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# Urinary Cadmium and Estimated Dietary Cadmium in the Women's Health Initiative

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## Abstract

Cadmium, a heavy metal dispersed in the environment as a result of industrial and agricultural applications, has been implicated in several human diseases including renal disease, cancers, and compromised bone health. In the general population, the predominant sources of cadmium exposure are tobacco and diet. Urinary cadmium (uCd) reflects long-term exposure and has been frequently used to assess cadmium exposure in epidemiological studies; estimated dietary intake

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

of cadmium (dCd) has also been used in several studies. The validity of dCd in comparison to uCd is unclear. This study aimed to compare dCd, estimated from food frequency questionnaires (FFQs), to uCd measured in spot urine samples from 1,002 participants of the Women's Health Initiative. Using linear regression, we found that dCd was not statistically significantly associated with uCd (β=0.006, p-value=0.14). When stratified by smoking status, dCd was not significantly associated with uCd both in never smokers (β=0.006, p-value=0.09) and in ever smokers (β=0.003, p-value=0.0.67). Our results suggest that because of the lack of association between estimated dietary cadmium and measured urinary cadmium exposure, dietary estimation of cadmium exposure should be used with caution in epidemiologic studies.

### Keywords

Metals; Cadmium; Urinary cadmium; Dietary cadmium; exposure misclassification

## INTRODUCTION

Cadmium is a heavy metal that has been associated with renal disease, impaired bone health, and cancers in occupational settings and in the general population (1–5). Cadmium occurs naturally in the environment at relatively low levels. However, cadmium contaminates agricultural land as a result of fertilizer, industrial and consumer wastes, and mining activity (1, 2, 4). Smoking is an important source of exposure in the general population due to the high accumulation of cadmium in tobacco leaves(6), but the primary source of non-occupational exposure to cadmium in non-smokers is believed to be through diet (7). Plants take up cadmium through contaminated soil, with high concentrations of cadmium in leafy vegetables, grains, and nuts (2, 8, 9). Approximately 3–5% of cadmium in food is absorbed into the body when ingested (10–12). Cadmium exposure also occurs through air and water, though these are minor sources of human exposure in the US and Europe (2, 13, 14).

Cadmium exposure in humans can be measured from biological samples including urine and blood, or estimated from diet (2, 15, 16)(2, 3). Because cadmium accumulates in the kidney, urinary cadmium is thought to reflect long-term exposure, with the half-life of cadmium being decades in humans (12, 16, 17).

Dietary estimation of cadmium exposure based on food frequency questionnaires (FFQs) or diet diaries linked to measurement of cadmium in food items has been used in several epidemiological studies (18–27). Estimation of cadmium levels from dietary data facilitates larger studies, and is an efficient use of commonly collected data in order to evaluate the association of cadmium exposure with multiple adverse health outcomes. However, the accuracy of dietary estimation of cadmium exposure compared to urinary cadmium remains unclear.

In the current study, we evaluated the relationship between urinary cadmium (uCd) and dietary cadmium intake (dCd) estimated from FFQs from a subsample of participants in the large and well-annotated Women's Health Initiative Cohort Initiative Clinical Trials and Observational Study (WHI) (28).

## MATERIALS and METHODS

### Study population

Participants were selected from the Women's Health Initiative (WHI), a large longitudinal in the United States study of postmenopausal women (age 50–79 years at enrollment) recruited from clinical centers nationwide. The WHI comprises clinical trials (CTs) and observational study (OS) arms designed to evaluate several interventions and risk factors in relation to cancer and cardiovascular disease risk. Extensive details of WHI study design and recruitment have been previously described (28–30). Briefly, recruitment occurred between 1993 and 1998 at 40 clinical centers across the US. In total, WHI enrolled 161,808 women. All participants provided written informed consent. Human subjects review committees at all participating sites approved WHI study protocols. The analyses presented here were reviewed and approved by Fred Hutchinson Cancer Research Center Institutional Review Board as an ancillary study to WHI and comply with all applicable US regulations.

For the current study, an age-stratified random sample of 1,050 participants was selected from 12,476 WHI women participating in the Bone Mineral Density study at three clinical centers (Pittsburgh, PA; Birmingham, AL; and Tucson, AZ), the only WHI sites which routinely collected urine samples (31). Since our study includes women who serve as controls in a study of breast cancer incidence, we excluded women who reported prior breast cancer; in addition, we excluded women with no urine sample in the WHI repository, or unknown baseline smoking status. For the present study, women with incomplete information on race/ethnicity, body mass index (BMI), education, parity, or an incomplete FFQ were excluded, resulting in a final study sample of 1,002 women.

### Data collection

All women completed extensive self-administered questionnaires at baseline enrollment. Questionnaires included detailed information on demographic characteristics, dietary habits, medical history and lifestyle factors including tobacco use and alcohol intake. Anthropometric measures were taken at baseline clinic visits using a standardized protocol (28).

Usual diet was assessed through a FFQ specifically developed for postmenopausal women (32), completed by all participants at baseline and at intervals, according to WHI study arm, during follow-up. The FFQ collected information on dietary intake over the previous 3 months from 122 individual line items each comprised of closely related foods or beverages, and included adjustment questions on food preparation and types of added fats (32). Previous evaluation of the WHI FFQ found that mean intake levels estimated by the FFQ were within 10% of those from food records and dietary recalls for a majority of nutrients; test-retest reliability of the FFQ was also high (Intraclass Correlations Coefficients from 0.67–0.84) (32). Total energy intake (kcal/day) was computed using the FFQ data (32). WHI discards FFQ data for women reporting <400 kcal or >5,000 kcal total energy intake per day. For this study, we used data from FFQ collected at baseline.

Dietary cadmium (dCd) was estimated using baseline FFQ data following dietary micronutrient methodology previously applied to dietary cadmium in the US (21, 25, 33). In

brief, a database of the cadmium content of component foods underlying each FFQ line item composite was constructed using measurements of the cadmium content of foods determined analytically by the US Food and Drug Administration (FDA) as a part of the Total Diet Study (TDS) (8, 34). TDS collected three representative market baskets per year from each of four regions throughout the US. Specific locations for collection within each region changed yearly. Foods were prepared according to predetermined recipes and analyzed by graphite furnace atomic absorption spectrometry for a number of nutrients and contaminants including cadmium (8, 34). TDS data are a publicly available resource accessible online (http://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/default.htm). The arithmetic mean of cadmium content (mg/100 g prepared weight) reported by the FDA for all available samples of each food was assigned as the cadmium concentration for that FFQ component food item. Cadmium content from the TDS was averaged over year and region. Individual measurements of food items below the levels of detection (LOD) were assigned values of zero(25).

WHI women were asked to collect a first morning void, record the time of void on the sample collection vial, and refrigerate the sample until attending the baseline clinical visit. Upon receipt at the clinic the sample was logged, centrifuged, aliquoted to cryovials, and frozen for shipment and storage at −70°C in the WHI repository.

For the present study, urinary cadmium (uCd) was measured using mass spectrometry (sector field inductively coupled plasma mass spectrometry (SF-ICPMS) on a Thermo-Finnigan Element 2 (Thermo Scientific, Waltham, MA) at the Wisconsin State Laboratory of Hygiene (Madison, WI), following quality control procedures similar to those previously described (3, 35). SF-ICPMS batches included participant samples, standard reference material aliquots, and multiple quality control samples (duplicates, spikes, check standards and blanks) (26). Duplicate samples resulted in a mean coefficient of variation (CV) of 2.7%. Values that were below or equal to the lowest level of quantification (LOQ) of 3.5 ng/L were assigned a value of 3.5/√2 ng/L. Of the final 1,002 women included in this analysis, 9 had cadmium levels below or equal to the LOQ.

## Statistical Analyses

For statistical analyses, uCd was divided by urinary creatinine for each participant and expressed as μg cadmium/g creatinine. Thus, uCd throughout statistical analyses was defined as creatinine-adjusted urinary cadmium. All regression models were conducted using the robust method to estimate standard errors.

The distributions of uCd and dCd were examined via histograms (Supplementary Figure 1). Both plots showed a right-skewed distribution. In sensitivity analyses, log-transformed values for both uCd and dCd were used in analyses. We selected untransformed results for ease of interpretation and presentation.

Multivariable linear regression was used to identify participant personal characteristics independently associated with dCd or uCd. Potential predictors of dCd or uCd included WHI study arm (CT or OS), WHI region, age at baseline, smoking status, total energy intake, race/ethnicity, body mass index (BMI), physical activity, multivitamin use, dietary

alcohol consumption, education level, postmenopausal hormone therapy use, age at menopause, and parity (Table 1). Smoking status is defined as never smoker, ever smoker, or current smoker. This categorized definition of smoking status was highly correlated with calculated pack years ($R^2$=0.83) within the data. Categorical variables were evaluated using a post estimation Wald statistic. Missing categories were created for variables with missing data; physical activity (N=36) and age at menopause (N=84). Age, smoking status and total energy intake were retained in all subsequent models of dCd and uCd as *a priori* covariates.

Multivariable linear regression was used to quantify the relationship of mean dCd with mean uCd, adjusting for personal characteristics identified *a priori* and independently associated with dCd or uCd as determined above. This relationship was quantified within the entire study sample and stratified by smoking status, WHI region, race/ethnicity, and current iron supplement use allowing the coefficient of dCd to vary between strata to test interactions with dCd in relation to uCd. The relationship was analyzed stratifying by use of any iron supplementation.

A stepwise regression model was applied to evaluate which food groups were most related to uCd. All *a priori* (age, smoking status, total energy intake) and covariates selected from the initial dCd and uCd models described above were retained throughout stepwise selection. The stepwise procedure inclusion criteria was set at P=0.15 and the exclusion criteria at 0.10. Food groups input for selection were fruits, vegetables, fish, red meat, poultry, soy, nuts, grains, whole grains, milks, and dairy all measured as medium servings/day and computed by the WHI study by aggregating data from the FFQ. Food groups rather than individual food items were input for selection in order to minimize over-fitting that could result from the inclusion of many individual food items in regression models. Stepwise selection was conducted in the overall study population, and separately in never smokers.

All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and Stata version 13.0 (StataCorp, College Station, TX).

## RESULTS

The mean age of participants was 63.4 years old and the majority (55.7%) were never smokers (Table 1). The mean (SD) uCd was 0.62 (0.50) μg/g creatinine (range: 0.0014 – 6.79 μg/g; interquartile range (IQR): 0.45 μg/g; geometric mean 0.48 μg/g). The mean (SD) dCd intake was 10.4 (4.7) μg/d(range: 1.74 – 31.6 μg/d; IQR: 6.2 μg/d; geometric mean 9.4 μg/d). dCd estimates did not vary substantially across most of the covariates evaluated, but were strongly correlated with estimated total energy intake. uCd was higher in older participants, smokers, and in participants reporting higher alcohol consumption. Thirty percent of participants were currently taking iron supplements, either as a single supplement or as part of a multivitamin.

Independent predictors of both dCd and uCd identified through separate multivariable linear regression models were age, race/ethnicity, physical activity, and parity. WHI study arm, WHI region, dietary alcohol consumption, and education were associated with dCd but not

uCd. Smoking status and BMI were associated with uCd but not dCd. For subsequent analyses, all of these variables were retained as adjustment covariates.

Each 1μg/d higher mean dCd was associated with 0.006 μg/g (95% CI: −0.002, 0.014 μg/g) higher mean uCd (Table 2). The association between dCd and uCd did not differ among never-smokers and ever smokers (P-interaction=0.77). The association was marginally stronger in never smokers compared to ever smokers (β=0.006, β=0.003, respectively), though neither of these stratified associations are statistically significant. By WHI region, the association was strongest within the Eastern region (β=0.014, 95%CI: 0.001–0.026), though there were no statistically significant differences in association by race/ethnicity, WHI region, or by current use of iron supplements. Furthermore, the association between uCd and dCd was qualitatively unchanged when log-transformed uCd and dCd were used in regression models (0.12% higher uCd for each 1% higher dCd (95% CI: −0.16% – 0.25%)), adjusted for the same covariates as described.

A stepwise selection model assessed fruits, vegetables, fish, red meat, poultry, nuts (including peanuts and peanut butter), grains, and dairy in addition to fixed adjustment covariates (age, total energy intake, smoking status, WHI study arm, WHI region, race/ethnicity, BMI, physical activity, dietary alcohol consumption, multivitamin use, education, and parity) in relation to uCd. The food groups retained as associated with uCd were fruits, vegetables, dairy, red meat, nuts, and milks (Table 3). This approach was repeated in never smokers resulting in the retention of nuts (β=0.21 (0.11–0.31) μg/g per daily medium serving, and grains (β=0.015 (0.001–0.029)).

## DISCUSSION

We observed at most a weak association between dCd intake, estimated from FFQs, and uCd. Although our study sample included smokers, when restricted to never-smokers, the association between dCd and uCd remained weak and not statistically significant. We observed no statistically significant differences in association by race/ethnicity or by WHI region.

The associations of uCd with age and smoking history were consistent with several previous reports from disparate populations (14, 16, 35–41). In women in our study, cadmium levels, as measured both in diet and urine, increased with higher alcohol consumption. This differs from what has been found in previous studies in women which have found inverse (14) or no association (35) of cadmium with alcohol consumption.

The results of the stepwise regression model used to evaluate the contribution of specific components of diet to urinary cadmium levels identified only intake of nuts in association with higher urinary cadmium. A larger number of vegetables was also suggested to be associated with higher mean urinary cadmium. Each of these food categories are known to contain more cadmium than, for example, meat or poultry. On the other hand, intake of grains, which may also have a relatively high cadmium content, were not retained (8).

From the stepwise selection model, an inverse association was suggested between uCd and consumption of red meat. Increased absorption of cadmium through the gastrointestinal tract

has been related to low iron stores, though this may not be as much of a concern in postmenopausal women (10, 42, 43). Vahter et al. conducted a study analyzing the bioavailability of cadmium comparing diets high in shellfish intake with “mixed diets”, and found that bioavailability differs by diet type, potentially as a result of differences in iron intake (11). In out study, the current use of iron supplements did not alter the relationship between uCd and estimated dCd, though only a minority of participants were taking supplements. Other dietary components that have been implicated with cadmium absorption include fiber, calcium, zinc and copper (10, 11, 44, 45), each of which is difficult to assess with recall-based dietary assessments such as FFQs. Hence, when attempting to approximate dietary exposure to cadmium, intake of dietary co-factors potentially involved with absorption presents an additional challenge.

Previous studies have found correlations between urine and diet cadmium. In Sweden, Julin et al. examined the relationship between dietary and urinary cadmium and found a correlation of r=0.43 (46). This study collected duplicate food portions and directly measured intake of cadmium using mass spectrometry in food consumed. Julin et al also found that the inclusion of iron status increased the prediction of the model (46).

Ikeda et al. conducted at study throughout several Japanese prefectures measuring cadmium levels in the environment, in food portions collected from those areas, and in urine samples and were able to find correlations between these measures (r=0.59–0.89) (47). The approach used in Sweden and Japan shows that diet is correlated to urinary cadmium when cadmium is measured in samples of the actual food items consumed, or food acquired locally, in contrast to our approach.

A Norwegian study measuring fish and game intake used specifically designed FFQs in areas known to have high cadmium contamination found no association with cadmium levels in either blood or urine in the overall population; in non-smokers they identified seafood, particularly crab, as a predictor of urinary cadmium (48). In the California Teachers Study, a similar method as the current study was used to determine cadmium levels using FFQs and extrapolating the FDA’s Total Diet Study cadmium measures found that diet cadmium was not a significant predictor of urinary cadmium (14). Thus, our results are generally consistent with previous studies that also compared FFQ and biological measures of cadmium exposure.

The weak association between urine and diet cadmium measures in our study population may be a result of measurement error introduced by our reliance on FFQ data. In part, this may stem from the imprecision of cadmium levels estimated from the Total Diet Study to approximate the actual cadmium levels in the food, as well as the limitation of FFQs to capture the totality of regular dietary intake, which has specifically been demonstrated using the WHI FFQ (49). In contrast to uCd, the dietary cadmium estimate does not account for other routes of exposure, though the associations here adjusted for smoking status, the main driver of cadmium levels outside of diet. Questionnaire data on occupation collected by WHI shows that occupational exposure in this cohort is unlikely (50).

A source of measurement error is the different time periods over which the FFQ used in our study and urinary cadmium assessed exposure. Urinary cadmium is widely believed to measure exposure over several decades(15, 16, 51). In contrast, the WHI FFQ was designed to evaluate diet in the prior 3 months(32). Therefore, changes in diet with age may be an important consideration in future diet-based assessments of cadmium exposure.

Cadmium levels likely differ by region and by food supplies. Here, we used national level estimates of cadmium contamination in food to make our diet estimates. Since the sources of food supply in the US population are relatively diverse, and since uptake of cadmium into foods such as vegetables depend upon growing conditions (52, 53), it may be that using cadmium quantifications measured from food items across the country did not provide enough specificity to accurately estimate individual intake of cadmium through diet. Using diet measures that are specific to both sub-populations and cadmium quantifications based on specific regions of food origin may improve the association of dietary and urinary cadmium measures.

The use of a stepwise regression model to evaluate which food groups contributed most to diet cadmium levels may be prone to over-fitting due to the number of variables provided for evaluation. We minimized this by using food groups in stepwise elimination, rather than many individual food items. Thus although over-fitting may be a concern, the results of this analysis may still provide some insight as to which food groups contribute most to urinary cadmium levels.

Finally, variation in uCd introduced by our use of a single urine sample may have attenuated any association between dietary and urinary cadmium. Most (84%) women recorded a time of collection before 8 a.m., suggesting a first morning void, which should have reduced diurnal variation in urinary cadmium (54). In addition, to account for dilution, we adjusted urinary cadmium for urinary creatinine; urinary creatinine has been observed to vary according to gender, age, body size, or meat intake (55). Because our study included only postmenopausal women, ages 50–79 years, and we adjusted for BMI, the influence of creatinine adjustment on our results was likely reduced.

Our study also has important strengths. We evaluated the association of estimated dietary cadmium intake and urinary cadmium intake in a sample of 1,002 postmenopausal women participating in the WHI, a well-annotated cohort study with extensive data on personal characteristics and behaviors. Our study included the largest sample sizes of comparable previous studies evaluating the relationship between diet and urinary cadmium in Western populations with similar exposure to cadmium(14, 35, 41, 46, 48); Asian studies have included more participants with higher exposure levels(47, 56)

In summary, in this study of postmenopausal women, we did not find a strong association between estimated dietary intake of cadmium and urinary cadmium. Diet remains the most likely source of cadmium exposure among non-smokers without occupational exposure (2). However, our results suggest that assessment of dietary cadmium with instruments such as food frequency questionnaires, combined with representative data on cadmium in foods,

may suffer from a large amount of measurement error that limits the usefulness of this approach in epidemiological studies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Appendix: Short List of WHI Investigators

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**Table 1**

Urine and diet cadmium levels according to selected participant characteristics at baseline: Women's Health Initiative.

| | | | Urine cadmium, μg/g creatinine | | Dietary cadmium, μg/day | |
|---|---|---|---|---|---|---|
| | N | % | Mean | Standard Deviation | Mean | Standard Deviation |
| All women | 1,002 | 100.0 | 0.62 | 0.50 | 10.4 | 4.7 |
| WHI Study Arm | | | | | | |
| Clinical Trial | 432 | 43.1 | 0.63 | 0.44 | 10.6 | 4.7 |
| Observational | 570 | 56.9 | 0.62 | 0.53 | 10.3 | 4.7 |
| WHI Region | | | | | | |
| East | 331 | 33.0 | 0.65 | 0.45 | 10.7 | 4.3 |
| South | 305 | 30.4 | 0.56 | 0.43 | 9.5 | 4.7 |
| West | 366 | 36.5 | 0.66 | 0.58 | 11.0 | 4.9 |
| Age at enrollment (y) | | | | | | |
| 50 to 54 | 130 | 13.0 | 0.49 | 0.43 | 10.8 | 5.1 |
| 55 to 59 | 186 | 18.6 | 0.58 | 0.39 | 10.7 | 4.9 |
| 60 to 69 | 458 | 45.7 | 0.65 | 0.48 | 10.3 | 4.5 |
| 70 to 79 | 228 | 22.8 | 0.69 | 0.61 | 10.4 | 4.6 |
| Smoking status | | | | | | |
| Never Smoked | 558 | 55.7 | 0.49 | 0.32 | 10.4 | 4.9 |
| Past Smoker | 354 | 35.3 | 0.72 | 0.59 | 10.7 | 4.5 |
| Current Smoker | 90 | 9.0 | 1.07 | 0.63 | 9.3 | 4.1 |
| Race/Ethnicity | | | | | | |
| White, non-Hispanic | 775 | 77.4 | 0.64 | 0.51 | 10.6 | 4.2 |
| Black/African-American | 144 | 14.4 | 0.52 | 0.35 | 9.1 | 5.2 |
| Hispanic/Latino | 55 | 5.5 | 0.59 | 0.41 | 10.7 | 7.3 |
| Other[1] | 28 | 2.8 | 0.81 | 0.80 | 12.0 | 6.2 |
| BMI ($kg/m^2$) | | | | | | |
| <25 | 328 | 32.7 | 0.69 | 0.52 | 10.4 | 4.5 |
| 25 to 29.9 | 371 | 37.0 | 0.65 | 0.54 | 10.4 | 4.7 |
| 30+ | 303 | 30.2 | 0.52 | 0.39 | 10.6 | 4.9 |
| Physical Activity (MET-h/wk) | | | | | | |

| | | | Urine cadmium, μg/g creatinine | | Dietary cadmium, μg/day | |
|---|---|---|---|---|---|---|
| | N | % | Mean | Standard Deviation | Mean | Standard Deviation |
| ≤2 | 266 | 26.6 | 0.59 | 0.39 | 9.4 | 4.7 |
| 3 to 10 | 286 | 28.5 | 0.63 | 0.52 | 10.3 | 4.3 |
| 11 to 20 | 224 | 22.4 | 0.60 | 0.48 | 10.6 | 4.6 |
| 20+ | 190 | 19.0 | 0.71 | 0.62 | 11.7 | 4.8 |
| Missing | 36 | 3.6 | 0.59 | 0.33 | 11.6 | 5.7 |
| Education, highest level attained | | | | | | |
| High school or less | 324 | 32.3 | 0.64 | 0.46 | 9.7 | 4.7 |
| Some college | 365 | 36.4 | 0.63 | 0.52 | 10.6 | 4.7 |
| College graduate or higher | 313 | 31.2 | 0.60 | 0.51 | 11.1 | 4.5 |
| Postmenopausal hormone use | | | | | | |
| Never used | 469 | 46.8 | 0.64 | 0.53 | 10.5 | 5.1 |
| Past user | 154 | 15.4 | 0.66 | 0.50 | 10.3 | 4.3 |
| Current user | 379 | 37.8 | 0.60 | 0.46 | 10.4 | 4.4 |
| Age at menopause (y) | | | | | | |
| <40 | 111 | 11.1 | 0.55 | 0.39 | 10.1 | 4.8 |
| 40 to 44 | 150 | 15.0 | 0.61 | 0.43 | 9.9 | 4.3 |
| 45 to 49 | 216 | 21.6 | 0.63 | 0.49 | 10.8 | 4.6 |
| 50 to 54 | 311 | 31.0 | 0.63 | 0.45 | 10.6 | 4.4 |
| 55+ | 130 | 13.0 | 0.66 | 0.56 | 10.1 | 4.9 |
| Missing | 84 | 8.4 | 0.64 | 0.75 | 10.8 | 5.8 |
| Parity | | | | | | |
| Nulliparous/Nulligravid | 119 | 11.9 | 0.58 | 0.42 | 10.0 | 4.2 |
| 1 to 2 | 318 | 31.7 | 0.60 | 0.46 | 10.7 | 4.8 |
| 3+ | 565 | 56.4 | 0.65 | 0.53 | 10.4 | 4.7 |
| Daily alcohol intake (grams) | | | | | | |
| <0.012 | 236 | 23.6 | 0.57 | 0.42 | 9.4 | 4.6 |
| 0.012 to 0.19 | 257 | 25.6 | 0.55 | 0.41 | 10.4 | 4.3 |
| 0.20 to 2.8 | 253 | 25.2 | 0.67 | 0.50 | 10.6 | 4.9 |
| >2.8 | 256 | 25.5 | 0.70 | 0.61 | 11.3 | 4.7 |
| Iron supplement use | | | | | | |

| | N | % | Urine cadmium, µg/g creatinine Mean | Standard Deviation | Dietary cadmium, µg/day Mean | Standard Deviation |
|---|---|---|---|---|---|---|
| Yes | 305 | 30.4 | 0.62 | 0.37 | 10.9 | 4.7 |
| No | 697 | 69.6 | 0.63 | 0.54 | 10.3 | 4.7 |
| Total energy intake (kcal/d) | | | | | | |
| 600 to 1152 | 250 | 25.0 | 0.64 | 0.45 | 6.5 | 2.8 |
| 1153 to 1535 | 251 | 25.0 | 0.65 | 0.55 | 9.2 | 3.1 |
| 1535 to 1955 | 250 | 25.0 | 0.61 | 0.55 | 11.1 | 3.2 |
| 1955 to 4849 | 251 | 25.0 | 0.59 | 0.42 | 14.9 | 4.8 |

[1]Other category comprised American Indian or Alaska Native (n=20), Asian or Pacific Islander (n=7), and Other (n=1).

**Table 2**

Association of urine cadmium (μg/g creatinine) with diet cadmium (μg/day)[1].

| | N | β[2] | 95% Confidence Interval | P-value | P-interaction |
|---|---|---|---|---|---|
| All women | 1,002 | 0.006 | (−0.002, 0.014) | 0.14 | |
| Stratified results: | | | | | |
| Smoking status | | | | | 0.77 |
| Smokers (Current/Past) | 444 | 0.003 | (−0.012, 0.019) | 0.67 | |
| Never smokers | 558 | 0.006 | (−0.001, 0.014) | 0.09 | |
| Ethnicity | | | | | 0.06 |
| White, non-Hispanic | 775 | 0.005 | (−0.005, 0.014) | 0.33 | |
| Black/African-American | 144 | 0.010 | (−0.009, 0.029) | 0.31 | |
| Hispanic/Latino | 55 | −0.005 | (−0.027, 0.018) | 0.68 | |
| Other | 28 | 0.086 | (−0.14, 0.31) | 0.40 | |
| WHI Region | | | | | 0.58 |
| East | 331 | 0.014 | (0.001, 0.026) | 0.03 | |
| South | 305 | −0.003 | (−0.016, 0.011) | 0.68 | |
| West | 366 | 0.006 | (−0.008, 0.019) | 0.42 | |
| Iron supplement use | | | | | 0.34 |
| Yes | 305 | 0.003 | (−0.009, 0.014) | 0.66 | |
| No | 697 | 0.006 | (−0.004, 0.018) | 0.20 | |

[1]Models adjusted for age, total energy intake smoking status, WHI study arm, WHI region, ethnicity, BMI, physical activity, dietary alcohol consumption, multivitamin use, education, and parity (as categorized in Table 1).

[2]μg/g urinary cadmium per g/d dietary cadmium

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## Table 3

Association of intake of selected food groups with urine cadmium resulting from stepwise selection applied to a linear regression model[1].

| Selected foods (medium servings/day) | β[2] | P-value | 95% Confidence Interval |
|---|---|---|---|
| Fruits | −0.024 | 0.08 | (−0.051, 0.003) |
| Vegetables | 0.022 | 0.10 | (−0.004, 0.048) |
| Red meat | −0.052 | 0.11 | (−0.115, 0.012) |
| Nuts | 0.121 | 0.04 | (0.006, 0.237) |

[1]Model adjusted for age, total energy intake smoking status, WHI study arm, WHI region, ethnicity, BMI, physical activity, dietary alcohol intake, multivitamin use, education, and parity. Variables input for stepwise selection were fruits, vegetables, fish, red meat, poultry, nuts, grains, dairy.

[2]μg/g urinary cadmium per daily medium serving of each food item.