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Dietary Predictors of Urinary Cadmium among Pregnant Women and Children[a]

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Abstract

Background—Cadmium is a toxic metal with modifiable exposure sources including diet. In pregnant women and children, unique dietary habits may contribute to DCd, and the relationship of diet to overall cadmium exposure can depend on specific factors during these transitional time periods.

Objectives—This study aimed to identify and quantify food sources of DCd, describe the distribution of UCd, and determine the relationship of DCd and intake of specific foods with UCd, stratified by maternal smoking history, among pregnant women and children in a well-characterized Mexico City birth cohort.

Methods—Our sample included 192 pregnant women (third trimester) and 223 children (7-15 years). DCd was calculated using FFQ and the U.S. TDS. We also measured UCd, maternal history of smoking, and additional covariates.

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[a]Supplemental Figures are available.

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Results—Pregnant women and children had geometric mean UCd concentrations of 0.19±0.78 μg/L and 0.14±0.60 μg/L, respectively. On average, estimated daily DCd intake was 9.3±3.5 μg for women and 12.2±5.4 μg for children. Adjusted linear regression models showed a positive association between DCd and UCd among women (p=0.03) and children (p=0.03) without a maternal history of smoking. Intake of fruit and vegetables among women and potato consumption among children were positively associated with UCd.

Conclusions—Pregnant women and their children are exposed to cadmium at dietary and urinary levels similar to those previously reported. Higher estimated DCd for children than for women could be attributed to the different FFQs or related to dietary pattern changes between age groups. DCd contributed to UCd in those without a maternal smoking history.

Keywords

metals; urinary cadmium; dietary cadmium

Introduction

Cadmium is a ubiquitous metal associated with renal and bone disease, cardio-metabolic dysfunction, cancer, and mortality even at low exposure levels (Järup and Åkesson 2009). The two main routes of human exposure to cadmium are inhalation and ingestion with relevant and modifiable sources: cigarette smoking and diet. Tobacco leaves accumulate high levels of cadmium from the soil—as do leafy vegetables, potatoes, grains, peanuts, soybeans, and sunflower seeds (U.S. Agency for Toxic Substances and Disease Registry 2012). Application of cadmium-containing fertilizers and sewage to agricultural fields, as well as deposition of atmospheric cadmium released from industrial processes, contributes to uptake in crops (World Health Organization 2010).

Identifying sources of cadmium exposure is a public health concern among vulnerable groups such as pregnant women and children, when during these sensitive time periods the health effects of cadmium could be most harmful (Gluckman and Hanson 2004). Since pregnant women have a low prevalence of smoking (Merzel et al. 2010), dietary intake can be the primary source of cadmium exposure in this population. Additionally, food intake increases during pregnancy, and children eat more than adults relative to their body mass. In countries undergoing rapid epidemiologic and demographic transitions, concurrent changes in diet could lead to differential exposure to cadmium (Rivera et al. 2004). Between 1990-2003 in the US, an increase of grain consumption contributed to the increase in cadmium intake (Egan et al. 2007). Therefore, quantifying amount and sources of dietary cadmium exposed by pregnant women and children in international settings is important.

Total diet surveys have commonly been used to estimate dietary cadmium (DCd) intake sources and levels in populations by combining food contamination concentrations obtained from market basket surveys with food consumption information (Egan et al. 2007). When DCd is used as the exposure variable in epidemiological studies, however, the relationship of estimated DCd to health outcomes, like cancer incidence, is heterogeneous (Cho et al. 2013). This is possibly due to measurement error in quantifying DCd or the assumption that DCd is

directly associated with biomarkers of internal dose; moreover, this relationship can be further complicated by factors such as smoking status.

Urinary cadmium (UCd) is a commonly used biomarker of internal dose to reliably estimate long-term cadmium exposure from all sources; it is proportional to the concentration of cadmium stored in the kidney over 10-30 years (Järup and Åkesson 2009). Previous studies have consistently found that DCd estimated from total diet surveys is positively associated with UCd among nonsmoking adult women (Birgisdottir et al. 2013; Gunier et al. 2013; Quraishi et al. 2015; Vacchi-Suzzi et al. 2015). However, no study analyzing this relationship has been performed on two vulnerable populations: women during pregnancy and pre- and adolescent children, when unique factors could impact any association between DCd and UCd. These include increased nutritional needs as both pregnancy and peripubertal transition are characterized by periods of rapid growth and changes in dietary behaviors (Åkesson et al. 2002; Julin et al. 2011; Silver et al. 2013).

The overall goal of this study was to determine the dietary contribution to cadmium exposure among pregnant women and their children. This objective was conducted in a well-characterized Mexico City birth cohort—the Early Life Exposures in Mexico to ENvironmental Toxicants (ELEMENT). We first estimated DCd intake and identified food sources that contributed to these DCd estimates using available food frequency questionnaires (FFQ) and the United State (U.S.) Total Diet Survey (TDS). We measured and described the distribution of UCd concentrations. Lastly, we examined the relationship between estimated DCd and intake of specific foods with UCd concentrations, stratified by maternal smoking history.

Methods

Study Population

The study population consists of a subset of participants from the ELEMENT project, wherein sequentially enrolled longitudinal cohorts were recruited from maternity hospitals in Mexico City serving low- to moderate-income populations. Standardized recruitment methods and measurement protocols made pooling across cohorts possible (Afeiche et al. 2011). Our analysis includes pregnant women recruited between 1997-2004 during their first trimester and followed throughout their pregnancy. During their third trimester, pregnant women provided a urine sample, anthropometry, and completed interview-based questionnaires. Mean gestational week for the third trimester visit was 34 weeks (SD=2.3, range 25.1-40.4). Between 2008-2011, a subset of child participants (n=250), who were now 7-15 years of age, were re-contacted depending on the availability of stored maternal third trimester urine and child cord blood samples to participate in follow-up studies. These children provided urine samples, anthropometry, and completed an interview-based questionnaire.

Anthropometric measurements were obtained upon removal of shoes and clothes besides under garments and covering with a hospital gown. Height and weight were obtained using professional scales (PAME, Puebla, Puebla) read to the nearest 0.1 cm and 0.1 kg, respectively, by trained staff using standard protocols in third trimester for pregnant women

and during study visit for children. Body mass index (BMI), defined as weight (kg) divided by height (m) squared ($\frac{\mathrm{kg}}{m^2}$), was calculated using measured anthropometry. For children, z-scores were defined as BMI for age and sex, using the World Health Organization's reference population (World Health Organization 2015). Common covariates for both pregnant women and child participants, e.g. self-reported social and demographic characteristics, including socioeconomic variables and maternal smoking status, were assessed at enrollment during pregnancy via the interviewer-administered questionnaire. Maternal smoking history was obtained as never-smoker or ever-smoker. Of the ever-smokers, two percent reported smoking during pregnancy. Ever-smokers, including those who reported currently smoking, were categorized as having a positive smoking history. Maternal smoking history obtained during pregnancy described women's direct exposure to cadmium from cigarettes, but it did not necessary reflect children's exposure to cigarette smoker. However, children in our sample with a maternal history of smoking are likely exposed from smokers in the home including mothers who often relapse by their child's first birthday (Homish and Leonard 2005; Merzel et al. 2010). Socioeconomic (SES) level was measured using an 13-item score commonly used in international settings to classify household assets (Mexican Association of Market Intelligence and Opinion).

The ethics and research committees of the Mexico National Institute of Public Health and the University of Michigan approved all research protocols, and all participants provided informed consent prior to enrollment.

Dietary intake

Diets of pregnant women were assessed during the third trimester using a interview-administered semi-quantitative FFQ designed to allow recall of dietary intake over the previous month (Willett 2013). The questionnaire was translated and validated for use in the Mexican Spanish-speaking adult women of reproductive age; the list of about 100 foods was built from items that proved most representative of local consumption under the 1983 Dietary Survey of the Mexican National Institute of Nutrition (Hernández et al. 1983; Willett et al. 1985).

Usual dietary intake of children over the past week was determined using a self-reported semi-quantitative FFQ adapted from the 2006 Mexican Health and Nutrition Survey, a national cross-sectional and representative survey (Villalpando et al. 2003). Separate questionnaires were used for children ages 7-11 years and 12 years or older. Children 7-11 years old were assisted by their mothers in answering the questionnaire to improve accuracy and precision of the self-reported intakes.

Daily energy intake was estimated as follows. The energy content of each item in the FFQ (for a standard portion size: one natural unit, cup, slice, piece, etc.) was obtained from food composition tables supplied by two sources (Instituto Nacional de Salud Pública 2002): 1) the United States Department of Agriculture (USDA) and 2) the Mexican National Institute of Nutrition and Medical Sciences Salvador Zubirán (Bourges 1996). Frequency values, ranging from never to six or more times a day, were multiplied by the energy amount in each

food item and then summed over all food sources to estimate the energy equivalent amount per day.

Cadmium intake

DCd was estimated using cadmium contamination of foods and dietary intake. Cadmium contamination of FFQ foods was estimated from measurements determined analytically by the U.S. Food and Drug Administration as part of the TDS (U.S. Food and Drug Administration 2013). TDS for the U.S. was applied to this population because no such market basket survey exists in Mexico. The arithmetic mean of cadmium content (mg/100g prepared weight) for available TDS food samples was assigned as the cadmium concentration for the FFQ food item based on similarity. For mixed dishes and inexact matches between TDS and FFQ foods, the arithmetic mean of cadmium content of multiple TDS foods was used. Per-subject daily cadmium consumption was calculated for each survey food using consumption information from FFQ and then aggregated to arrive at total dietary estimate of cadmium intake per-subject. Cadmium content obtained from the TDS was averaged over region and year, matching time of recruitment and collection of dietary data for pregnant women and children. Individual measurements of food items below the levels of detections were assigned values of zero.

In addition to total daily DCd intake, DCd was described by food or food group. Foods or food groups included red meat, poultry, dairy, fish, fruit, legumes, refined grains, whole grains, avocado, vegetables, potato, corn, Mexican foods, and dessert. For children, additional foods were used to reflect the updated FFQ for this age group: nuts and pizza. These food groups represented the majority of foods consumed but did not include all the foods quantified for cadmium. The cadmium concentrations (μg/g food) were averaged across food items that contributed to the food group. Food consumption (g/day) and DCd (μg/L) were included. Data used to estimate DCd by food or food group is displayed in Table 1.

Urinary cadmium

UCd was measured in maternal third trimester (fasting spot) and child (arbitrary spot) urine. Urine was collected in sterile cups and samples were aliquot an hour after collection, frozen at -20 degrees Fahrenheit, and then moved to -70 degree Fahrenheit freezer for storage. The UCd was determined as previously described (Basu et al. 2010; Srigboh et al. 2016). Briefly, 0.5 mL of sample was digested with an equal volume of concentrated nitric acid and allowed to sit overnight in a fume hood. The following morning Milli-Q water was carefully added to the digest to bring the acid content to 2% (Srigboh et al. 2016). The digest was analyzed for Cd using an Inductively Coupled Plasma Mass Spectrometer (ICPMS; Varian 820MS). Potential elemental interferences are minimized via the ICPMS' collision reaction interface. The analytical accuracy was determined using a urinary reference material obtained from the Institut National de Santé Publique du Québec (QMEQAS10U-04) that has certified values for Cd (and other trace elements). Every batch of 20 samples included a reference material and in total 25 measures were taken. The mean (SD) concentration of Cd measured in the reference material was 1.7 (0.1) ug/L compared to the actual certified value of 2.1 ug/L thus resulting in an accuracy of 82%. The analytical precision of urinary Cd was determined by

creating a pool of urine that was run in each batch so that inter-day variability could be assessed. Every batch of 20 samples included a pooled sample and in total 25 measures were taken. The mean (SD) concentration of Cd measured in the pool was 0.13 (0.02) ug/L which provides a coefficient of variation (or precision) of 16%. In addition, each batch run contained procedural blanks which yielded a value of 0.01 (0.01) ug/L. The analytical detection limit was set as three times the standard deviation of the mean blank value, and was set at 0.04 ug/L.

Statistical Analysis

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA). Cadmium concentrations in the urine were analyzed for 214 third trimester maternal samples and 250 childhood samples between ages 7-15 years. The analytic datasets were limited to 192 pregnant women and 223 children, with complete information on the primary exposure of DCd and response variable of UCd, and other covariates (maternal smoking history, sex, age, socioeconomic level, and BMI), a strategy consistent with other reports based on these data (Watkins et al. 2014). No statistically significant difference was detected in mean DCd and UCd, maternal smoking history, or any of the covariates between those included versus excluded from the analytic samples.

The limit of detection (LOD) for UCd was 0.04 ug/L; 190 (99%) of pregnant women and 215 (95%) of child samples were greater than or equal to the LOD. For participants with UCd concentrations below the LOD, the values between zero and the LOD obtained from the instrument were used. UCd was corrected for specific gravity using the following equation: $P_c=P[(SG_p-1)/(SG_i-1)]$ where P_c is SG-corrected UCd (μg/L), P is the measured UCd, SG_p is the population-specific median urinary specific gravity (pregnant women=1.013, children=1.018), and SG_i is the individual's urinary specific gravity. Specific gravity (SG) was measured using a handheld digital refractometer (Atago Co., Ltd., Tokyo, Japan). DCd was adjusted for total energy intake using the residual method (Willett 2013).

The distributions of UCd and DCd were examined via histograms for pregnant women and their children separately. In both populations, UCd distributions were non-normal right-skewed; ln-transformed UCd concentrations provided bell-shaped distributions and were used in analyses (Supplemental Figure 1a). Through the residual analysis, the appropriateness of such transformation was confirmed by the quantile-quantile normal plot (Supplemental Figure 1b). Only in children was the DCd distribution right-skewed. Sensitivity analysis was performed for ln-transformed and untransformed DCd; untransformed DCd was used for both pregnant women and children in analyses (Supplemental Figure 2).

Bivariate correlation coefficients were used to identify covariates marginally associated with UCd or DCd. Potential predictors of UCd or DCd included cohort, sex, age, SES, and BMI.

Multiple linear regression was used to quantify the relationship of DCd with UCd, adjusting for covariates. The relationship was quantified within the entire analytic sample and in separate analyses stratified by maternal smoking history, defined as never- or ever-smoker. Maternal smoking history was considered an effect modifier of the relationship between

dietary and urinary cadmium in all analyses. To test for interactions of smoking status with DCd, a product term of smoking status and DCd was included in the model and the significance of its coefficient was assessed.

Robust multiple linear regression was deemed for stable results in the presence of substantial outliers in the UCd data. We used the multiple M-estimation (in short, MM estimation) procedure that combines high breakdown value estimation (Least Trimmed Squares) and conventional Huber's M estimation (Yohai 1987). These models included all covariates previously adjusted for in the analysis of DCd-UCd relationships.

A stepwise regression model was applied to determine the association between intake according to food groups and UCd. Stepwise regression is a commonly used model building technique to determine parsimonious relationships among a large number of predictor variables (Quraishi et al. 2015). The stepwise procedure inclusion criteria was set at 0.20 and the exclusion criteria at 0.10. All covariates adjusted for in the previous DCd and UCd models were retained throughout the stepwise selection. In addition to this approach, we performed separate analyses where the foods and food groups identified above were individually regressed against UCd and compared effect size and significance to stepwise regression results.

Results

Demographic characteristics and estimated DCd of the pregnant women (n=192) and children (n=223) sample populations are presented in Table 2, stratified by maternal smoking history. On average, pregnant women were of age 27 years and had a mean BMI of 29.6 kg/m^2. Pregnant women without a history of smoking were older (p=0.01) and had lower BMI (p=0.03) than those with a history of smoking. Pregnant women consumed an average of 9.3±3.5 μg cadmium per day (0.136 μg/kg/day); those without a history of smoking consumed marginally more than those with a history of smoking, 10.3 and 8.2 μg/day, respectively (p=0.09). More than half of children were female (52.9%), had a mean age of 10 years, and were overweight (BMI z-score=0.85). Children consumed on average 12.2±5.4 μg of cadmium per day (0.345 μg/kg/day), with no difference by sex (p=0.66) or between those with and without a maternal history of smoking (p=0.94).

Dietary contributions to DCd by food group can be seen in Table 3. Refined grains and vegetables contributed the majority to DCd for pregnant women and children, with over 60 percent of the vegetable contribution coming from leafy greens. However, children were asked about their nut consumption, which contributed 14.5 percent to DCd, slightly more than refined grains.

Table 4 shows the distribution of cadmium concentrations measured in urine in the two populations and stratified by maternal smoking history. All reported UCd values are corrected for specific gravity and means are geometric unless otherwise noted. The UCd concentrations of the pregnant women ranged from 0.02 to 17.06 ug/L with a mean of 0.19 ug/L. The cadmium concentrations in children ranged from 0.01 to 1.16 ug/L with a mean concentration of 0.14 ug/L. The lower concentrations in children were expected given their

younger age and thus less time to accumulate cadmium internally than their mothers. UCd increased with age in pregnant women (p=0.005) but not children (p=0.71). UCd concentrations did not differ based on maternal smoking history for pregnant women (p=0.18) or children (p=0.33). UCd levels in children were not different for females and males (p=0.51). Spearman correlation coefficients were calculated between the UCd concentrations for the subsample of mother-child pairs (n=192); there was an insignificant negative correlation (r=-0.03, p=0.70).

Table 5 displays the percent change in UCd stratified by maternal smoking history; the interaction term between maternal smoking history and DCd was significant (Pregnant women: p=0.01; Child: p=0.04). In unadjusted analyses, DCd was positively associated with UCd in pregnant women (p=0.005) and in children (p=0.08) without a maternal history of smoking: for every μg/day increase in DCd, there was a 6.6 and 2.1 percent increase in average UCd concentrations in women and children, respectively. Adjusting for covariates among those without a smoking history attenuated the positive association in pregnant women (%Δ=5.1, p=0.03) and strengthened the magnitude of the association in children (%Δ=2.6, p=0.03). In adjusted analyses of those with a maternal history of smoking, a negative but not statistically significant association was observed in pregnant women and children. A one-year increase in age was associated with a 3.2 percent increase in UCd in pregnant women with a smoking history (p=0.03) and a one-unit increase in BMI z-score was associated with 9.4 percent decrease UCd in children without a maternal smoking history (p=0.049).

The robust regression results were in agreement with those obtained from the multiple regression results: DCd remained positively and statistically significantly associated with UCd in both pregnant women and children without a maternal history of smoking. For pregnant women with a history of smoking, the negative association of DCd with UCd strengthened in magnitude and became statistically significant (%Δ=-4.94, 95% CI=-8.66,-1.07, p=0.01). Three influential outliers identified in the women's dataset corresponded to the three highest UCd concentrations values: 17.06, 3.99, and 2.54 μg/L. One influential outlier was identified in the children's dataset with UCd value of 0.54 ug/L.

Table 6 shows the percent change in UCd per 100 g/day increase in selected foods. This analysis was limited only to those without a maternal history of smoking given the results from the DCd-UCd associations. In pregnant women, the analysis suggested that intake of fruit (%Δ=6, p=0.001) and vegetables (%Δ=17, p=0.04) were positively associated with UCd. In children, the model indicated intake of avocado (%Δ=62, p=0.07) and potato (%Δ=327, p=0.07) were positively, and pizza (%Δ=-48, p=0.02) negatively, associated with UCd. Food groups differed slightly for pregnant women and children because the FFQ was updated to include food groups such as pizza and nuts for the children.

Discussion

In this study, we measured cadmium exposure using both an estimate of dietary intake (DCd) and biomarker of exposure (UCd) in a population of pregnant women and their children. Dietary sources of cadmium were similar between pregnant women and children.

We found a positive correlation between DCd and UCd among those without a maternal history of smoking, and intake of specific food groups - fruits and vegetables - positively associated with UCd.

Our estimation of mean DCd intakes in pregnant women was 9.3±3.5 μg/day and in children was 12.2±5.4 μg/day. Similar means were reported in 2003 for U.S. adult females 25-30 years (10.33 μg/day) and children 10 years (9.17 μg/day) (Egan et al. 2007). In a review paper, reported DCd averages ranged from 8 to 25 μg/day in different settings (Järup and Åkesson 2009). In our study, DCd was higher for children than for pregnant women (p<0.0001). This could be attributed to methodological issues as different FFQ were used for pregnant women versus their children. For example, only children were asked about nut consumption, which contributed almost 15 percent to daily DCd intake. Alternatively, as Mexico undergoes a nutrition transition, evidence of shifting dietary patterns toward increased consumption of refined grains and processed foods could explain different levels of dietary exposure to cadmium between the pregnant women and child populations (Rivera et al. 2004). In our sample, children consume a greater amount of refined grains, desserts, fruit, and vegetables than their mothers during pregnancy, all foods which contribute to DCd (Table 1). Our findings are supported by trends in the U.S.: while cadmium content in foods has remained stable between 1990 to 2003, changes in dietary patterns over this period have resulted in increased exposure to cadmium with 60 percent of the total increase due to increased consumption of grains and mixtures, particularly from sunflower seeds (Egan et al., 2007).

Sources of DCd were similar for pregnant women and their children, who both consume greater than 70 percent of their DCd from grains, vegetables, and fruit and less than 10 percent from animal products. These results are confirmed by other studies among women and children where the majority of daily intake of DCd is attributed to grains, vegetables, and potato (Egan et al. 2007; Järup and Åkesson 2009; Olsson et al. 2002; Ysart et al. 2000). In a study among the Spanish population, grains were the highest contributor to dietary intake of DCd among adult females (37.9%) and children (50.3%); however different from our results, fish and shellfish was the second highest contributor for female adults and children, 23.9 and 14.1 percent, respectively (Llobet et al. 2003).

Little is known about the distribution of UCd in Mexican populations, except in locations with known environmental contamination. Two studies have analyzed UCd concentrations in regions of Mexico, finding elevated concentrations among children 6-12 years (Moreno et al. 2010; Trejo-Acevedo et al. 2009). In order to assess the relevance of our study findings, we compared UCd concentrations in our cohort to the U.S. population. The geometric mean concentration of UCd (uncorrected for specific gravity 0.12±0.66 μg/L) among our sample of children, ages 7-15 years, was higher than in children 6-11 years (0.06 μg/L) and 12-19 years (0.09 μg/L) from the 2008 U.S. National Health and Nutrition Examination Survey (Riederer et al. 2013). This is unsurprising given that Mexican Americans born outside the U.S. had significantly higher UCd than Non-Hispanic Whites born in the U.S. among both children and adults (Riederer et al. 2013). We did not observe the reported difference in UCd among U.S. nonsmoking and smoking adults, 0.20 and 0.32 μg/L, respectively (Riederer et al. 2013). Instead, we found UCd concentrations trended higher in both pregnant women and

their children without a maternal history of smoking. Our findings are corroborated by previous literature specific to smoking history that has found no difference in UCd with concentrations dependent on current versus past smokers (Chaumont et al. 2013; Huang et al. 2011; Jain 2013; Paschal et al. 2000). Additionally, pregnant women who had a history of smoking have presented with significantly lower UCd concentrations than non-smokers, which could be related to the declining levels of UCd observed over pregnancy trimesters (Jain 2013).

We then examined to what extent DCd intake related to internal dose as measured by UCd. The elucidation of this relationship will inform the validity of epidemiologic studies that use DCd as a less invasive and inexpensive estimation of cadmium exposure. In the present study, DCd was positively associated with UCd only among both pregnant women and children without a maternal history of smoking. A comprehensive literature search of studies applying similar methods to estimate DCd – by using a database like TDS applied to consumption data – largely support a direct relationship between DCd and UCd dependent on smoking status. DCd was positively associated with UCd in non-smokers from multiple populations: U.S. and Danish postmenopausal women (Quraishi et al. 2015; Vacchi-Suzzi et al. 2015) and Norwegian men and women over 40 (Birgisdottir et al. 2013). However, findings from the California Teachers Study did not support these findings: dietary estimates of cadmium exposure were not significant predictors of UCd, even when limiting to women who had reported never smoking (Gunier et al. 2013).

Our findings that DCd contributes to UCd are reinforced by published studies utilizing a more exact estimation of DCd where duplicate samples of the actual food items consumed were measured for cadmium. In such studies, strong positive correlations were observed between DCd and UCd among non-smoking adult women in both Sweden (r=0.54, $p<0.001$) (Julin et al. 2011) and Japan (r=0.89, $p<0.01$) (Ikeda et al. 2006). However, in a cohort of children in Japan, negative correlations were observed between DCd and UCd (r=-0.49, $p<0.01$) (Watanabe et al. 2015). This study among children conflicted with our findings but did not account for cigarette smoke exposure, a potential source of confounding. Smoking status consistently moderates the relationship between DCd and UCd, as seen in our study and other published literature.

The positive correlation between DCd and UCd is suggestive of a dietary contribution to UCd. We evaluated the contribution of specific foods (grams/day) to UCd concentrations in pregnant women and children without a maternal smoking history using stepwise regression models.

In pregnant women, the intake of fruit and vegetables was associated with higher UCd. Fruit and vegetables are known to be high in cadmium content and significant contributors to DCd (Egan et al. 2007; U.S. Agency for Toxic Substances and Disease Registry 2012). However, a previous study has reported marginal negative associations of fruit with UCd (Quraishi et al. 2015).

Stepwise selection results in children included previously unreported findings with regards to pizza. Although pizza contributes on average five percent of daily DCd among our sample

of children – based on its match with the TDS food item “Pizza, cheese and pepperoni, regular crust, from pizza carry-out” – it is negatively associated with UCd. Consumption of pizza positively correlates with red meat consumption, where previous reports observe consistent negative associations between red meat intake and UCd in postmenopausal women (Quraishi et al. 2015; Vacchi-Suzzi et al. 2015). This could be related to the high zinc content in red meat, which is known to reduce bioavailability of cadmium from food (Reeves and Chaney 2008). Also, pizza consumption could be confounded by low intake of fruits and vegetables, which as seen in pregnant women were positively associated with UCd. Additional findings unique to our study include the marginal contribution of avocado to UCd. Potato marginally contributed to UCd, as seen in prior studies (Haswell-Elkins et al. 2007). Findings in children suggest that consumption of pizza and potatoes, foods indicative of the nutrition transition, could have contrasting impacts on dietary contributions to cadmium exposure.

Our study described cadmium exposure in two vulnerable populations using both dietary estimates and internal dose, however there were several limitations. Use of a single urine sample to quantify UCd does not account for within-person variation and could have led to an attenuated relationship with DCd (Gunier et al. 2013). However, adjustment for urinary specific gravity can account for urine dilution. Estimation of DCd relied on FFQ and TDS data. Incomplete estimation of DCd was likely due to the limited set of food items on the questionnaire. FFQ and TDS foods had to be matched based on similarity with averages used for inexact matches and mixed dishes leading to imprecise quantification of DCd. Also, the TDS database may have limited applicability in specific populations as the amount of cadmium in plants can vary based on soil concentrations which depend on proximity to industrial processes and level of emissions, use of phosphate fertilizers, and crop rotation (Jafarnejadi et al. 2013; Yang et al. 2009). While DCd exposure from local produce may not be captured, an estimated 80 percent of food consumed in Mexico City is supplied by sources in other Mexican states or imported (Food and Agriculture Organization of the United Nations 2015), and crops from Mexico are likely to be represented in the TDS market basket survey due to the large amounts of trade with the U.S. since implementation of the North American Free Trade Agreement in 1994 (Johnson 2014). Also, the process of quantification of DCd from the FFQ and TDS was applied uniformly to the women and child samples, thus inter-individual differences are meaningful even if subject to measurement error. When estimating the relationship between DCd with UCd, the timing of the measures may be misaligned. UCd is used to describe long-term exposure over years, yet DCd was assessed via FFQ according to the previous month or week, for pregnant women and children, respectively. However, compared to other dietary assessments such as 24-hour recall, FFQ estimates have less intra-individual variability (Willett 2013). In addition, the prediction model of internal cadmium dose is reliant on aspects of food besides their cadmium content which we did not account for, including nutritional status of the host (Silver et al. 2013) and intake of micronutrients (Riederer et al. 2013). Finally, while we were able to account for proximal measures of cigarettes exposure, more precise measures such as cotinine level and smoking habits of children could be better at elucidating the relationship between DCd and UCd. Given the positive relationship between DCd and UCd

observed in pregnant women and children without a maternal smoking history, it is likely that diet is a source of long-term cadmium exposure.

Conclusions

In this sample, pregnant women and their children are exposed to cadmium at levels similar to those in cited in the literature. The positive association between DCd and UCd could indicate diet to be an important source of cadmium exposure among nonsmoking pregnant women and their children in Mexico City. However, use of DCd to estimate cadmium exposure and relate to health outcomes in epidemiologic studies should be done with caution, given its relation to internal dose can depend on estimation methodology and characteristics of the study sample.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

UCd	Urinary cadmium
DCd	Dietary cadmium
SES	Socioeconomic status
BMI	Body mass index
TDS	Total Diet Survey

Highlights

- Dietary sources of cadmium include grains, vegetables, and nuts for vulnerable populations.
- Direct relationship of dietary with urinary cadmium in those with no maternal smoking history.
- Intake of fruit and vegetables, including potatoes, predicted urinary cadmium.

Table 1

Daily intake of DCd (μg/day and food (g/day), contamination of foods (μg Cd/g food), and number of foods by food group.

	Cd (μg/day)[a]		Food (g/day)[a]		μg Cd/g food[a]		#Foods from FFQ[b]		#Foods from TDS[b]	
Food Group	**Women**	**Children**	**Women**	**Children**	**Women**	**Children**	**Women**	**Children**	**Women**	**Children**
Avocado	0.81 ± 0.86	0.23 ± 0.20	37 ± 40	11 ± 19	0.02 ± 0.00	0.01 ± 0.00	1	1	1	1
Corn	0.89 ± 0.74	0.03 ± 0.02	55 ± 41	32 ± 39	0.00 ± 0.00	0.00 ± 0.00	2	1	3	2
Dairy	0.12 ± 0.10	0.11 ± 0.05	494 ± 398	647 ± 265	0.00 ± 0.00	0.00 ± 0.01	8	10	13	17
Dessert	0.20 ± 0.34	0.76 ± 1.35	23 ± 42	111 ± 102	0.02 ± 0.01	0.01 ± 0.01	3	7	8	17
Fish	0.23 ± 0.26	0.10 ± 0.07	20 ± 20	11 ± 11	0.01 ± 0.01	0.01 ± 0.01	4	3	6	4
Fruit	0.77 ± 0.89	0.95 ± 0.77	350 ± 351	416 ± 309	0.00 ± 0.00	0.00 ± 0.00	15	12	48	52
Legumes	0.23 ± 0.26	0.07 ± 0.05	60 ± 58	28 ± 21	0.00 ± 0.00	0.00 ± 0.00	3	3	3	4
Mexican food	0.20 ± 0.30	0.72 ± 0.58	22 ± 23	56 ± 50	0.02 ± 0.00	0.01 ± 0.01	2	2	2	3
Nuts		1.88 ± 1.42		4 ± 6		0.22 ± 0.00		1		2
Pizza		0.59 ± 0.46		8 ± 19		0.02 ± 0.00		1		1
Potato	0.61 ± 0.47	0.54 ± 0.49	26 ± 20	4 ± 7	0.02 ± 0.00	0.02 ± 0.00	1	1	7	3
Poultry	0.07 ± 0.04	0.05 ± 0.04	32 ± 19	41 ± 31	0.00 ± 0.00	0.00 ± 0.00	1	1	5	4
Red meat	0.12 ± 0.09	0.19 ± 0.43	91 ± 55	67 ± 60	0.00 ± 0.00	0.00 ± 0.00	9	6	13	17
Refined grains	1.89 ± 1.12	1.77 ± 0.81	102 ± 62	165 ± 64	0.02 ± 0.01	0.01 ± 0.01	7	8	17	13
Vegetables	2.85 ± 2.29	4.31 ± 5.15	138 ± 100	162 ±115	0.03 ± 0.03	0.03 ± 0.04	9	9	16	15
Whole grains	0.13 ± 0.24	0.68 ± 0.57	11 ± 18	13 ± 24	0.02 ± 0.01	0.02 ± 0.01	3	4	7	9

[a] Mean ± SD.

[b] Sum.

Table 2

Characteristics of pregnant women in third trimester and children by maternal smoking history.[a]

	Women (All)	Women (+Smoke)	Women (−Smoke)	Children (All)	Children (+Smoke)	Children (−Smoke)
N	192	94	98	223	112	111
Sex Female	192 (100)	94 (100)	98 (100)	118 (52.9)	57 (50.9)	61 (55.0)
Sex Male				105 (47.1)	55 (49.1)	50 (45.0)
Age (years)	27.4 ± 5.9	26.4 ± 5.2	28.5 ± 6.3	10.3 ± 1.6	10.2 ± 1.5	10.4 ± 1.7
SES level	8 ±3.2	8 ± 3.3	8 ± 3.2	8 ± 3.3	9 ± 3.3	8 ± 3.3
BMI[b]	29.6 ± 4.0	30.2 ± 4.2	29.0 ± 3.8	0.85 ± 1.2	0.95 ± 1.3	0.74 ± 1.2
Weight (kg)	70.0 ± 10.2	71.9 ± 10.8	68.1 ± 9.2	38.0 ± 10.8	38.4 ± 10.2	37.6 ± 11.4
DCd (μg/day)[c]	9.3 ± 3.5	8.2 ± 3.1	10.3 ± 3.8	12.2 ± 5.4	12.4 ± 5.7	11.9 ± 5.0
DCd (μg/kg/day)[c]	0.136 ± 0.06	0.123 ± 0.05	0.148 ± 0.06	0.345 ± 0.21	0.353 ± 0.23	0.336 ± 0.19

[a] Mean ± SD or N (%).

[b] Maternal BMI units in kg/m^2; children's BMI units in z-score.

[c] DCd is energy adjusted.

Table 3

Percentage of food group contribution to daily intake of DCd.

Food Group	Women	Children
Avocado	8.85	1.78
Corn	9.73	0.24
Dairy	1.32	0.82
Dessert	2.20	5.88
Fish	2.47	0.79
Fruit	8.45	7.34
Legumes	2.52	0.57
Mexican food	2.19	5.56
Nuts	0.00	14.46
Pizza	0.00	4.51
Potato	6.67	4.14
Poultry	0.74	0.42
Red meat	1.30	1.46
Refined grains	20.81	13.63
Vegetables	31.33	33.18
Whole grains	1.43	5.22

Table 4

Concentration of UCd (μg/L) for pregnant women in third trimester and their children.[a]

Population	N	GM[b]	GSD[c]	Min	25th	50th	75th	95th	Max
Mother (All)	192	0.19	0.78	0.02	0.12	0.18	0.28	0.60	17.06
Mother (+Smoke)	94	0.19	0.68	0.02	0.11	0.16	0.28	0.60	1.70
Mother (−Smoke)	98	0.20	0.87	0.06	0.12	0.18	0.27	0.99	17.06
Child (All)	223	0.14	0.60	0.01	0.11	0.14	0.18	0.37	1.16
Child (+Smoke)	112	0.14	0.58	0.01	0.11	0.14	0.17	0.34	0.80
Child (−Smoke)	111	0.14	0.62	0.01	0.11	0.14	0.18	0.45	1.16

[a] UCd values are specific gravity adjusted.

[b] GM=geometric mean.

[c] GSD=geometric standard deviation.

Table 5

Percent change (95% confidence interval) in UCd for pregnant women in third trimester and children by maternal smoking history.

	Pregnant women				Children			
	+Smoke		−Smoke		+Smoke		−Smoke	
	%Δ (95%CI)	*p*	%Δ (95%CI)	*p*	%Δ (95%CI)	*p*	%Δ (95%CI)	*p*
Unadjusted								
DCd (μg/day)[a]	-1.79 (-6.07, 2.7)	0.43	6.58 (2.00, 11.36)	0.01	-0.37 (-2.25, 1.53)	0.70	2.10 (-0.22, 4.48)	0.08
Adjusted[b]								
DCd (μg/day)[a]	-3.39 (-7.67, 1.08)	0.14	5.10 (0.70, 9.70)	0.03	-0.40 (-2.34, 1.58)	0.69	2.63 (0.24, 5.09)	0.03
Age (year)	3.19 (0.42, 6.04)	0.03	0.78 (-1.82, 3.44)	0.56	3.74 (-10.29, 19.96)	0.62	5.20 (-9.25, 21.96)	0.50
BMI[c]	1.48 (-1.85, 4.93)	0.39	1.91 (-2.43, 6.44)	0.40	-0.49 (-9.33, 9.22)	0.92	-9.36 (-17.70, -0.18)	0.05

[a] DCd is energy adjusted.

[b] Multiple linear regression models for pregnant women and children additionally adjusted for cohort, sex, and SES level.

[c] Maternal BMI units in kg/m^2; children's BMI units in z-score.

Table 6

Percent change (95% confidence interval) in UCd per 100 g/day increase in selected food intake.

Food groups (g/day)	**%Δ (95%CI)**	***p***
Pregnant Women[a]		
Fruit	6 (3, 10)	0.001
Vegetable	17 (1, 34)	0.037
Children[a]		
Avocado	62 (-3, 171)	0.068
Potato	327 (-7, 1850)	0.065
Pizza	-48 (-70, -11)	0.018

[a]Analysis limited to those pregnant women and children without a maternal history of smoking and adjusted for cohort, sex, age, total energy intake, SES, and BMI.