Environmental Research 187 (2020) 109618

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Blood cadmium levels and sources of exposure in an adult urban population in southern Brazil

Airton C. Martins[a,1], Mariana R. Urbano[b,1], Ana Carolina B. Almeida Lopes[c], Maria de Fatima H. Carvalho[d], Marcia L. Buzzo[d], Anca O. Docea[e], Arthur E. Mesas[f], Michael Aschner[a,g], Ana Maria R. Silva[c], Ellen K. Silbergeld[h], Monica M.B. Paoliello[a,c,*]

[a] Department of Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, 10461, Bronx, NY, USA
[b] Department of Statistics, State University of Londrina, Rodovia Celso Garcia Cid, Km 380, S/no, Campus Universitário, 86057-970, Londrina, PR, Brazil
[c] Graduate Program in Public Health, Center of Health Sciences, State University of Londrina, 60 Robert Koch Avenue, 86038-350, Londrina, PR, Brazil
[d] Inorganic Contaminants Department, Adolfo Lutz Institute, Sao Paulo, Avenida Doutor Arnaldo, 355, 01246-000, São Paulo, SP, Brazil
[e] Department of Toxicology, University of Medicine and Pharmacy of Craiova, 200349, Craiova, Romania
[f] Universidad de Castilla-La Mancha, Facultad de Enfermería, Edificio Melchor Cano, Campus Universitario de Cuenca, Camino de Pozuelo, S/n 16071, Cuenca, Spain
[g] I. M. Sechenov First Moscow Medical University (Sechenov University), Bolshaya Pirogovskaya St., 19-1, 119146, Moscow, Russia
[h] Emerita Professor, Johns Hopkins University, Bloomberg School of Public Health, 615 N Wolfe St, 21205, Baltimore, MD, USA

ARTICLE INFO

Keywords:
Blood cadmium
Adults
General population

ABSTRACT

Background: Cadmium (Cd) is a toxic metal that is widely present in the environment due to geologic and anthropogenic sources. Exposures to high Cd levels may cause nephrotoxicity, carcinogenicity, pulmonary and cardiovascular disease, among others. The goal of this study was to investigate in an adult urban population whether an association exists between sources and levels of Cd exposure and blood Cd concentrations.

Methods: Using a census-based design, a total of 959 adults, aged 40 years or older, were randomly selected. Information on socio-demographics, dietary, and lifestyle background was obtained by household interviews. Blood Cd levels were measured by inductively coupled-plasma mass spectrometry. Geometric means (GM) (95% CI) and the 50th percentile were determined, stratified by sex, age, race, education, income class, smoking status, consumption of vegetables, red meat and milk, occupation and blood pressure. To assess the association between Cd exposure and the aforementioned variables, we estimated the geometric mean ratio (GMR) (95%CI) of blood Cd concentrations.

Results and conclusion: The geometric mean (95%CI) of blood Cd levels in the total population was 0.25 (0.22, 0.27) ug/dL. In a univariate analysis, significantly higher blood Cd levels were found in men ($p < 0.001$), current and former smokers ($p < 0.001$), alcohol drinkers ($p < 0.001$), those who never or almost never consumed milk ($p < 0.001$), and in subjects with higher diastolic blood pressure ($p = 0.03$). Significant correlations were found between the number of cigarettes consumed daily and blood Cd levels. Multivariate analysis confirmed higher blood Cd concentrations were associated with alcohol consumption (GMR 95%CI = 1.28, 1.04–1.59) and in former and current smokers (GMR 95% IC = 1.33, 1.06–1.67 and 4.23, 3.24–5.52, respectively). Our results shed novel information on variables associated with blood Cd levels in an urban Brazilian population, and should encourage additional research to prevent environmental Cd exposure, both in Brazil and globally.

1. Introduction

Cadmium (Cd) is a toxic metal that is widely present in the environment due to geologic and anthropogenic sources. Cadmium can have negative health consequences, including increased risk of cancer, kidney dysfunction, skeletal damage, pulmonary disease and cardiovascular diseases, possibly being harmful to endothelial cells (Hecht et al., 2016; Jarup and Akesson, 2009; Luckett et al., 2012; Madrigal et al., 2019).

Cd is ranked 7th in the list of Hazardous Substance Priority List

* Corresponding author. Department of Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, 10461, Bronx, NY, USA.
E-mail addresses: monibas2@gmail.com, monica.paoliello@einstein.yu.edu, monica.paoliello@einsteinmed.org (M.M.B. Paoliello).
[1] Both authors have equally contributed to this manuscript.

https://doi.org/10.1016/j.envres.2020.109618
Received 30 March 2020; Received in revised form 24 April 2020; Accepted 29 April 2020
Available online 13 May 2020
0013-9351/

established by the US ATSDR (ATSDR, 2019).

The most common sources of Cd exposure in the general population include food and cigarette smoke. Smoking status predicts blood Cd concentrations, with significant differences in mean blood Cd levels between never *versus* former and current smokers (Abass et al., 2017; Hecht et al., 2016; Jarup et al., 1998; Nisse et al., 2017; Wiseman et al., 2017). In addition, the number of daily smoked cigarettes is associated with blood Cd concentrations (Hecht et al., 2016).

For the non-smoking population, diet is the most important source of Cd exposure (Garner and Levallois, 2016). A study in Canada showed that Cd had a high soil-to-root translocation, and high environmental mobility and solubility, therefore, when present in agricultural soils, Cd may be readily taken up by several cultivars (Wiseman et al., 2014, 2017). Generally, some cereals and vegetables are important dietary sources of Cd (Ahn et al., 2017b; Olsson et al., 2002). Various milk products, red meat and particularly processed meat consumption have been shown to be negatively associated with Cd concentration in blood or urine (Krajcovicova-Kudladkova et al., 2006; Olmedo et al., 2017; Wiseman et al., 2017). In addition to diet, an association between blood Cd levels and age may also exist (Garner and Levallois, 2016; Nisse et al., 2017). Given the long half-life of Cd and its propensity to accumulate in the kidney over time (Franceschini et al., 2017), urinary Cd levels may represent an optimal biomarker for assessment of the relationship between Cd and age.

Blood Cd is the most reliable biomarker of recent exposure and is usually assessed in whole blood (Jarup and Akesson, 2009). In addition, Roels et al. (1999) have demonstrated the utility of urinary cadmium as a biomarker in workers chronically exposed to Cd, reflecting largely past and life-time exposures (Roels et al., 1999). Furthermore, blood Cd concentrations show a good correlation with urine Cd levels (Gil et al., 2011; Hecht et al., 2016; Sun et al., 2016).

Taken together, the goal of this study was to investigate in an adult urban population whether an association exists between sources and levels of Cd exposure and blood Cd concentration. In addition, we aimed to verify whether there is a relationship between blood Cd levels and blood pressure in the same population.

2. Methods

This study followed the "Strengthening the Reporting of Observational studies in Epidemiology" (STROBE) guidelines.

2.1. Study population and sampling process

The present study used a census-based design in a general population, aged 40 or older, living in the urban area from the city of Cambe, Southern Brazil. At the time of the recruitment the city had a total of 92,888 inhabitants, of whom around 33% were in the defined age group (IBGE, 2009). All census tracts in the urban region were included in the study and the number of subjects to be interviewed in each tract was calculated proportionally to the amount of men and women aged 40 or older. The sample size was calculated using the StatCalc application Epi Info 3.5.1 program, and the final sample size was estimated in 1066 subjects. Predicting losses and refusals, the sample was increase by 25%. A total of 1180 of the selected participants completed the interview and 959 of these volunteers performed blood collection. Complete information of the study design and sampling has already been published (Almeida Lopes et al., 2015).

This research was approved by the Ethics Committee of the State University of Londrina (research protocol number 236/10). During data collection, all the participants were asked to sign a consent form after being aware of the research objectives.

2.2. Data collection and study variables

Data collection was performed by a household interview carried out by trained personnel, followed by anthropometric and blood pressure measurements. At the time of the interview, the collection of biological material was scheduled. A pilot test was carried out with volunteers in a nearby city to optimize the questionnaire.

Information on gender, age, race, education, income class, occupation, vegetables, red meat and milk consumption, smoking, alcohol consumption and hypertension status was obtained from each subject.

Systolic and diastolic blood pressure were measured by digital equipment Omron HEM 742. The measures were in accordance with the guidelines of the VI Brazilian Guidelines on Hypertension (SBH, 2010) where three measurements were taken with 1-min interval between them. The mean of the last two blood pressure measurements was considered the most accurate blood pressure. Participants were considered as hypertensive if any of the following criteria were present: a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or self-reported use of antihypertensive medication.

According to self-reported answers, race was categorized as white and non-white, and education was based in the number of years of education completed (0–3, 4–7, 8–11, and 12 or more years of study).

Income class was set according to the Brazilian Association of Research Companies (ABEP, 2010), that estimates the purchasing power and economic status of participants. This variable was categorized for this study as A/B classes (corresponding to the higher income levels), C class (medium income level), and D/E classes (related to the lower income levels). Potential exposure to cadmium by volunteers in occupational settings was verified through self-reported current or former employment.

During the household interview, we asked participants how many days during the week he/she ate at least one type of the following vegetables: lettuce, tomato, cabbage, chayote, eggplant, or zucchini. Consumption data were categorized into never/almost never, 1 to 4 times a week and 5 to 7 times a week. The volunteers also reported on the weekly frequency of red meat consumption: never/almost never, 1 to 4 times a week and 5 to 7 times a week.

Smoking status was based on self-report that was categorized as never-smoker, former smoker and current smoker. Current smoker was defined as someone who has smoked at least 1 cigarette every day of the 30 days before the interview, and former smoker as one who has smoked at least 100 cigarettes in his/her lifetime, but who quit smoking at the time of interview (NHIS, 2017). To assess the influence of the number of cigarettes smoked on blood Cd levels, groups of smokers were established up to 9 cigarettes per day, 10 to 20 cigarettes and over 20 cigarettes per day.

Alcohol consumption was stratified by the amount and frequency of drinking. Drinkers were classified as individuals who drank occasionally (less than twice a week), frequently (two to six times a week), or daily. Drinkers not fitting in the above groups but consuming alcohol over the last 30 days were divided into those binging on 4 (women) or 5 (men) alcohol drinks at least on one occasion (over the last 30 days). Binging reflects 4 to 5 cans of beer, 4 to 5 glasses of wine or 4 to 5 drinks containing sugar cane, whiskey or other distilled beverages.

2.3. Blood sampling and determination of blood Cd levels

Whole blood samples (5 ml) were obtained by venipuncture, collected in heparinized metal-free containers (BD Vacutainer®, Plymouth, UK), and stored at −20 °C until processed. Blood cadmium determinations were performed using an Inductively Coupled Plasma Mass Spectrometry (ICP-MS), model Elan DRC II, PerkinElmer (Norwalk, CT, EUA), in the Adolfo Lutz Institute, São Paulo, Brazil.

In order to determine Cd levels in blood, an aliquot of 100 µl total blood, previously heparinized, was diluted in 1900 µl solution containing 0.05% v/v Triton® X-100 PA, CAS 9002-93-1 (Merck, Darmstadt – Germany) plus 0.2% (v/v) HNO_3 65% Suprapur ®, CAS 7697-37-2 (Merck, Darmstadt – Germany). Samples were analyzed against matrix-

Table 1
Participants' characteristics and blood cadmium levels (μg/L).

Characteristic	n (%)	Percentile 50 th	Interquartile range	Min-max values	GM (95% CI)	p-value*
Overall	959 (100)	0.37	0.28	0.04–3.77	0.25 (0.22, 0.27)	
Sex						< 0.001
Men	426 (44.4)	0.4	0.28	0.004–3.08	0.28 (0.24, 0.32)	
Women	533 (55.6)	0.36	0.26	0.004–3.77	0.22 (0.19, 0.25)	
Age (years)						0.35
40–49	388 (40.5)	0.38	0.25	0.004–2.76	0.25 (0.22, 0.30)	
50–59	300 (31.3)	0.37	0.31	0.004–3.08	0.26 (0.22, 0.31)	
≥60	271 (28.2)	0.36	0.28	0.004–3.77	0.22 (0.18, 0.27)	
Race						0.44
White	570 (59.4)	0.37	0.26	0.004–3.08	0.25 (0.22, 0.28)	
Non white	389 (40.6)	0.38	0.31	0.004–3.77	0.24 (0.20, 0.28)	
Education (years)						0.06
0–3	233 (24.3)	0.36	0.28	0.004–3.77	0.22 (0.18, 0.28)	
4–7	360 (37.5)	0.39	0.3	0.004–3.08	0.26 (0.22, 0.31)	
8 or more	366 (38.2)	0.37	0.27	0.004–2.86	0.25 (0.21, 0.29)	
Income class[a]						0.41
A and B	373 (39.1)	0.37	0.24	0.004–2.86	0.24 (0.21, 0.28)	
C	500 (52.1)	0.37	0.32	0.004–3.08	0.26 (0.22, 0.29)	
D and E	84 (8.8)	0.39	0.27	0.004–3.77	0.20 (0.14, 0.30)	
Smoking						< 0.001
Never[a]**	505 (52.6)	0.32	0.23	0.004–3.77	0.17 (0.15, 0.20)	
Former[b]	271 (28.3)	0.38	0.24	0.004–1.82	0.23 (0.19, 0.28)	
Current[c]	183 (19.1)	0.81	0.57	0.004–3.08	0.74 (0.66, 0.83)	
Alcohol intake						< 0.001
Do not drink	593 (61.8)	0.35	0.29	0.004–3.77	0.21 (0.18, 0.24)	
Drink	366 (38.2)	0.41	0.26	0.004–3.08	0.32 (0.28, 0.37)	
Vegetable intake[c]						0.311
Never-almost never	67 (6.9)	0.38	0.3	0.004–2.05	0.31 (0.22, 0.44)	
1–4 days/wk	264 (27.5)	0.38	0.32	0.004–1.98	0.24 (0.20, 0.29)	
5–7 days/wk	627 (65.4)	0.37	0.26	0.004–3.77	0.24 (0.21, 0.27)	
Red meat intake						0.27
Never-almost never	51 (5.3)	0.39	0.24	0.004–1.82	0.29 (0.20, 0.43)	
1–4 days/wk	516 (53.8)	0.37	0.27	0.004–3.77	0.23 (0.20, 0.27)	
5–7 days/wk	391 (40.9)	0.37	0.31	0.004–3.08	0.26 (0.22, 0.30)	
Milk intake[c]						< 0.001
Never-almost never[a]**	307 (32.0)	0.42	0.3	0.004–3.77	0.30 (0.25, 0.36)	
1–4 days/wk[a]	131 (13.7)	0.4	0.29	0.004–2.86	0.31 (0.24, 0.40)	
5–7 days/wk[b]	520 (54.3)	0.34	0.26	0.004–3.08	0.21 (0.18, 0.24)	
Occupation[d]						0.36
Non exposed	847 (88.3)	0.37	0.27	0.004–3.77	0.25 (0.22, 0.27)	
Exposed	112 (11.7)	0.41	0.35	0.004–2.56	0.24 (0.17, 0.33)	
Systolic blood pressure[e]						0.49
< 140 mm Hg	603 (63.6)	0.38	0.29	0.004–2.86	0.25 (0.22, 0.28)	
≥140 mm Hg	345 (36.4)	0.37	0.27	0.004–3.77	0.25 (0.21, 0.29)	
Diastolic blood pressure						0.03
< 90 mm Hg	714 (75.3)	0.37	0.27	0.004–3.77	0.24 (0.21, 0.27)	
≥90 mm Hg	234 (24.7)	0.4	0.29	0.004–3.08	0.28 (0.23, 0.34)	
Hypertension[e,f]						0.79
No	550 (57.3)	0.37	0.29	0.004–2.86	0.24 (0.21, 0.28)	
Yes	398 (41.5)	0.38	0.28	0.004–3.77	0.25 (0.22, 0.29)	

GM: geometric mean.
*p-value obtained in the Mann-Whitney test (Wilcoxon Rank Sum Test) or Kruskal-Wallis test.
**Equal letters indicate that there are no differences between blood Cd levels among the groups, and different letters indicate that there are such differences.
[b]According to Associação Brasileira de Empresas de Pesquisa, 2012.
[c]Data missing for one participant.
[d]Participants working in industries located in the urban area, classified according with CNAE (National Classification of Economic Activities).
[e]11 missing data on these variables (n = 948).
[f]Hypertension defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or current antihypertensive medication.

matching calibration. As internal standard, a solution of Indium 5 μg/L was used. The monitored isotopes were ^{111}Cd and ^{115}In. All sample preparation procedures and reagents were performed in an ISO class 7 cleanroom, equipped with an ISO class 5 laminar flow hood.

To evaluate the accuracy of the results, the standard reference material Toxic Metals in Bovine Blood, from National Institute of Standards and Technology (NIST 966 level 2) was used. The obtained result was: 5.19 ± 0.24 μg/L, showing good agreement with the certified value, 5.22 ± 0.16 μg/L. The within-and-between batch precision were 4.2% and 4.6% respectively. The detection limit (LOD) and the quantification limit (LOQ) were obtained by 10 consecutive measurements of a blood sample with low cadmium concentration. The LOD and LOQ were 0.002 μg/L and 0.005 μg/L, respectively.

2.4. Statistical analysis

For samples where the blood Cd levels were below the LOQ, we used values corresponding to the LOQ divided by the square root of two (LOD/√2), considering that most of the metals are log distributed. Therefore, LOD/√2 better corresponds (than LOQ/2) to what would be the median of the distribution of values below the LOQ.

Analyses were performed using the statistical software R Core Team

Table 2
Male and female' differences on smoking behaviors in the studied population.

Smoking	Sex		
	Female	Male	Total
Never			
N	349[aa]	156[ba]	505
%	65.5	36.6	52.7
Former			
N	106[aa]	165[ba]	271
%	19.9	38.7	28.3
Current			
N	78[aa]	105[ba]	183
%	14.6	24.6	19.1

[a] Equal letters indicate that there are no differences between blood Cd levels among the groups, and different letters indicate that there are such differences.

(2020). In order to identify the variables related to blood Cd levels, univariate analysis was performed followed with multivariate analysis to further identify confounding variables. Geometric means (GM) and corresponding 95% confidence intervals (95% CI) and the percentile 50th were determined, stratified by sex, age, race, education, income class, smoking status, consumption of vegetables, red meat and milk, occupation and blood pressure. We also determined the coefficient of skewness for all stratified variables.

For blood Cd level comparisons for variables with two groups (for example, sex), we applied Mann-Whitney test (Wilcoxon Rank Sum Test). For comparisons of blood Cd concentrations for variables with three groups (for example, smoking) we applied the Kruskal-Wallis test followed by a *post hoc* test. Statistical significance was set at $p < 0.05$.

To assess the association between Cd exposure and socio-demographic, lifestyle variables and blood pressure, we estimated the geometric mean ratio (GMR) and corresponding 95% confidence intervals (95% CI) of blood Cd concentrations. The estimates were obtained by fitting linear regression models, considering log (Cd) as response variable and the others as explanatory variables. GMR [exp (Beta)] and the respective confidence intervals were extracted from the model parameters.

For comparisons of blood Cd levels for variables with two groups (for example, sex) we applied the Wilcoxon test. For comparisons of blood Cd concentrations for variables with three groups (for example, smoking) we applied the Kruskal-Wallis test followed by a *post hoc* test. Statistical significance was set at $p < 0.05$.

To assess the association between Cd exposure and socio-demographic, lifestyle variables and blood pressure, we estimated the geometric mean ratio (GMR) and corresponding 95% confidence intervals (95% CI) of blood Cd concentrations.

For comparisons of blood Cd levels in groups related to the number of cigarettes smoked daily, we used ANOVA (data was transformed using the Box-Cox transformation) followed by the Tukey test for multiple comparisons.

3. Results and discussion

3.1. Participants characteristics and blood Cd distribution

This study presents data on blood Cd concentrations in an urban population in Southern Brazil, aged 40 years and older. Furthermore, the study evaluated the association between blood Cd levels, sources of Cd human exposure and blood pressure. Participants completed the interview, performed anthropometric measurements and blood samples were obtained from the 959 individuals.

As can be seen in Table 1, 55.6% of the participants were women, and 40.5% of the subjects were in the 40–49 age group, with approximately 28% being 60 years or older. More than half of the participants belonged to economic class C and 38.2% had 8 or more years of education. Most of the subjects never smoked (52.6%) and did not drink (61.8%).

The coefficient of skewness measures the symmetry of data distribution, and in the present study it varied from 1.49 to 5.96 for the different variables. For blood Cd levels, the percentage of samples with values below the LOQ were 11% which may contribute to a skewed distribution. To address this issue, we used the adjusted geometric mean ratio (GMR) (95% CI) of blood Cd concentrations by studied variables. GMR has been proposed as alternative effect measure for skewed continuous data (Friedrich et al., 2012).

Table 1 shows that the geometric mean (95%CI) of blood Cd levels in the total population was 0.25 (0.22, 0.27) μg/dL, and significantly higher in men than women (GM 95%CI = 0.28, 0.24–0.32 *vs* 0.22, 0.19–0.25 μg/dL, respectively) ($p < 0.001$). We also found significant differences in blood Cd levels between non-smoking, former smoking and current smoking participants (GM 95%CI = 0.17, 0.15–0.20; 0.23, 0.19–0.28; 0.74, 0.66–0.37 μg/dL, respectively) ($p < 0.001$). In addition, higher levels of blood Cd levels were found in smokers – up to 9, from 10 to 20 and more than 20 cigarettes/day (0.75 μg/dL, 0.98 μg/dL, and 1.21 μg/dL respectively, n = 183) compared to non-smokers (0.17 μg/dL, n = 505). Significant differences were observed between the group that consumed up to 9 cigarettes/day and the other two groups with higher consumption. Table 2 presents smoking status, showing significant differences between males *vs.* females (categorized as non-smoker, former and current smoker), showing that men smoked significantly more than women. The univariate analysis (Table 1) also showed that alcohol drinkers had blood Cd levels significantly higher than non-drinkers (GM 95% CI = 0.32, 0.28–0.37 *vs* 0.21, 0.18–0.83 μg/L, respectively) ($p < 0.001$). Significant differences in blood Cd concentrations were found between subjects that never or almost never consumed milk, those who consumed milk one to four days a week and five to seven days a week (GM (95%CI) = 0.30, 0.25–0.36; 0.31, 0.24–0.40 and 0.21, 0.18–0.24 μg/L, respectively) (< 0.001). Participants with higher blood Cd levels had higher diastolic blood pressure than those with normal diastolic blood pressure (GM 95%CI = 0.28, 0.23–0.34 *vs* 0.24, 0.21–0.27 μg/dL) ($p = 0.03$) (Table 1).

In the multivariate analysis (Table 3) smoking was associated with blood Cd concentrations for former and current smokers (GMR 95% IC = 1.33, 1.06–1.67 and 4.23, 3.24–5.52, respectively). Alcohol consumption was also associated with blood Cd concentrations (GMR 95%CI = 1.28, 1.04–1.59). As shown in Table 3, univariate analysis established milk consumption was inversely associated with blood Cd levels, whereas for higher consumption of milk the GMR 95%IC was equal to 0.69, 0.55–0.85 μg/dL. However, in the adjusted model, the association was not confirmed. Systolic and diastolic blood pressure and hypertension were not associated with blood Cd levels in the multivariable analysis. The same held up for the other studied variables (Table 3).

3.2. Blood Cd concentrations and co-variates

3.2.1. Smoking

A strong association between Cd blood concentration and smoking was noted, corroborating previous studies (Bjermo et al., 2013; Garner and Levallois, 2017; Hecht et al., 2013; Madeddu et al., 2011; McKelvey et al., 2007; Nisse et al., 2017; Richter et al., 2009; Takeda et al., 2017; Tellez-Plaza et al., 2010). Recently, Repic et al. (2020) showed that smokers had 3.5 times higher blood Cd levels than non-smokers. Our study also showed that blood Cd levels increase with the number of cigarettes smoked, corroborating findings by Hecht et al. (2016) and Korečková-Sysalová. (1997), and establishing that tobacco smoking is an important source of Cd exposure (Koreckova-Sysalova, 1997).

The high concentration of Cd in cigarette reflects the ability of tobacco plants to absorb Cd from the soil and concentrate high levels of the metal in its leaves (around 650–3630 ng/g tobacco) (Piade et al.,

Table 3
- Ratio (95% CI) of the geometric means of blood cadmium levels (μg/L) by socioeconomic and lifestyle variables.

		Crude GM	Adjusted[a] GM
	n	Ratio (95%CI)	Ratio (95%CI)
Sex			
Female	533	1.00 (reference)	1.00 (reference)
Male	426	1.28 (1.05, 1.56)	0.98 (0.79, 1.23)
Age (years)			
40–49	388	1.00 (reference)	1.00 (reference)
50–59	300	1.03 (0.81, 1.30)	1.06 (0.85, 1.34)
≥60	271	0.87 (0.69, 1.11)	1.00 (0.76, 1.32)
Race			
White	570	1.00 (reference)	1.00 (reference)
Non-white	389	0.94 (0.77, 1.15)	0.88 (0.72, 1.07)
Education (years)			
0–3	233	1.00 (reference)	1.00 (reference)
4–7	360	1.15 (0.89, 1.49)	1.01 (0.77, 1.32)
8 or more	366	1.11 (0.86, 1.43)	1.05 (0.77, 1.42)
Income class			
A and B	373	1.00 (reference)	1.00 (reference)
C	500	1.05 (0.85, 1.29)	0.95 (0.76, 1.19)
D and E	84	0.83 (0.57, 1.20)	0.81 (0.55, 1.20)
Smoking			
Never	505	1.00 (reference)	1.00 (reference)
Former	271	1.37 (1.10, 1.70)	1.33 (1.06, 1.67)
Current	183	4.33 (3.38, 5.55)	4.23 (3.24, 5.52)
Alcohol intake			
Do not drink	593	1.00 (reference)	1.00 (reference)
Drink	366	1.54 (1.25, 1.88)	1.28 (1.04, 1.59)
Vegetable intake			
Never – almost never	67	1.00 (reference)	1.00 (reference)
1–4 days/wk	264	0.77 (0.50, 1.17)	0.94 (0.63, 1.40)
5–7 days/wk	627	0.77 (0.52, 1.15)	0.98 (0.67, 1.44)
Red meat intake			
Never – almost never[a]	51 (5.3)	1.00 (reference)	1.00 (reference)
1–4 days/wk[a]	516 (53.8)	0.80 (0.51, 1.26)	0.78 (0.50, 1.20)
5–7 days/wk[b]	391 (40.9)	0.88 (0.56, 1.39)	0.71 (0.45, 1.10)
Milk intake			
Never – almost never	307	1.00 (reference)	1.00 (reference)
1–4 days/wk	131	1.04 (0.76, 1.43)	1.07 (0.79, 1.44)
5–7 days/wk	520	0.69 (0.55, 0.85)	0.88 (0.71, 1.09)
Occupation			
Not exposed	847	1.00 (reference)	1.00 (reference)
Exposed	112	0.96 (0.71, 1.31)	0.78 (0.58, 1.06)
Systolic blood pressure[e]			
< 140 mm Hg	603 (63.6)	1.00 (reference)	1.00 (reference)
≥140 mm Hg	345 (36.4)	0.99 (0.80, 1.21)	0.86 (0.55, 1.36)
Diastolic blood pressure[e]			
< 90 mm Hg	714 (75.3)	1.00 (reference)	1.00 (reference)
≥90 mm Hg	234 (24.7)	1.18 (0.94, 1.49)	0.93 (0.67, 1.29)
Hypertension[e,f]			
No	550 (57.3)	1.00 (reference)	1.00 (reference)
Yes	398 (41.5)	1.04 (0.85, 1.27)	1.27 (0.75, 2.15)

[a] Adjusted for sex, age, race, education, income class, smoking, alcohol consumption, vegetables consumption, milk intake and occupation.

2015). Cd in tobacco may be volatilized by high temperatures during the burning process, generating particulate matter that is readily inhaled and absorbed (Cuello-Nunez et al., 2018; Pappas et al., 2015). In general, cigarettes contain 1–2 μg of Cd, with ~50% of the being Cd inhaled and absorbed upon smoking (Elinder et al., 1976; Jarup et al., 1998; Nordberg and Nordberg, 1987). Moreover, it has been estimated that a person smoking 20 cigarettes/day will absorb 1 μg of Cd (Jarup et al., 1998).

3.2.2. Diet

For nonsmokers, several studies have demonstrated the impact of diet on blood Cd levels in the general population (Ghoochani et al., 2019; Krajcovicova-Kudladkova et al., 2006; Olsson et al., 2002).

Vegetables and fruits, whole grain products, grain sprouts, and seeds are known sources of Cd in the general population, and appear to have more impact on blood Cd levels than other sources of food such as meat (Krajcovicova-Kudladkova et al., 2006). Kim et al. (2018) noted that lettuce intake contributed to total intake of Cd (14%) in Caucasian and Black US residents; however, this study included children as well as adults (Kim et al., 2018). We failed to observe an association between blood Cd levels and vegetable intake. Other authors have also failed to note an association between vegetable, nut and seed, as well as fruit intake with blood Cd concentrations (Bjermo et al., 2013; Garner and Levallois, 2017; Olsson et al., 2002). Nonetheless, in another study, increased consumption of leafy vegetables (Sakellari et al., 2016) and green vegetables (Park and Lee, 2013) were both associated with higher blood Cd levels.

Dietary rice is an important source of Cd, especially in Asia, and it has been shown to be positively associated with blood Cd levels (Huang et al., 2019; Park and Lee, 2013). Brazil is the greatest non-Asian rice producer, with an average yearly consumption of 50 kg/person (Almeida Lopes et al., 2019; Paulelli et al., 2019). Kato et al. (2019) have compared the amount of Cd in rice in three different geographic regions in Brazil (Rio Grande do Sul, Santa Catarina, and Mato Grosso States), noting that the production method (flooded or upland), soil properties, water, and other local characteristics can lead to differences in Cd content in rice. However, all rice samples showed Cd level below the maximal limit established by the National Agency of Health Surveillance (ANVISA, 2013; Kato et al., 2019). We did not collect information on rice consumption, therefore we are not able to analyze the relationship between rice intake and blood Cd levels in our study population. Furthermore, although we have plentiful data on vegetable consumption habits, we lack information on the consumption of other plant-derived foods, thus we are unable to fully characterize the dietary Cd sources. However, it should be kept in mind that overall dietary differences explain only a small percentage of variation in blood Cd levels (Garner and Levallois, 2016).

We noted lack of significant differences in blood Cd levels in consumers *vs.* non-consumers of red meat; beef was the most consumed type of meat in our population. In another study blood Cd concentrations were negatively associated with red meat intake (Bjermo et al., 2013). An analogous relationship was noted with increased blood Cd concentrations upon decreased meat consumption, and a significantly higher mean blood Cd levels in vegetarians *vs.* non-vegetarians (Krajcovicová-Kudláková et al., 2006). While Olmedo et al. (2017) reported that processed meat may be a potential dietary source of Cd, it needs to be considered that the study analyzed urinary Cd (and not blood) as a biomarker of exposure. Caution should be exercised in contrasting these studies given that the studied populations consume different diets.

We found that participants with higher cow's milk consumption (not including soy milk) had significantly lower blood Cd levels, however this finding was not confirmed in the adjusted analyses. In the study by Wiseman et al. (2017), milk consumption was negatively associated with blood Cd concentrations in the adjusted regression model ($p < 0.001$). There is substantial evidence that Cd absorption is modulated by metals, such as Zn, Fe and Ca, and that a low dietary intake of these micronutrients may result in higher rates of gastrointestinal absorption and accumulation of Cd (Vesey, 2010; Wiseman et al., 2017). In the study of Madeddu et al. (2011), the intake of Ca was negatively correlated with blood Cd levels in females.

Global variations in toxicants exposures need to be considered. It is noteworthy that the above cited studies were performed in different countries and at times in different regions within a particular country. Therefore, the differences in Cd concentrations in soil and food may reflect the differences in the observed blood Cd levels in these populations. In addition, the smoking status of the population may also contribute to differences in blood Cd levels.

3.2.3. Alcohol consumption

Exposure to Cd and drinking remains a controversial issue. We

found that drinkers had blood Cd levels significantly higher than non-drinkers (GM 95% CI = 0.32, 0.28–0.37 *vs* 0.21, 0.18–0.83 μg/L, respectively) ($p < 0.001$), and this finding was corroborated in the adjusted analysis, where drinking was associated with higher blood Cd levels (GMR 95%CI = 1.28, 1.04–1.59). Beer and draft beer are the most consumed alcoholic beverage (nearly 60%) by Brazilian adults of both genders, followed by wine (Laranjeira et al., 2010). Notably, alcohol consumption was positively associated with higher blood Cd concentrations in the study of Park and Lee, 2013. In a multivariate logistic regression analysis, alcohol consumption (OR = 4.31) was found as independent predictor of higher blood Cd levels in Korean adolescents (Ahn et al., 2017). On the other hand, Forte et al. (2011), Bjermo et al. (2013) and Huang et al. (2013) reported that alcohol intake did not influence blood Cd levels in the general population. In a study addressing the influence of alcohol on Cd turnover in rats, Brzóska et al. (2013) demonstrated that excessive alcohol consumption combined with long-term moderate or relatively high exposure to Cd resulted in lower body burden of Cd. Accordingly, it seems possible that the body burden of Cd in individuals drinking alcohol may be lower compared to nondrinking counterparts. Thus, drinking habits must be taken into account as confounding factors in the monitoring of Cd exposure (Brzoska et al., 2013).

3.2.4. Sex and age

Our study showed no significant differences between blood Cd levels and age. Several studies have shown a positive association between blood Cd levels and age, where older people had higher blood Cd concentrations (Bjermo et al., 2013; Huang et al., 2013; Kira et al., 2016; Krajcovicova-Kudladkova et al., 2006; Olsson et al., 2002; Sakellari et al., 2016). These findings can be explained by the long biological half-life of Cd in the body (Krajcovicová-Kudládková et al., 2006). Corroborating our results, a recent Brazilian study of an Amazonian population reported that age did not affect blood Cd levels (Naka et al., 2020). However, considering that Cd has a long half-life in kidneys (Franceschini et al., 2017), urinary Cd may be a better biomarker for the relationship between age and accumulation, representing cumulative exposure and body-burden of this metal (Sun et al., 2016).

We observed significantly higher blood Cd levels in males than in females, but these differences were not achieved in the adjusted analysis. Men and women differ in the extent to which sources of exposure are related to overall blood and urinary cadmium levels (Garner and Levallois, 2017). Our sample showed significant differences in smoking behaviors between males and females. Compared to males, we noted greater number of females who never smoked, and vice versa, more current and former smoking males compared to females. As previously discussed, smoking was strongly associated with blood Cd levels both in our study and those reported by others (Tellez-Plaza et al., 2010; Hecht et al., 2013). Therefore, smoking habits should be considered as a potential confounding variable when evaluating the relationship between sex and blood Cd levels. Our findings are consistent with observations in Brazil (Naka et al., 2020; Kira et al., 2016) China (Li et al., 2014) and Finland (Abass et al., 2017). On the other hand, several studies have shown higher blood Cd levels in females than in males (Garner and Levallois, 2017), attributable to lower serum ferritin levels and an associated increase in gastrointestinal Cd uptake (Berglund et al., 1994; Bjermo et al., 2013; Ghoochani et al., 2019; Kippler et al., 2007; Madeddu et al., 2011; Meltzer et al., 2010; Olsson et al., 2002). Sakellari et al. (2016), and Nisse et al. (2017) found no differences in blood Cd levels between the sexes.

3.2.5. Blood pressure

Previous epidemiological studies have evaluated the association between Cd and blood pressure. However, conflicting results have been reported on the effect of Cd on blood pressure and its role in hypertension (Afridi et al., 2010; Ahn et al., 2017a, Chen et al., 2013; Franceschini et al., 2017; Satarug and Moore, 2004; Tellez-Plaza et al., 2008; Vallee et al., 2020). Our study demonstrated a significant difference in blood Cd concentration between participants with higher diastolic and normal diastolic blood pressure. However, we did not confirm it in the adjusted analysis. Furthermore, we failed to find a difference in blood Cd levels in participants with high systolic blood pressure and hypertension, compared to those with normal systolic blood pressure and normotensive subjects. Our criteria for hypertension was elevated blood pressure (systolic and/or diastolic) and/or use of antihypertensive medication. Other epidemiological studies have also corroborated the lack of association between Cd exposure and increased blood pressure or risk for hypertension (Ahn et al., 2017; Mordukhovich et al., 2012; Schutte et al., 2008). In contrast, Tellez-Plaza et al. (2008) reported a positive association between Cd blood levels and diastolic blood pressure. Studies in a Korean population (data from 2005 derived from the Korean National Health and Nutrition Examination Survey - KNHANES) showed a positive association between blood Cd levels with both blood pressure and risk of hypertension (Eum et al., 2008; Lee et al., 2011) The same findings were reported in Chinese population (Chen et al., 2013; Liu et al., 2018) and in Canadian adults (Garner and Levallois, 2017). In participants with metabolic syndrome, significant differences in blood Cd levels were noted in individuals with elevated systolic and diastolic blood pressure compared to normotensive subjects in the KNHANES study, from 2008 to 2012 (Lee and Kim, 2016). Other cardiovascular diseases have been associated with Cd exposure, in addition to blood pressure and hypertension. A meta-analysis review showed that in cross-sectional studies high blood Cd levels were associated with coronary heart disease prevalence, higher stroke risk and higher peripheral artery disease risk (Tinkov et al., 2018).

4. Study strengths and limitations

Some positive points to be highlighted in our study are the census based enrollment and the spatial analysis used for recruitment of the participants. We also included the measurement of multiple anthropometric and socioeconomic characteristics and the standardization of blood pressure measurements (≥ 3 readings) according to the Brazilian Guidelines, performed by trained researchers. Furthermore, an advantage was the precise and accurate analytical method used with extensive use of reference materials and participation in Interlaboratory Quality Control Programs.

The present study had some limitations. Analogous to many previous reports, our results were based on cross-sectional analysis, therefore, we did not determine temporal relationships or establish causality of the reported associations. Another possible limitation is the lack of urinary Cd, a biomarker of lifetime exposure to Cd, that could be useful in evaluating Cd exposure in tandem with blood Cd levels. In addition, we did not collect complete dietary intake data from the studied population; therefore, we cannot specifically comment on the contribution of rice-derived Cd (and other potential sources) to blood Cd levels.

5. Conclusions

Our findings in an urban population in Southern Brazil establish that both smoking and ethanol drinking were associated with higher blood Cd concentrations. In addition, blood Cd levels were elevated with increased number of daily smoked cigarettes. Increased milk intake and higher diastolic blood pressure were associated with blood Cd concentrations only in a univariate analysis, but could not be confirmed in the adjusted model. Before adjustments, higher blood Cd levels were found in males *vs*. females, likely reflecting a higher number of male smokers. Our results shed novel information on variables associated with blood Cd levels in an urban Brazilian population, and should encourage additional research on the relationship between environmental exposure to Cd and its health risks, both in Brazil and globally.

Author statment

Martins, A.C.: data collection, original draft preparation, editing; Urbano, M.R.: statistics, Methodology, writing; Almeida Lopes, A.C.: data collection, Conceptualization, Methodology; Carvalho, M.F.H.: analytical analysis, writing; Buzzo, M.L.: analytical analysis, writing; Docea, A.O.: reviewing, advice; Mesas, A.E.: Conceptualization, Methodology; Aschner, M.: Conceptualization, reviewing and editing; Silva, A.M.R.: Methodology, reviewing; Silbergeld, E.K.: Conceptualization, reviewing and editing; Paoliello, M.M.B.: Conceptualization, original draft preparation, reviewing.

Declaration of competing interest

The authors have no perceived or known conflict of interest.

Acknowledgements

We would like to thank the population of Cambe, State of Parana, Brazil, for data and biological collection, and the staff of the Municipality Health Services, who supported this research. This work was supported by the Coordination for the Improvement of Higher Level or Education Personnel (CAPES), Ministry of Health, Brazil.

References

Abass, K., Koiranen, M., Mazej, D., Tratnik, J.S., Horvat, M., Hakkola, J., Jarvelin, M.R., Rautio, A., 2017. Arsenic, cadmium, lead and mercury levels in blood of Finnish adults and their relation to diet, lifestyle habits and sociodemographic variables. Environ. Sci. Pollut. Res. Int. 24, 1347–1362.

ABEP, 2010. Critério de Classificação Econômica, Brasil. Associação Brasileira de Empresas de Pesquisa.

Afridi, H.I., Kazi, T.G., Kazi, N.G., Jamali, M.K., Arain, M.B., Sirajuddin, Baig, J.A., Kandhro, G.A., Wadhwa, S.K., Shah, A.Q., 2010. Evaluation of cadmium, lead, nickel and zinc status in biological samples of smokers and nonsmokers hypertensive patients. J. Hum. Hypertens. 24, 34–43.

Ahn, S.C., Chang, J.Y., Lee, J.S., Yu, H.Y., Jung, A.R., Kim, J.Y., Choi, J.W., Hong, Y.S., Do Yu, S., Choi, K., 2017. Exposure factors of cadmium for residents in an abandoned metal mine area in Korea. Environ. Geochem. Health 39, 1059–1070.

Ahn, B., Kim, S.H., Park, M.J., 2017. Blood cadmium concentrations in Korean adolescents: from the korea national health and nutrition examination survey 2010-2013. Int. J. Hyg Environ. Health 220, 37–42.

Almeida Lopes, A.C., Navas-Acien, A., Zamoiski, R., Silbergeld, E.K., Carvalho Mde, F., Buzzo, M.L., Urbano, M.R., Martins Ada Jr., C., Paoliello, M.M., 2015. Risk factors for lead exposure in adult population in southern Brazil. J. Toxicol. Environ. Health 78, 92–108.

Almeida Lopes, A.C.B., Martins, A.C., Urbano, M.R., Buzzo, M.L., Camargo, A.E.I., Peixe, T.S., Aschner, M., Barbosa, F., Silva, A.M.R., Paoliello, M.M.B., 2019. Blood reference values for metals in a general adult population in southern Brazil. Environ. Res. 177, 108646.

ANVISA, 2013. Maximum Limits of Inorganic Contaminants in Food. Brazilian Health Regulatory Agency.

ATSDR, 2019. Substance Priority List. Agency for Toxic Substances and Disease Registry.

Berglund, M., Akesson, A., Nermell, B., Vahter, M., 1994. Intestinal absorption of dietary cadmium in women depends on body iron stores and fiber intake. Environ. Health Perspect. 102, 1058–1066.

Bjermo, H., Sand, S., Nalsen, C., Lundh, T., Enghardt Barbieri, H., Pearson, M., Lindroos, A.K., Jonsson, B.A., Barregard, L., Darnerud, P.O., 2013. Lead, mercury, and cadmium in blood and their relation to diet among Swedish adults. Food Chem. Toxicol. 57, 161–169.

Brzoska, M.M., Galazyn-Sidorczuk, M., Dzwilewska, I., 2013. Ethanol consumption modifies the body turnover of cadmium: a study in a rat model of human exposure. J. Appl. Toxicol. 33, 784–798.

Chen, X., Zhu, G., Lei, L., Jin, T., 2013. The association between blood pressure and blood cadmium in a Chinese population living in cadmium polluted area. Environ. Toxicol. Pharmacol. 36, 595–599.

Cuello-Nunez, S., Benning, J., Liu, C., Branton, P., Hu, J., McAdam, K.G., Coburn, S., Braybrook, J., Goenaga-Infante, H., 2018. Fractionation of cadmium in tobacco and cigarette smoke condensate using XANES and sequential leaching with ICP-MS/MS. Anal. Bioanal. Chem. 410, 6795–6806.

Elinder, C.G., Lind, B., Kjellstrom, T., Linnman, L., Friberg, L., 1976. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Estimation of biological half time in kidney cortex, considering calorie intake and smoking habits. Arch. Environ. Health 31, 292–302.

Eum, K.D., Lee, M.S., Paek, D., 2008. Cadmium in blood and hypertension. Sci. Total Environ. 407, 147–153.

Forte, G., Madeddu, R., Tolu, P., Asara, Y., Marchal, J.A., Bocca, B., 2011. Reference intervals for blood Cd and Pb in the general population of Sardinia (Italy). Int. J. Hyg Environ. Health 214, 102–109.

Franceschini, N., Fry, R.C., Balakrishnan, P., Navas-Acien, A., Oliver-Williams, C., Howard, A.G., Cole, S.A., Haack, K., Lange, E.M., Howard, B.V., Best, L.G., Francesconi, K.A., Goessler, W., Umans, J.G., Tellez-Plaza, M., 2017. Cadmium body burden and increased blood pressure in middle-aged American Indians: the Strong Heart Study. J. Hum. Hypertens. 31, 225–230.

Friedrich, J.O., Adhikari, N.K., Beyene, J., 2012. Ratio of geometric means to analyze continuous outcomes in meta-analysis: comparison to mean differences and ratio of arithmetic means using empiric data and simulation. Stat. Med. 31, 1857–1886.

Garner, R., Levallois, P., 2016. Cadmium levels and sources of exposure among Canadian adults. Health Rep. 27, 10–18.

Garner, R.E., Levallois, P., 2017. Associations between cadmium levels in blood and urine, blood pressure and hypertension among Canadian adults. Environ. Res. 155, 64–72.

Ghoochani, M., Dehghani, M.H., Rastkari, N., Nodehi, R.N., Yunesian, M., Mesdaghinia, A., Houshiarrad, A., Saraei, M., 2019. Association among sources exposure of cadmium in the adult non-smoking general population of tehran. Biol. Trace Elem. Res. 191, 27–33.

Gil, F., Hernandez, A.F., Marquez, C., Femia, P., Olmedo, P., Lopez-Guarnido, O., Pla, A., 2011. Biomonitorization of cadmium, chromium, manganese, nickel and lead in whole blood, urine, axillary hair and saliva in an occupationally exposed population. Sci. Total Environ. 409, 1172–1180.

Hecht, E.M., Landy, D.C., Ahn, S., Hlaing, W.M., Hennekens, C.H., 2013. Hypothesis: cadmium explains, in part, why smoking increases the risk of cardiovascular disease. J. Cardiovasc. Pharmacol. Therapeut. 18, 550–554.

Hecht, E.M., Arheart, K., Lee, D.J., Hennekens, C.H., Hlaing, W.M., 2016. A cross-sectional survey of cadmium biomarkers and cigarette smoking. Biomarkers 21, 429–435.

Huang, M., Choi, S.J., Kim, D.W., Kim, N.Y., Bae, H.S., Yu, S.D., Kim, D.S., Kim, H., Choi, B.S., Yu, I.J., Park, J.D., 2013. Evaluation of factors associated with cadmium exposure and kidney function in the general population. Environ. Toxicol. 28, 563–570.

Huang, L., Liu, L., Zhang, T., Zhao, D., Li, H., Sun, H., Kinney, P.L., Pitiranggon, M., Chillrud, S., Ma, L.Q., Navas-Acien, A., Bi, J., Yan, B., 2019. An interventional study of rice for reducing cadmium exposure in a Chinese industrial town. Environ. Int. 122, 301–309.

IBGE, 2009. Censo Demografico 2007. Instituto Brasileiro de Geografia e Estatistica. http://www.ibge.gov.br.

Jarup, L., Akesson, A., 2009. Current status of cadmium as an environmental health problem. Toxicol. Appl. Pharmacol. 238, 201–208.

Jarup, L., Berglund, M., Elinder, C.G., Nordberg, G., Vahter, M., 1998. Health effects of cadmium exposure–a review of the literature and a risk estimate. Scand. J. Work. Environ. Health 24 (Suppl. 1), 1–51.

Kato, L.S., De Nadai Fernandes, E.A., Raab, A., Bacchi, M.A., Feldmann, J., 2019. Arsenic and cadmium contents in Brazilian rice from different origins can vary more than two orders of magnitude. Food Chem. 286, 644–650.

Kim, K., Melough, M.M., Vance, T.M., Noh, H., Koo, S.I., Chun, O.K., 2018. Dietary cadmium intake and sources in the US. Nutrients 11.

Kippler, M., Ekstrom, E.C., Lonnerdal, B., Goessler, W., Akesson, A., El Arifeen, S., Persson, L.A., Vahter, M., 2007. Influence of iron and zinc status on cadmium accumulation in Bangladeshi women. Toxicol. Appl. Pharmacol. 222, 221–226.

Kira, C.S., Sakuma, A.M., De Capitani, E.M., de Freitas, C.U., Cardoso, M.R.A., Gouveia, N., 2016. Associated factors for higher lead and cadmium blood levels, and reference values derived from general population of Sao Paulo, Brazil. Sci. Total Environ. 543, 628–635.

Koreckova-Sysalova, J., 1997. Determination of cadmium and lead levels in human blood of a general Czech population by GFAAS. Biol. Trace Elem. Res. 56, 321–329.

Krajcovicova-Kudladkova, M., Ursinyova, M., Masanova, V., Bederova, A., Valachovicova, M., 2006. Cadmium blood concentrations in relation to nutrition. Cent. Eur. J. Publ. Health 14, 126–129.

Laranjeira, R., Pinsky, I., Sanches, M., Zaleski, M., Caetano, R., 2010. Alcohol use patterns among Brazilian adults. Braz. J. Psychiatry 32 231–41.

Lee, B.K., Kim, Y., 2016. Association of blood cadmium level with metabolic syndrome after adjustment for confounding by serum ferritin and other factors: 2008-2012 Korean national health and nutrition examination survey. Biol. Trace Elem. Res. 171, 6–16.

Lee, M.S., Park, S.K., Hu, H., Lee, S., 2011. Cadmium exposure and cardiovascular disease in the 2005 korea national health and nutrition examination survey. Environ. Res. 111, 171–176.

Li, J., Cen, D., Huang, D., Li, X., Xu, J., Fu, S., Cai, R., Wu, X., Tang, M., Sun, Y., Zhang, J., Zheng, J., 2014. Detection and analysis of 12 heavy metals in blood and hair sample from a general population of Pearl River Delta area. Cell Biochem. Biophys. 70, 1663–1669.

Liu, H., Xia, W., Xu, S., Zhang, B., Lu, B., Huang, Z., Zhang, H., Jiang, Y., Liu, W., Peng, Y., Sun, X., Li, Y., 2018. Cadmium body burden and pregnancy-induced hypertension. Int. J. Hyg Environ. Health 221, 246–251.

Luckett, B.G., Su, L.J., Rood, J.C., Fontham, E.T., 2012. Cadmium exposure and pancreatic cancer in south Louisiana. J. Environ. Public Health 2012, 180186.

Madeddu, R., Solinas, G., Forte, G., Bocca, B., Asara, Y., Tolu, P., Delogu, L.G., Muresu, E., Montella, A., Castiglia, P., 2011. Diet and nutrients are contributing factors that influence blood cadmium levels. Nutr. Res. 31, 691–697.

Madrigal, J.M., Ricardo, A.C., Persky, V., Turyk, M., 2019. Associations between blood cadmium concentration and kidney function in the U.S. population: impact of sex, diabetes and hypertension. Environ. Res. 169, 180–188.

McKelvey, W., Gwynn, R.C., Jeffery, N., Kass, D., Thorpe, L.E., Garg, R.K., Palmer, C.D., Parsons, P.J., 2007. A biomonitoring study of lead, cadmium, and mercury in the

blood of New York city adults. Environ. Health Perspect. 115, 1435–1441.
Meltzer, H.M., Brantsaeter, A.L., Borch-Iohnsen, B., Ellingsen, D.G., Alexander, J., Thomassen, Y., Stigum, H., Ydersbond, T.A., 2010. Low iron stores are related to higher blood concentrations of manganese, cobalt and cadmium in non-smoking, Norwegian women in the HUNT 2 study. Environ. Res. 110, 497–504.
Mordukhovich, I., Wright, R.O., Hu, H., Amarasiriwardena, C., Baccarelli, A., Litonjua, A., Sparrow, D., Vokonas, P., Schwartz, J., 2012. Associations of toenail arsenic, cadmium, mercury, manganese, and lead with blood pressure in the normative aging study. Environ. Health Perspect. 120, 98–104.
Naka, K.S., de Cassia Dos Santos Mendes, L., de Queiroz, T.K.L., Costa, B.N.S., de Jesus, I.M., de Magalhaes Camara, V., de Oliveira Lima, M., 2020. A comparative study of cadmium levels in blood from exposed populations in an industrial area of the Amazon, Brazil. Sci. Total Environ. 698, 134309.
NHIS, 2017. Adult Tobacco Use- Glossary. National Health Interview Survey.
Nisse, C., Tagne-Fotso, R., Howsam, M., Members of Health Examination Centres of the Nord - Pas-de-Calais region, n.,Richeval, C., Labat, L., Leroyer, A., 2017. Blood and urinary levels of metals and metalloids in the general adult population of Northern France: the IMEPOGE study, 2008-2010. Int. J. Hyg Environ. Health 220, 341–363.
Nordberg, G.F., Nordberg, M., 1987. Different binding forms of cadmium–implications for distribution and toxicity. J. UOEH 9 (Suppl. l), 153–164.
Olmedo, P., Grau-Perez, M., Fretts, A., Tellez-Plaza, M., Gil, F., Yeh, F., Umans, J.G., Francesconi, K.A., Goessler, W., Franceschini, N., Lee, E.T., Best, L.G., Cole, S.A., Howard, B.V., Navas-Acien, A., 2017. Dietary determinants of cadmium exposure in the strong heart family study. Food Chem. Toxicol. 100, 239–246.
Olsson, I.M., Bensryd, I., Lundh, T., Ottosson, H., Skerfving, S., Oskarsson, A., 2002. Cadmium in blood and urine–impact of sex, age, dietary intake, iron status, and former smoking–association of renal effects. Environ. Health Perspect. 110, 1185–1190.
Pappas, R.S., Fresquez, M.R., Watson, C.H., 2015. Cigarette smoke cadmium breakthrough from traditional filters: implications for exposure. J. Anal. Toxicol. 39, 45–51.
Park, S., Lee, B.K., 2013. Strong positive association of traditional Asian-style diets with blood cadmium and lead levels in the Korean adult population. Int. J. Environ. Health Res. 23, 531–543.
Paulelli, A.C.C., Martins Jr., A.C., Batista, B.L., Barbosa Jr., F., 2019. Evaluation of uptake, translocation, and accumulation of arsenic species by six different Brazilian rice (Oryza sativa L.) cultivars. Ecotoxicol. Environ. Saf. 169, 376–382.
Piade, J.J., Jaccard, G., Dolka, C., Belushkin, M., Wajrock, S., 2015. Differences in cadmium transfer from tobacco to cigarette smoke, compared to arsenic or lead. Toxicol. Rep. 2, 12–26.
R Core Team, 2020. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Austria. https://www.R-project.org/.
Repic, A., Bulat, P., Antonijevic, B., Antunovic, M., Dzudovic, J., Buha, A., Bulat, Z., 2020. The influence of smoking habits on cadmium and lead blood levels in the Serbian adult people. Environ. Sci. Pollut. Res. Int. 27, 751–760.
Richter, P.A., Bishop, E.E., Wang, J., Swahn, M.H., 2009. Tobacco smoke exposure and levels of urinary metals in the U.S. youth and adult population: the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Int. J. Environ. Res. Publ. Health 6, 1930–1946.
Roels, H.A., Hoet, P., Lison, D., 1999. Usefulness of biomarkers of exposure to inorganic mercury, lead, or cadmium in controlling occupational and environmental risks of nephrotoxicity. Ren. Fail. 21, 251–262.
Sakellari, A., Karavoltsos, S., Kalogeropoulos, N., Theodorou, D., Dedoussis, G., Chrysohoou, C., Dassenakis, M., Scoullos, M., 2016. Predictors of cadmium and lead concentrations in the blood of residents from the metropolitan area of Athens (Greece). Sci. Total Environ. 568, 263–270.
Satarug, S., Moore, M.R., 2004. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environ. Health Perspect. 112, 1099–1103.
SBH, 2010. Sociedade Brasileira de Hipertensão. VI Diretrizes Brasileiras de Hipertensão. Arq. Bras. Cardiol. 95, 1–51.
Schutte, R., Nawrot, T., Richart, T., Thijs, L., Roels, H.A., Van Bortel, L.M., Struijker-Boudier, H., Staessen, J.A., 2008. Arterial structure and function and environmental exposure to cadmium. Occup. Environ. Med. 65, 412–419.
Sun, H., Wang, D., Zhou, Z., Ding, Z., Chen, X., Xu, Y., Huang, L., Tang, D., 2016. Association of cadmium in urine and blood with age in a general population with low environmental exposure. Chemosphere 156, 392–397.
Takeda, S.H.K., Kuno, R., Barbosa Jr., F., Gouveia, N., 2017. Trace element levels in blood and associated factors in adults living in the metropolitan area of Sao Paulo, Brazil. J. Trace Elem. Med. Biol. 44, 307–314.
Tellez-Plaza, M., Navas-Acien, A., Crainiceanu, C.M., Guallar, E., 2008. Cadmium exposure and hypertension in the 1999-2004 national health and nutrition examination survey (NHANES). Environ. Health Perspect. 116, 51–56.
Tellez-Plaza, M., Navas-Acien, A., Crainiceanu, C.M., Sharrett, A.R., Guallar, E., 2010. Cadmium and peripheral arterial disease: gender differences in the 1999-2004 US national health and nutrition examination survey. Am. J. Epidemiol. 172, 671–681.
Tinkov, A.A., Filippini, T., Ajsuvakova, O.P., Skalnaya, M.G., Aaseth, J., Bjorklund, G., Gatiatulina, E.R., Popova, E.V., Nemereshina, O.N., Huang, P.T., Vinceti, M., Skalny, A.V., 2018. Cadmium and atherosclerosis: a review of toxicological mechanisms and a meta-analysis of epidemiologic studies. Environ. Res. 162, 240–260.
Vallee, A., Gabet, A., Grave, C., Blacher, J., Olie, V., 2020. Associations between urinary cadmium levels, blood pressure, and hypertension: the ESTEBAN survey. Environ. Sci. Pollut. Res. Int. 27, 10748–10756.
Vesey, D.A., 2010. Transport pathways for cadmium in the intestine and kidney proximal tubule: focus on the interaction with essential metals. Toxicol. Lett. 198, 13–19.
Wiseman, C.L., Zereini, F., Puttmann, W., 2014. Metal translocation patterns in Solanum melongena grown in close proximity to traffic. Environ. Sci. Pollut. Res. Int. 21, 1572–1581.
Wiseman, C.L.S., Parnia, A., Chakravartty, D., Archbold, J., Zawar, N., Copes, R., Cole, D.C., 2017. Blood cadmium concentrations and environmental exposure sources in newcomer South and East Asian women in the Greater Toronto Area, Canada. Environ. Res. 154, 19–27.