFSA, 2012). However studies that have investigated specific foods as predictors of blood or U–Cd concentrations have shown weak and inconsistent results (Quraishi et al., 2016; Vacchi-Suzzi et al., 2015). Accordingly, in our study, U–Cd variation explained by diet was less than 2% in the entire sample, and around 4% in non-smokers. We only found a limited relation of reported food intake with U–Cd levels, and, again, the associations were sex-specific. In men, those who consumed eggs above the median had higher U–Cd concentrations. Recently, Echeverría et al. (2019) reported a positive association between eggs consumption and Cd concentrations in Spanish people, that they attributed to the grain based diet of hens and the content of fat and albumin, which exhibit high affinity for Cd. Interestingly, the absorption of persistent pollutants by chickens and their excretion through eggs has been a matter of concern for decades (Lovett et al., 1998; Van Eijkeren et al., 2006). However, we did not find this association in women.

On the other hand, in women, but not in men, increasing rice consumption was positively associated with U–Cd concentrations, although the association weakened and became not significant in the multivariate analysis. Rice is the most important dietary source of Cd for many Asian population(Lu et al., 2019; Tsukahara et al., 2003), however, its importance as a source of Cd in Spanish population has not been stablished. A high consumption of tubers marginally increased U–Cd concentrations in women, which is consistent with the results of Martí-Cid et al. (2008), who found that the highest contribution to total Cd intake in Catalonian population corresponded to pulses and tubers. Other foods that have been considered important dietary sources of Cd in adults and elderly people, such as offal, processed meats, and green leafy vegetables (EFSA, 2012), were not associated with increased U–Cd concentrations in our multivariate models, neither in men nor in women. Biological reasons, but also sex differences in food consumption patterns could partially explain the observed results. We evaluated the association of individual food item or food groups collected by the FFQ with U–Cd levels, but our data suggest that men and women may differ in overall dietary patterns, that were not analyzed in our study and that as a whole could impact on the U–Cd levels.

The strengths of our study include the population-based origin of our participants, a relatively large sample size, the availability of information on most of the factors that have previously been related to U–Cd levels, including dietary data collected with a validated food frequency questionnaire (FFQ), and the inclusion of elder and non-active working participants, which have been scarcely studied in previous research on this topic in Spain. Also, we explored possible modification effects of sex in the association between the studied factors and U–Cd.

Our study also has some limitations. The FFQ explored retrospectively the diet of the year prior to the inclusion in the study and therefore it may not accurately reflect cumulative lifetime exposure and may be subject to some degree of measurement error. Although we estimated dietary Fe intake, we did not measure ferritin concentrations, a biomarker of Fe status that can influence the gastrointestinal absorption of Cd (Gallagher et al., 2010; Julin et al., 2011), possibly leaving residual confounding, especially in women who, due to their menstrual and reproductive characteristics, frequently have iron deficiency.

Likewise, the use of self-reported information on exposure to secondhand smoke and the lack of information on the duration and intensity of such an exposure does not allow ruling out possible misclassification of the study subjects. However, given that participants did not know their U–Cd levels, we expect that the possible misclassification

would lead to a non-differential measurement error.

Another limitation is that we used a spot urine sample from each participant. Some studies have observed only a moderate within-person correlation for repeated measures of U–Cd concentrations (Gunier et al., 2013; Yamagami et al., 2008), suggesting that a single measurement could not accurately reflect medium-to long-term body burden. However, a recent review shows a high degree of temporal stability in the U–Cd biomarker, as evidenced by intraclass correlation coefficient values ranging from 0.66 to 0.81 regardless of spot samples or first morning voids, suggesting that short-term variability in dietary exposures is likely only a small contributor to the U–Cd measure (Vacchi-Suzi et al., 2016).

5. Conclusions

The levels of U–Cd found in the study participants could represent a potential risk of Cd related adverse health outcomes.

The observed differences in U–Cd levels among the studied regions and by season suggest that there are local and/or seasonal unknown conditions involved in the exposure to cadmium that warrant further investigation. Differences between men and women in relation to some sociodemographic and dietary variables associated with U–Cd concentration highlight the relevance of studying them separately. In general, the diet contribution to U–Cd levels is small, although it seems to be more important in non-smokers. Smoking status is the main modifiable predictor of U–Cd concentration, both in men and women but second-hand smoke exposure could be an important source of cadmium exposure in women.

These findings are highly relevant from a public health point of view and highlight the importance of maintaining and strengthening actions to combat tobacco consumption, as well as to include cadmium in human biomonitoring surveys.

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Ethical statement

All procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human subjects and with The Code of Ethics of the World Medical Association (Declaration of Helsinki). MCC-Study was approved by the Ethics Committees of the participating centers, and the specific study reported here was approved by the Ethics and Animal Welfare Committee of the Carlos III Institute of Health (reference CEI PI 44_2012).

Declaration of competing interest

The authors declare that they have no conflicts of interest. This article presents independent research. The views expressed are those of the authors and not necessarily those of the Carlos III Institute of Health.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.112959.

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