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

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ABSTRACT

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 $\leq 10\ \mu m$ (PM_{10}) 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.

1. Introduction

Cadmium (Cd) is a heavy metal posing a broad spectrum of serious environmental health hazards to humans (Akesson 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.

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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 and Vinceti, 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 Helmoltz 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 ^{103}Rh as internal standard. The final ^{103}Rh 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 ^{111}Cd 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-BD-150/11.4 ± 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 related 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% (11.4 μg/kg /11.4 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 (PM_{10}) 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 PM_{10} concentration at these locations in 2006 using the complex approach implemented for that year with the CAlifornia LINE version 4 (CALINE4) 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 (Drufuca et al., 2007). This model had been satisfactorily validated in the study area by comparing measured and modeled PM_{10} 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/serviziostatistica/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.