Determinants of serum cadmium levels in a Northern Italy community: A cross-sectional study

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A B S T R A C T

Introduction: Cadmium (Cd) is a heavy metal and a serious environmental hazard to humans. Some uncertainties still exist about major sources of Cd exposure in non-occupationally exposed subjects in addition to cigarette smoking, such as diet and outdoor air pollution. We sought to determine the influence of these sources on a biomarker of exposure, serum Cd concentration.

Methods: We recruited 51 randomly selected residents from an Italian urban community, from whom we obtained detailed information about dietary habits and smoking habits, and a blood sample for serum Cd determination. We also assessed outdoor air Cd exposure, by modeling outdoor air levels of particulate matter ≤ 10 μm (PM10) from motorized traffic at geocoded subjects’ residence.

Results: In crude analysis, regression beta coefficients for dietary Cd, smoking and PM10 on serum Cd levels were 0.03 (95% CI -0.83 to 0.88), 6.96 (95% CI -0.02 to 13.95) and 0.62 (95% CI -0.19 to 1.43), respectively. In the adjusted analysis, regression beta coefficients were -0.34 (95% CI -1.40 to 0.71), 5.81 (95% CI -1.43 to 13.04) and 0.47 (95% CI -0.35 to 1.29), respectively.

Conclusion: Cigarette smoking was the most important factor influencing serum Cd in our non-occupationally exposed population, as expected, while dietary Cd was not associated with this biomarker. Outdoor air pollution, as assessed through exposure to particulate matter generated by motorized traffic, was an additional source of Cd exposure.

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1. Introduction

Cadmium (Cd) is a heavy metal posing a broad spectrum of serious environmental health hazards to humans (Akeesson et al., 2014; Larsson and Wolk, 2015). Among the toxic effects of this heavy metal, Cd compounds have been recently classified as carcinogenic to humans (Straif et al., 2009; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012), due to the epidemiological data suggesting causal associations with lung, prostate, breast, and kidney cancer (Vinceti et al., 2007; Garcia-Esquinas et al., 2014; Luevano and Damodaran, 2014; Larsson et al., 2015).

Some uncertainties exist about the main sources of Cd exposure in humans, in addition to cigarette smoking and occupational environments. In particular, the role of diet, particularly for non-smoking subjects (European Food Safety Authority, 2012), and outdoor pollution due to industrial emissions, fossil fuel combustion, solid waste incineration and traffic exhausts is still not well defined, since little epidemiologic evidence is available (Hogervorst et al., 2007; Liu et al., 2015). In this study, we aimed to assess Cd exposure in the general population of a Northern Italian community, and in addition we sought to identify the independent role of three sources of Cd exposure: smoking habits, diet and outdoor air pollution.
2. Methods

2.1. Study participants

We have described elsewhere the methodology for the recruitment of the study population (Vinceti et al., 2015a). Briefly, we recruited a random sample of fifty residents in the Modena municipality located in the Emilia-Romagna region (around 180,000 inhabitants), to investigate exposure to selenium and Cd in this community. To do so, following study approval by the local Ethics Committee and after selecting a sample of eligible subjects from each sex- and age-specific subgroup of Modena residents using the Stata sample routine (Stata statistical software, Stata Corp., College Station, TX), we contacted these subjects in 2011 by phone asking for their participation in the study. Those giving their written consent to participate were invited to the Modena Health Unit, to give a venous blood sample in morning fasting state. Blood samples were collected in a plastic tube, immediately centrifuged for 10 min at 3000 rpm and stored as serum aliquots of 1 ml at −15 °C until use. The participation rate was 34%. We also administered two questionnaires to all study subjects: one collected information on several variables including smoking habits and occupational history, the second investigated dietary habits through a semi-quantitative food frequency questionnaire used for the Central-Northern Italian population within the EPIC study (Pasanisi et al., 2002; Pala et al., 2003). This questionnaire assessed the frequency and amount of consumption of 188 food items over the previous year, and allowed the frequency and quantity of consumption of foodstuffs and the related intake of nutrients and contaminants to be calculated using an ad hoc software (Malavolti et al., 2013; Malagoli et al., 2015). This database included among other trace elements selenium and Cd, and was largely based on chemical analyses of foodstuffs distributed in Northern Italy performed at the University of Modena and Reggio Emilia for both selenium (Vinceti et al., 2015b) and Cd (Bottecchi et al., 2012; Malavolti et al., 2015). We adjusted the estimates of dietary Cd for total energy intake, using the Willett’s residual method (Willett et al., 1997; Willett, 2013), in order to reduce the influence of measurement errors frequently associated with the use of food frequency questionnaires, by decreasing artificial inter-individual variation introduced by under and over-reporting of food intake.

2.2. Laboratory analyses

We determined serum Cd concentrations at the Munich Helmholtz Zentrum laboratory, where a 1 ml aliquot for each study subject was transferred frozen in dry ice, using a previously described methodology (Ebrahim et al., 2012; Junemann et al., 2013). Briefly, we slowly thawed the samples in a refrigerator at 4 °C, vortexed and subsequently diluted samples 1:10 with Milli-Q water, containing 103Rh as internal standard. The final 103Rh concentration in the diluted serum samples was 1 μg/L. Serum Cd levels were determined using inductively coupled plasma – sector field – mass spectrometry: An ELEMENT 2, ICP-SF-MS instrument (Thermo Scientific, Bremen, Germany) was employed for 111Cd determination in low resolution mode. Sample introduction was carried out using an ESI-Fast-system (Elemental Scientific, Mainz, Germany) connected to a Micromist nebulizer with a cyclone spray chamber. The RF power was set to 1200 W, the plasma gas was 15 L Ar/min, whereas the nebulizer gas was approximately 0.9 L Ar/min after daily optimization. The determination method had been validated by regular laboratory intercomparison studies (GEQUAS quality control scheme and participation in certification campaign of IRMM/EU) and by regular analysis of adequate certified reference materials. During analysis of samples the following certified reference materials (CRM) were analyzed (name of CRM/ certified value/ found value): ERM-BD150/11.4 ± 2.9 μg/kg/ 11.4 ± 0.5 μg/kg (corresponding to 31 ng/L Cd in measurement solution), ERM-CD281/120 ± 7 μg/kg/125 ± 5 μg/kg, (corresponding to 340 ng/L Cd in measurement), Recipe RM ClinCal Plasma/ 13.7 μg/L/13.6 ± 0.8 μg/L.

The limit of quantification of the determination method was 18 ng/L relative to native serum. Precision was determined at 2.05% (n=10). According to IUPAC recommendations, accuracy should be derived from comparison with CRM. Here accuracy was derived from CRM ERM-BD 150 as the measurement concentration (~30 ng/L) was about the lower concentrations in serum. Accuracy was determined at 100% (114 μg/kg /114 μg/kg).

2.3. Exposure assessment

We assessed study subjects’ personal exposure to traffic contaminants as a proxy of outdoor environmental Cd exposure, by estimating the concentration of particulate matter < 10 μm size (PM10) with an approach described in detail elsewhere (Vinceti et al., 2012; Vinceti et al., 2016), considering that traffic is the main source of exposure for the Modena population considering the distribution of urban and extra-urban roads and waste incinerator plant in the municipality (Fig. 1), and of the absence of major industrial emissions. Briefly, we geocoded the current residence of all study subjects, and we modeled ambient air PM10 concentration at these locations in 2006 using the complex approach implemented for that year with the California LINE version 4 (CA-LINE4) air quality dispersion model for roads and other linear sources (Benson, 1989). CALINE4 estimates the dispersion and deposition of pollutants such as carbon monoxide, particulate matter, nitrogen dioxide, benzene and other contaminants at predefined spatial receptors (Benson, 1989). The 2006 assessment carried out in Modena (Vinceti et al., 2012) was generated using a model that incorporated demographic and occupational information for all residents of the province, and detailed personal mobility information collected by the National Institute of Statistics 2001 Census, also validated through ad hoc surveys and automatic vehicle counters in a few major roads. The model allowed to compute a matrix of vehicle movements for each road, on the basis of daily movements estimated for Modena residents taking into account their age, sex, family structure and occupation (Drufua et al., 2007). This model had been satisfactorily validated in the study area by comparing measured and modeled PM10 at the air monitoring stations (Vinceti et al., 2012). Since the year of exposure assessment (2006) until the beginning of the study (2011), limited changes occurred in the municipal territory with reference to circulating vehicles (from 117,310 to 115,887) and to the adult population (from 152,372 to 155,998), according to data released by the Modena municipality (www.comune.modena.it/serviziostistica/pubblicazioni/annuari/annuario2012/incidenti2012/inci_tav2012.shtml).

2.4. Data analysis

We evaluated the relation between serum and dietary intake of Cd by computing Pearson’s correlation coefficient, and we compared serum Cd content across subgroups using a non-parametric equality-of-medians test. To investigate the influence of potentially confounding variables, we used both crude and multivariate linear regression models, estimating their beta (β) coefficient and its 95% confidence interval (CI). Smoking habits were coded 0, 1 and 2 for never, former and current smokers respectively, and pack-years as an indicator of lifetime tobacco were also calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.
3. Results

The characteristics of the study population are reported in Table 1. The age of the study subjects ranged from 35 to 71 years, with men and women equally represented. None of the subjects was employed in agriculture, six worked in the engineering industry, half in ‘services’, a section encompassing workers in the health system, education, and business, while eleven were retired. Nine subjects were current smokers, while sixteen and twenty-six were former-and never-smokers, respectively. Pack-year values were similar for former and current smokers, though results were less consistent in sex-specific analysis.

Table 2 shows the distribution of serum and dietary Cd in the study population. Serum Cd median value was 40.6 ng/L (interquartile range (IQR) 30.1-53.5), with a tendency for higher concentrations in the youngest and overweight subjects. In relation to smoking habits, serum Cd concentrations revealed markedly increasing levels from never smokers to former smokers, the highest levels being detected in current smokers. In sex-specific analysis, females showed increasing levels of serum Cd from never smokers to former and to current smokers, while in males former smokers (the subgroup with the highest pack-year score) were the subgroup with the highest concentrations. Daily Cd dietary intake was 13.4 µg/day (IQR 10.4-16.8), with minimal change according to gender, age and body mass index.

Fig. 1. Map of the study area, the Modena municipality, reporting residences of study subjects (diamonds) and the main sources of PM10 exposure: highway (black line), urban and extra-urban roads (gray line) and municipal solid waste incinerator plant (triangle).
correlated with serum Cd both in the entire study population (Table 3).

and the adjusted analyses, though there was some indication for a generally limited correlations with serum Cd levels in both the crude

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unrelated to serum levels in the crude and multivariate analyses, dietary intake was substantially exposure on serum Cd levels. Dietary intake was substantially

As reported in Table 3, age and body mass index showed generally limited correlations with serum Cd levels in both the crude and the adjusted analyses, though there was some indication for a direct relation with body mass and an inverse one for age (Table 3).

Table 4 and Fig. 2 show the influence of potential sources of Cd exposure on serum Cd levels. Dietary intake was substantially unrelated to serum levels in the crude and multivariate analyses, while we observed a direct association for both smoking habits and outdoor PM10 concentrations. Dietary Cd alone was uncorrelated with serum Cd both in the entire study population ($r = -0.126$, 95% CI $-0.388$ to $0.155$, $P=0.378$), and this was confirmed both in males ($r = -0.122$, 95% CI $-0.487$ to $0.278$, $P=0.552$) and in females ($r = -0.273$, 95% CI $-0.603$ to $0.137$, $P=0.186$). However, when we analyzed the association between average consumption of specific foodstuffs previously identified as the major sources of Cd intake in the Emilia-Romagna population and serum Cd levels (Malavolti et al., 2015), the latter directly correlated with consumption of "mushrooms", "sweets (including chocolate, puddings, and cakes)", and in females only, “row leafy vegetables”.

We eventually examined the potential confounding effect of selenium, a metalloid which may bind to Cd and interfere with its toxicity, and to which humans are exposed through diet and to a lesser extent through tobacco and air pollution (Heck et al., 2014; Jablonska and Vinceti, 2015). No substantial effect on study results was induced after adding serum selenium levels in the multivariate analyses (data not shown).

4. Discussion

Despite the increasing awareness of the toxicity of Cd in humans even at very low levels, and the growing recognition of its environmental presence, limited evidence is available as yet about the exact role and relevance of the environmental sources of this heavy metal in non-occupationally exposed subjects (Jarup and Akesson, 2009). Biological monitoring in occupationally exposed workers showed that blood Cd levels were influenced not only by current exposure, but also by body burden (Alessio et al., 1999); indeed the Cd half-life in blood displayed a fast component of 3–4 months and a slow component of about 10 years after cessation of exposure, probably due to a slow release from the kidney and liver, two organs that contain about 50% of the body’s burden accumulation (Ellis et al., 1979; Jarup et al., 1983; Hazardous substances database (HSDB), 2006).

Our survey assessed Cd exposure in a representative and generally occupationally unexposed sample of Modena municipality using a biomarker, serum Cd, which is rarely used in epidemiologic and biomonitoring studies despite allowing greater flexibility in collecting, storing, and transporting samples compared with blood cells. The reasons for the rare adoption of serum Cd for exposure biomonitoring appear to be its low content of the metal, as well as its uncertain correlation with Cd erythrocyte content. In fact, only 10% of blood Cd is found in plasma, where it is linked to metallothionein or to other proteins such as albumin and globulins (Nordberg et al., 1971; Kjellstrom and Nordberg, 1978; DFG Deutsche Forschungsgemeinschaft, 2006). During the 24 h following experimental Cd injection, there appears to be a continuous clearance of the heavy metal from plasma with consequent build up in blood cells, where it is in large part bound to a protein having the same size as metallothionein and it is not readily exchangeable with plasma Cd (Kjellstrom and Nordberg, 1978; DFG Deutsche Forschungsgemeinschaft, 2006). Also considering the long biological half-life of Cd, 10–20 years (DFG Deutsche Forschungsgemeinschaft, 2006), these observations suggest that serum Cd levels are considerably stabler than those in whole blood or erythrocytes and are less influenced long-term by external sources of exposure, though large studies using both multiple biomarkers of exposure are clearly required to confirm such hypothesis. It should also be noted that, compared with the limited biomonitoring studies which used serum Cd, the levels found in our study population were similar (Minoia et al., 1990; Alimonti et al., 2005; Goullet et al., 2005) or lower (Krachler et al., 1999; Rahil-Khazen et al., 2000; Hossny et al., 2001; Faro et al., 2014; Wang et al., 2016), also falling below the recently estimated EFSA limits (European Food Safety Authority, 2012), since the weekly average Cd intake in our study was 1.38 μg/Kg (upper 95th
Table 3

<table>
<thead>
<tr>
<th></th>
<th>β*</th>
<th>95% CI</th>
<th>P</th>
<th>β*</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
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<td>Age</td>
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<td>(−1.20 to 0.08)</td>
<td>0.086</td>
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<td>(−1.18 to 0.08)</td>
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<td>Body mass index</td>
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<td>(0.36 to 2.50)</td>
<td>0.138</td>
<td>1.10</td>
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<tr>
<td>Age</td>
<td>−0.79</td>
<td>(−1.97 to 0.40)</td>
<td>0.383</td>
<td>−0.84</td>
<td>(−2.11 to 0.41)</td>
<td>0.176</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.40</td>
<td>(−2.91 to 3.72)</td>
<td>0.803</td>
<td>0.90</td>
<td>(−2.54 to 4.35)</td>
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</tr>
<tr>
<td>Females (n=25)</td>
<td></td>
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</tr>
<tr>
<td>Age</td>
<td>−0.36</td>
<td>(−0.93 to 0.21)</td>
<td>0.209</td>
<td>−0.26</td>
<td>(−0.74 to 0.22)</td>
<td>0.266</td>
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<tr>
<td>Body mass index</td>
<td>1.32</td>
<td>(0.31 to 2.32)</td>
<td>0.012</td>
<td>1.16</td>
<td>(0.22 to 2.11)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

* Crude analysis.

* Multivariate analysis adjusting for age or body mass index.

* Multivariate analysis adjusting for age or body mass index, and for energy intake.

Table 4

Determinants of serum Cd levels in crude and multiple linear regression models. Results expressed as regression coefficients (β) with their 95% confidence interval (CI) and P-values (P).

<table>
<thead>
<tr>
<th>Unadjusted analysis</th>
<th>Adjusted analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>β</td>
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</tr>
<tr>
<td>Dietary Cd</td>
<td>−0.42</td>
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<tr>
<td>Smoking habits†</td>
<td>6.96</td>
</tr>
<tr>
<td>PM10</td>
<td>0.62</td>
</tr>
</tbody>
</table>

* Adjusting for the remaining factors listed in the table (dietary Cd, smoking and PM10 exposure).

† Smoking habits coded as 0, 1 and 2 for never, former and current smokers, respectively.

percentile 2.92 μg/kg). It is also possible that higher levels of Cd exposure than those experienced by our study population are required to detect stronger relations between serum Cd and the sources of exposure investigated.

In our study, serum Cd levels were weakly and statistically imprecisely associated with body mass and showed some inverse association with age, unlike other investigations which found a gradually increasing Cd body burden with age (Alessio et al., 1993; dell'Omo et al., 1999; Madeddu et al., 2009; Forte et al., 2011; Madeddu et al., 2011; Faro et al., 2014; Freire et al., 2015; Yang et al., 2015), though not all studies are consistent (Roggi et al., 1995; Moreno et al., 1999). This might be due to the low sample size in our study or, alternatively, indicate a different behavior of serum Cd levels compared with blood or erythrocytes Cd in relation to age, which warrants further investigation.

Only six study subjects were employed in the metal industry, and they exhibited slightly higher median levels than other workers (44.4 vs. 39.8 ng/L, P=0.357), thus ruling out the occurrence of higher occupational exposures.

We found that smoking habits were a main source of Cd, as largely expected (Madeddu et al., 2009; Agency for Toxic Substances and Disease Registry (ATSDR), 2012; Iarc Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; German Research Foundation, 2015). A monotonic dose-response relationship between smoking and Cd was found for increasing categories of tobacco exposure, with higher serum Cd levels in current compared with former and with never smokers, despite the lack of strong correlation between pack-years or other quantitative estimates of smoking and serum Cd content (data not shown). In sex-specific analysis, however, we unexpectedly found in males a slightly higher Cd serum content among former smokers compared with current smokers. A possible explanation of this finding may be the long persistence and half-life of Cd even after cessation (Pocock et al., 1988; Shaham et al., 1996): when we used pack-year analysis for assessing the smoking burden of subjects, we found no difference for the whole population, while an analysis specific to former male smokers reported a history of heavy smoking habits (19.4 pack-years vs. 9.0 in current smokers). Also, we cannot rule out some degree of misclassification of tobacco consumption depending on the intensity of smoking habits and particularly the tobacco chemical composition, taking into account its uneven Cd content, ranging from 5 to 200 ng/Cd/cigarette (Pappas et al., 2014). We also noted a higher influence of outdoor PM10 on Cd serum levels in current smokers, while in former smokers dietary Cd intake showed a greater influence on blood Cd than in the two other smoking categories, thus suggesting possible life-style differences including dietary patterns (Whichelow et al., 1991; Margetts and Jackson, 1993). In fact, Cd-rich foodstuffs, such as pasta or rice, seafood and fresh vegetables but also offal, mushrooms and chocolate (Olsson et al., 2002; Martí-Cid et al., 2008; Forte et al., 2011; Madeddu et al., 2011; Bottecchi and Vinceti, 2012) were characterized by higher consumption in former than in current smokers (Whichelow et al., 1991; Margetts and Jackson, 1993; Madeddu et al., 2011).

We were unable to find an association between dietary Cd intake and serum Cd levels, despite food being generally acknowledged as the main source of human exposure in the non-smoking population (Madeddu et al., 2011), and despite some indications that consumption of specific foodstuffs recognized as major sources of Cd intake in the local population (Malavolti et al., 2015) was associated with higher serum Cd concentrations. A correlation of dietary Cd, as assessed with food frequency questionnaires, with Cd levels in blood and urine has been found in some studies but not in others (Julin et al., 2011; Wang et al., 2012; Ikeda et al., 2015; Vacchi-Suzzi et al., 2015; Wang et al., 2015). Factors explaining this low concordance in the present study may be an inadequate assessment of dietary intake owing to an imprecise estimate of Cd content in foodstuffs, the low gastrointestinal absorption of Cd, generally in the order of 5% in adults (Andersen et al., 1992), the influence of other dietary variables such as fiber and iron which may modify Cd intake and metabolism (Berglund et al., 1994; Akesson et al., 2002; Olsson et al., 2002; Julin et al., 2011), and particularly the limited sample size. However, it is possible that the kinetics of Cd in serum as well as its very low concentration in this matrix, as compared to erythrocytes, may explain the lack of correlation between dietary intake and serum levels of this heavy metal we observed. Further studies are clearly needed to elucidate this issue, also to investigate which mechanisms might influence the clearance and the persistence of Cd in the serum/plasma compartment, which may also differ according to sources of Cd exposure and other factors influencing its absorption and metabolism.
Our results indicated that airborne particulate or more generally outdoor air pollution may be a significant source of Cd exposure, and this represents a major finding of this study. High Cd levels in industrial and urban polluted areas with higher concentration in winter than in summer, and high Cd content in PM have been described in a few studies (Lauwerys et al., 1991; Balachandran et al., 2000; Batonneau et al., 2004; Khillare et al., 2004; Sun et al., 2004; Samara and Voutsas, 2005; Karar et al., 2006).Very few studies have investigated internal human exposure in the general population, one showed that indoor dust Cd content influences body Cd burden even more than vegetable intake, particularly in a heavily polluted area (Hegervorst et al., 2007). In the second study, recently carried out in outdoor workers (municipal policemen) exposed to urban pollutants and asked not to smoke during the study period, air Cd content strongly correlated with urine and blood Cd concentrations (Ciarrocca et al., 2015). In the present study, we used particulate matter as a proxy of Cd exposure through outdoor air, taking into account that the model we used has been validated in the study area and that Cd compounds have low volatility and are mainly found in air as bound to particles (Agency for Toxic Substances and Disease Registry (ATSDR), 2012), further adding to the potential hazard of long-term PM exposure under a public health perspective (Kampa and Castanas, 2008; Pun et al., 2014). The association we found is also of interest since some study subjects were also smokers, thus suggesting the significant importance of outdoor pollution compared with other sources in increasing Cd exposure, and since the study area could not be considered as a polluted one. In fact, average Cd levels characterizing outdoor air Cd levels in the Modena province were low (0.23 ng/m³ in 2011, according to the air monitoring stations (ARPA, 2015)), far below the Italian and European Union Cd standard in particulate matter of 5 ng/m³ (50/2008/EC; Dlgs 155/2010). We also examined the potential influence on Cd exposure of emissions from the municipal solid waste incinerator, but we found only two subjects residing in the area influenced by that source (Vinceti et al., 2008), however having low serum Cd levels, i.e. below the median value (36.9 and 18.5 ng/L). So, this possible source of environmental Cd did not appear to confound our analyses, and limited evidence is also available on its significance as a source of Cd environmental pollution (Vilavert et al., 2012).

This study has some limitations worth outlining. First, its small sample size, due to difficulties in recruiting healthy subjects despite our efforts, and consequently the limited statistical power reflected by the generally wide confidence intervals of the point estimates. This limited participation rate might also have induced some degree of selection bias: however, we did not detect major lifestyle-related differences, such as for smoking habits or other personal characteristics, between the study subjects and the overall population on the basis of published data (Ferrante et al., 2012; Gruppo Tecnico PASSI Emilia-Romagna, 2012). Another study limitation is lack of assessment of indoor Cd levels apart from active smoking, since other factors such as passive smoking or cooking may contribute to indoor Cd levels, even if indoor air chemical composition is also influenced by outdoor air (Perrino et al., 2015).

In conclusion, the results of our study suggest that outdoor air pollution in a not heavily polluted urban area may influence serum Cd concentrations, suggesting that this potential source of exposure needs to be considered, in addition to smoking, occupational environment and diet, in the assessment of human Cd exposure.

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