Effects of Exposure to Low Levels of Environmental Cadmium on Renal Biomarkers

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We conducted a study among residents of a small community contaminated with heavy metals from a defunct zinc smelter and residents from a comparison community to determine whether biologic measures of cadmium exposure were associated with biomarkers of early kidney damage. Creatinine-adjusted urinary cadmium levels did not differ between the smelter and comparison communities; thus we combined individuals from both communities (n = 361) for further analyses. The overall mean urinary cadmium level was low, 0.26 μg/g creatinine, similar to reference values observed in the U.S. general population. For children ages 6–17 years, urinary concentration of *N*-acetyl-β-D-glucosaminidase (NAG), alanine aminopeptidase (AAP), and albumin were positively associated with urinary cadmium, but these associations did not remain statistically significant after adjusting for urinary creatinine and other potential confounders. For adults ages 18 or older, urinary concentration of NAG, AAP, and albumin were positively associated with urinary cadmium. The associations with NAG and AAP but not with albumin remained statistically significant after adjusting for creatinine and other potential confounders. We found a positive dose–effect relationship between levels of creatinine-adjusted urinary cadmium and NAG and AAP activity, and statistically significant differences in mean activity for these two enzymes between the highest (≥ 1.0 μg cadmium/g creatinine) and the lowest (< 0.25 μg cadmium/g creatinine) exposure groups. The findings of this study indicate that biologic measures of cadmium exposure at levels below 2.0 μg/g creatinine may produce measurable changes in kidney biomarkers. *Key words*: **alanine aminopeptidase, albumin, β_2-microglobulin, cadmium, kidney, *N*-acetyl-β-D-glucosaminidase.** *Environ Health Perspect* **110:151–155 (2002). [Online 16 January 2002]**
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Cadmium is a common environmental contaminant and is associated with nephrotoxic effects, particularly at high exposure levels (*1*). Various tests with differing degrees of sensitivity and clinical significance have been used among cadmium-exposed populations to assess nephrotoxicity. Among these, elevated urinary albumin in the absence of an increase in low-molecular-weight protein excretion is an early indicator of glomerular damage and is observed at urine cadmium concentrations from 3.6 to 4.2 μg urinary cadmium/g creatinine (*2*). Increased albumin excretion and proteinuria is associated with excess cardiovascular disease, mortality, and renal disease (*3*), but these clinical implications have not been specifically associated with cadmium toxicity. Elevations in the excretion of low-molecular-weight proteins, such as β_2-microglobulin, α_1-microglobulin, or retinol-binding protein, have been used as indicators of damage to the tubular protein absorption capability. Low-molecular-weight proteinuria among exposed workers with > 10 μg urinary cadmium/g creatinine was irreversible and exacerbated the age-related decline in the glomerular filtration rate (*4–6*). Elevations in enzymes primarily of renal tubular origin, such as *N*-acetyl-β-D-glucosaminidase (NAG) and alanine aminopeptidase (AAP), have been observed at occupational cadmium exposures of 3.7–6.3 μg urinary cadmium/g creatinine (*2,4,7*). Increases in these enzymes have been associated with chemical-induced renal tubular damage (*8,9*)

Most studies of cadmium-induced renal effects using these and other biomarkers have been conducted among individuals with occupational or high environmental exposures (*4,7,10–16*). Results of a national health survey indicate that the geometric mean value (and 95th percentile) for urinary cadmium among the U.S. general population age 6 years or older is approximately 0.27 (1.48) μg/g creatinine (*17*), but little information is available on renal effects that may occur in people with urinary cadmium levels < 2 μg/g. Recent findings indicate that changes in sensitive renal biomarkers may occur at lower urinary cadmium levels than previously estimated among populations exposed to environmental cadmium (*18–21*).

The data for this study were collected in 1991 by the Agency for Toxic Substances and Disease Registry in a small community in the northeastern United States that had been the site of zinc smelting operations from 1898 through 1980 and in a nearby community that was demographically similar to the target area (*22,23*). Exposure among adults could reflect past airborne routes and possibly occupational exposure, as people from both towns worked in industrial jobs. Exposure among children reflects primarily contact with contaminated soil. The objective of this study was to determine the extent to which exposure to cadmium in these individuals was associated with biomarkers of early kidney damage. The panel of biomarkers consisted of two high-molecular-weight proteins, NAG and AAP, to indicate direct release of kidney tubular tissue into urine; the intermediate-molecular-weight protein albumin to indicate glomerular damage when excretion of low-molecular-weight protein was normal; and the low-molecular-weight protein β_2-microglobulin to indicate impaired tubular reabsorption.

Methods

Study participants included residents of Palmerton and Aquashicola, Pennsylvania, a community with past zinc smelting activity, and residents of East Jim Thorpe, Pennsylvania, a comparison community located approximately 10 miles from the defunct smelting facility. We selected the comparison area on the basis of similar demographics and age of housing, and because it was not affected by zinc smelting, coal mining, or other heavy industrial operations. Because previous analyses found that urinary cadmium levels among these study participants did not differ by area of residence (*22,23*), we combined individuals from both target and comparison communities to evaluate the effect of low-level cadmium exposure on kidney biomarkers. A complete door-to-door census was taken to determine the total population and to generate a list of eligible residents. Random

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samples of residents, 6 months through 75 years of age, who had resided in their homes during the 6 months previous to the study were selected. The mean time of residency among adults in their respective communities was 32 years. Trained interviewers administered a standardized questionnaire, which included information on occupational exposures, health status, and health behaviors (e.g., lifetime consumption of alcohol and tobacco). Parents or guardians answered questions for children under 12 years of age. Informed consent was obtained from the participants or from the parent or guardian of minors.

Specimen collection and analyses. We collected spot urine specimens from participants to measure cadmium, AAP, NAG, albumin, β_2-microglobulin, and creatinine. Cadmium-free collection materials were provided by the National Center for Environmental Health (NCEH), Division of Environmental Health Laboratory Services, Centers for Disease Control and Prevention, Atlanta, Georgia. Urine samples were frozen and sent by overnight delivery to NCEH, Division of Environmental Health Laboratory Services, for analysis.

We determined urine cadmium levels using established procedures (*7,24*), and quality-control procedures included performing 10% replicates and 5–15% controls and using field blanks for urine cadmium tests. As described previously, AAP was measured by an automated Jung and Scholz method (*25*), and NAG was measured by the Leaback and Walker method (*26*) and automated for the centrifugal analyzer Cobas Fara II (Roche Diagnostic Systems, Basel, Switzerland) (*27*). We measured albumin by enzyme immunosorbent assay, and assayed β_2-microglobulin using Pharmacia Diagnostics Phadebas β_2-Microglobulin Test Kits (Uppsala, Sweden) (*7*). Quality-control design for AAP, NAG, albumin, and β_2-microglobulin involved three bench pools, assayed in duplicate in each run. We measured urinary creatinine with an automated clinical Kodak 250 Analyzer (Ortho Clinical Diagnostics, Rochester, NY) using a single-slide, two-point enzymatic method according to the manufacturer's directions. Quality-control design for creatinine involved one low-, one medium- and one high-control analyzed in quadruplicate per run.

Data adjustment and exclusion criteria. We used urine creatinine to control for differences in urine dilution. Urine creatinine concentrations are proportional to muscle mass and vary by age and sex (*28*). We were able to adjust for age and sex in the multivariate analyses but not for muscle mass because height and weight data were not collected. Urine specimens with creatinine levels < 30 mg/dL were not included in the analyses, to eliminate the potential for imprecise and unreliable results from highly dilute urine samples. One creatinine-adjusted albumin value, 1,585 mg/g, was excluded from the analyses because it was well above the 95th percentile for the study, 45 mg/g. This single value would have inflated the mean urinary albumin concentration by 36% in the group of participants with the highest urinary cadmium values (≥ 1.0 µg/g creatinine). When this albumin value was included in the analyses, no change was observed in the nonparametric correlation analysis. Urine specimens with cadmium measures below the detection limit (0.1 µg/L) were assigned a value of one-half the detection limit. Our findings were similar when these individuals were excluded from the analyses. The results presented below excluded the lowest age group, 6–71 months of age, because 45% of this group had creatinine values < 30 mg/dL and 69% had urinary cadmium levels below the detection limit. We also excluded 164 urine samples with a pH less than 6.0 from the analysis of β_2-microglobulin because this protein is unstable in acidic media (*29*).

Six participants with self-reported kidney disease were removed from the analyses. Adults reporting diabetes (n = 6) and thyroid disease (n = 6) had higher urinary cadmium levels, and these conditions were associated with at least one of the kidney biomarkers. Variables to indicate the self-reporting of these two diseases were included in the multivariate analyses for adults. Other self-reported conditions such as hepatitis, other urinary tract disease, arthritis, leukemia, or other cancer were not associated with the biomarkers, and participants reporting these conditions remained in the analyses. The magnitude of effect between urinary cadmium and the kidney biomarkers did not change when individuals with these reported conditions were removed from the analyses. Among children, those reporting diabetes (n = 1) or thyroid disease (n = 1) were removed from the analyses.

Data analysis. Statistical analyses were done with version 6.12 of the Statistical Analysis Software (SAS; SAS Institute, Inc., Cary, NC, USA). All biologic test data were log-transformed for statistical analysis to approximate normality. We assessed differences in creatinine-adjusted urinary cadmium and creatinine-adjusted renal biomarker values by area of residence, age, sex, medical conditions, and behavioral factors using analysis of variance.

Recent studies indicate that children are more likely to have high urinary albumin concentrations (*30,31*), an association that may be attributed partially to stage of puberty (*30*). Given this and the possibility that other biomarkers may be affected in a similar manner, we performed separate correlation analyses for adults aged 18 years or older, and children 6–17 years. We calculated crude Spearman correlation coefficients, uncorrected for creatinine, for each kidney biomarker with urinary cadmium. We calculated partial Spearman correlation coefficients for adults after adjusting for creatinine, age, sex, smoking, and self-reported diabetes or thyroid disease. We also calculated partial Spearman correlation coefficients for children after adjusting for creatinine, age, and sex.

To characterize dose–effect relationships between urinary cadmium and the kidney proteins and enzymes, we grouped adult participants into five categories of creatinine-adjusted urinary cadmium. We used Dunnett's two-tailed t-test to determine whether the mean enzyme activity or protein concentration for each of the four higher categories of creatinine-adjusted urinary cadmium was significantly different from the lowest category (i.e., < 0.25 µg cadmium/g creatinine). We then calculated least-squares means by exposure group, adjusted for age, sex, smoking, and self-reported diabetes or thyroid disease, for each of the creatinine-adjusted kidney biomarkers. The differences between the adjusted mean levels of each kidney biomarker in the high- and low-exposure groups were compared statistically, using the least-significant-difference method in SAS.

Results

We collected urine samples from 361 persons, ages 6 through 74 years, reflecting a 50% participation rate for the comparison area and a 64% participation rate for the smelter (target) area. Of these, 46 had creatinine values < 30 mg/dL, and some individuals did not have valid data for one or more of the renal biomarkers. The geometric mean (and 95th percentile) creatinine-adjusted urinary cadmium was 0.13 µg/g creatinine (1.01). Only three subjects had values > 2.0 µg/g creatinine, with the maximum value at 2.15 µg/g creatinine. Geometric mean values of creatinine-adjusted urinary cadmium and renal biomarkers for selected variables are presented in Table 1. Area of residence was not associated with concentrations of urinary cadmium or renal biomarkers. We observed differences between males and females for some of the renal biomarkers but not for urinary cadmium. Among participants who smoke cigarettes, pack-years (i.e., the number of cigarette packs per day multiplied by the number of years smoking) was positively associated with urinary cadmium, and there was a linear relationship between pack-years and some of the kidney biomarkers.

Results from the correlation analyses are presented in Table 2. For children ages 6–17 years, urinary cadmium was associated with NAG, AAP, and albumin. None of these biomarkers remained significantly associated with cadmium after adjusting for creatinine, age, and sex. β_2-Microglobulin was not associated with urinary cadmium for this age group. For adults age 18 years or older, urinary cadmium was also positively associated with NAG, AAP, and albumin. After adjusting for creatinine, age, sex, smoking, and self-reported diabetes or thyroid disease, the partial correlations for urinary cadmium with NAG and AAP remained statistically significant ($p < 0.05$ for each enzyme). The partial correlation coefficient for urinary cadmium with albumin was reduced in comparison with the crude correlation and was no longer statistically significant. The observed correlations were of a similar direction and magnitude when target and comparison areas were analyzed separately (data not shown).

When the adults were grouped by five creatinine-adjusted urinary cadmium levels, the mean enzyme activity levels for both NAG and AAP demonstrated a positive linear relationship. Individuals in the highest exposure group (≥ 1.0 µg cadmium/g creatinine) had statistically significant increases of 53% and 43% for NAG and AAP, respectively, when compared with the lowest exposure group (< 0.25 µg cadmium/g creatinine) (data not shown). After adjusting for age, sex, smoking, and self-reported diabetes or thyroid disease, the differences in the mean levels of NAG and AAP between the highest and lowest categories of urinary cadmium remained statistically significant. These two enzymes demonstrated a positive dose–effect relationship among adult participants across the five categories of creatinine-adjusted urinary cadmium (Figure 1A,B). For mean concentrations of both albumin and β_2-microglobulin grouped by the five categories of creatinine-adjusted urinary cadmium, we found no consistent linear relationship (data not shown).

Discussion

The geometric mean urinary cadmium level among adults in this study (0.23 µg/g creatinine) is similar to the levels found in the U.S. general population (0.27 µg/g creatinine) (*17*). The finding of a positive association between urinary cadmium and renal biomarkers is consistent with the results of previous studies that found a positive association between cadmium and kidney enzymes and proteins at higher exposure levels (*4,7,10–16*). The enzymes NAG and AAP are not normally filtered through the glomerulus, so their presence in urine may indicate subclinical proximal tubular injury (*29*). AAP is localized to the brush border of the proximal tubule, and release of this enzyme may indicate membrane damage to tubular cells. The lysosomal enzyme NAG also is present in high concentrations in proximal tubule cells (*29*). NAG in urine is associated with increased necrotic or apoptotic cell turnover, but its presence can result from effects other than nephrotoxicity (*32*). An association between AAP and urinary cadmium was previously observed in studies of individuals with high occupational exposures (*7,11*), and NAG has been used as a marker of cadmium nephrotoxicity in several occupational and environmental studies (*7,10–12,33,34*).

The evaluation of different exposure levels in our study sample suggested a dose–effect relationship at levels < 2.0 µg urinary cadmium/g creatinine. Previous studies of highly exposed populations have demonstrated threshold of effects for renal biomarkers at 2.4–11.5 µg urinary cadmium/g creatinine (*2,4*). However, recent studies have found that effects may be seen at lower levels in the general population. A cross-sectional study in Sweden found that people with 1.0 µg urinary cadmium/g creatinine had a 3-fold increase in risk of having tubular proteinuria, as measured by α_1-microglobulin (*21*). Total NAG was also associated with creatinine-adjusted urinary cadmium ($p < 0.05$ for linear regression) among an environmentally exposed population in Sweden with relatively low urinary cadmium concentrations (median = 1.0 µg cadmium/g creatinine, range = 0.1–3.2 µg cadmium/g creatinine) (*20*). A study conducted in areas of Japan

Table 2. Spearman correlation coefficients (95% confidence interval) between urinary cadmium levels and biomarkers of early kidney damage.

Urinary cadmium	NAG (U/L)	AAP (U/L)	Albumin (mg/L)	β_2-Microglobulin (mg/L)
Age 6–17 years (*n*)	159	159	159	105
Crude correlation	0.25	0.24	0.17	0.09
	(0.10–0.40)	(0.10–0.39)	(0.02–0.32)	(–0.10–0.29)
Partial correlation[a]	0.09	0.15	0.03	–0.01
	(–0.07–0.24)	(0.00–0.30)	(–0.12–0.19)	(–0.20–0.19)
Age ≥ 18 years (*n*)	150	150	150	63
Crude correlation	0.30	0.37	0.26	0.18
	(0.15–0.44)	(0.23–0.51)	(0.12–0.41)	(–0.06–0.43)
Partial correlation[b]	0.20	0.21	0.09	–0.02
	(0.05–0.36)	(0.05–0.36)	(–0.07–0.25)	(–0.27–0.24)

[a]Adjusted for creatinine, age, and sex. [b]Adjusted for creatinine, age, sex, smoking, and self-reported diabetes or thyroid disease.

Table 1. Geometric mean values (95% confidence intervals) of urinary markers for selected characteristics.

Characteristics	No.[a]	Cadmium (µg/g creatinine)	NAG (Ug/g creatinine)	AAP (Ug/g creatinine)	Albumin (mg/g creatinine)	β_2-Microglobulin (mg/g creatinine)
Area						
Smelter	168	0.14 (0.12–0.17)	0.73 (0.65–0.81)	4.38 (3.98–4.82)	7.34 (6.58–8.19)	0.13 (0.11–0.14)
Comparison	144	0.12 (0.10–0.14)	0.73 (0.65–0.82)	4.62 (4.20–5.09)	8.45 (6.58–9.73)	0.12 (0.10–0.13)
Age/sex						
6–17 years						
Female	71	0.08 (0.07–0.10)	0.82 (0.74–0.92)*	4.53 (3.99–5.13)	10.38 (8.76–12.30)*	0.12 (0.10–0.14)
Male	88	0.07 (0.06–0.08)	0.57 (0.50–0.63)	4.50 (3.96–5.12)	7.00 (6.08–8.06)	0.12 (0.10–0.14)
≥ 18 years						
Female	80	0.23 (0.18–0.30)	0.83 (0.69–1.00)	3.82 (3.25–4.49)*	7.96 (6.68–9.48)	0.14 (0.11–0.19)
Male	71	0.24 (0.18–0.32)	0.75 (0.62–0.90)	5.30 (4.68–6.00)	6.67 (5.36–8.30)	0.11 (0.09–0.13)
Smoking (pack-years)[b]						
0	69	0.18 (0.14–0.22)*	0.85 (0.69–1.03)	4.39 (3.68–5.23)**	7.64 (6.20–9.42)	0.11 (0.10–0.13)
< 10	27	0.16 (0.10–0.25)	0.65 (0.46–0.92)	3.82 (3.18–4.60)	5.80 (4.49–7.49)	0.12 (0.08–0.20)
< 30	29	0.35 (0.23–0.53)	0.74 (0.53–1.03)	4.02 (3.14–5.17)	6.49 (4.76–8.86)	0.17 (0.08–0.36)
≥ 30	23	0.56 (0.40–0.79)	0.89 (0.66–1.20)	6.42 (5.07–8.13)	10.45 (6.69–16.33)	0.13 (0.06–0.29)

[a]Number of subjects for each biomarker vary because of missing values. [b]Data on smoking for adults only. *$p < 0.01$, analysis of variance. **$p < 0.05$, analysis of variance.

with no industrial cadmium exposures observed geometric mean urinary values of 1.3 µg cadmium/g creatinine and found a significantly positive association for NAG and β_2-microglobulin (*18*). Another investigation combining cadmium-exposed smelter workers with members of a control group found significant elevations of NAG among those excreting 0.5–2.0 µg cadmium/g creatinine, compared with those excreting < 0.5 µg cadmium/g creatinine (*12*).

In the present study, we observed statistically significant positive correlations between urinary albumin concentrations and urinary cadmium for both children and adults, but neither remained significant after adjusting for creatinine and selected confounders. Results from previous studies of high occupational cadmium exposures have suggested that urinary albumin may be a sensitive indicator of cadmium-induced renal effects (*7*). Cadmium levels in the high-exposure groups from these studies ranged from 6 µg to 16 µg cadmium/g creatinine (*7*), well above the levels observed in this study's environmentally exposed population.

We did not observe an association between β_2-microglobulin and urinary cadmium. β_2-Microglobulin is a low-molecular-weight protein that is normally reabsorbed by the renal tubules, and its presence in urine indicates compromised tubular reabsorption function. Currently, α_1-microglobulin or retinol-binding protein are more commonly used as low-molecular-weight proteins for studies of nephrotoxicity because of the instability of β_2-microglobulin in acidic environments (*29,35*). Our analysis of β_2-microglobulin was restricted to urine samples with pH values ≥ 6.0, but this does not rule out the potential for breakdown of the protein in the bladder before excretion. This restriction reduced the sample size for this biomarker by almost 50% and limited the statistical power to detect small differences in protein levels between the highest and lowest exposure groups.

Conclusions from this study must take into account some of the recognized limitations. First, because levels of urinary cadmium for individuals in the target and comparison areas were similar, the data from both groups were combined. Despite similar demographic characteristics of the two communities, individuals from the more industrialized target community could have a greater potential for exposure to other nephrotoxic substances. However, we observed similar associations between urinary cadmium and kidney biomarkers when area of residence was included in the multivariate models and when the target and comparison areas were analyzed separately. Secondly, we used urinary creatinine to adjust for either highly dilute or highly concentrated urine samples, but creatinine levels can vary by age, sex, and body mass (*28*). The multivariate statistical models were adjusted for age and sex, but data on height and weight were not available for body mass adjustment. The use of creatinine to standardize urinary metal values for children has been particularly problematic, and exposure values might be expected to be artificially inflated among this age group (*36*). The creatinine-adjusted urinary cadmium levels in this study, however, are significantly lower among children (Table 1), as would be expected when this marker of chronic body burden is used. Finally, we based information on kidney disease or other health conditions that may have affected individuals' kidney function on self-reported data, and we were unable to verify these conditions. Under conditions of extensive cadmium-induced renal tubular damage, urinary cadmium levels have been shown to rise sharply, but this effect does not necessarily occur under conditions of tubular dysfunction unrelated to cadmium exposure (*4*). The subjects evaluated in this study did not have abnormal levels of the urinary biomarkers that could indicate extensive renal damage, but we cannot exclude the possibility of subclinical renal conditions.

Results of previous investigations have suggested that proteinuria resulting from high cadmium exposures has been irreversible and progressive (*13,37*), but reversibility of minor renal changes was found among workers following a reduction in cadmium exposure (*38*). The clinical significance of the observed relationship between low-level urinary cadmium and urinary NAG and AAP is difficult to discern. The association between increased urinary excretion of NAG and renal damage has not been fully determined and may reflect increased lysosomal activity. Given that cadmium is stored in the renal tubule, it is possible that the correlation of the metal and these biomarkers is the result of a common association with another factor (e.g., the natural turnover rate and exfoliation of tubular cells). However, in a study of cancer patients, urinary levels of NAG and AAP were associated with loss of renal tubular secretion function in response to the chemotherapeutic agent cisplatin (*8,9*). For low-level cadmium exposure, it is unclear whether the observed differences in the levels of these tubular enzymes indicates subclinical toxicity that may cause cumulative renal deficiencies. Results of a 5-year follow-up study in Belgium indicated that a rise in urinary cadmium over time was a predictor of an increase in NAG, but there was no strong evidence that elevated NAG at baseline resulted in decreases in creatinine clearance or increases in albumin excretion at follow-up (*39*). In another 5-year follow-up study of populations with low-level cadmium exposure from three different areas of the United States, individuals with baseline elevations in preclinical biomarkers such as NAG and selected health conditions were more likely to show early indicators of kidney disease (i.e., elevated serum creatinine, elevated serum cystatin C, and decreased creatinine clearance) at follow-up (*40*). Further, participants who had these underlying health conditions at baseline, yet did not initially have an elevated biomarker, appeared to be at lower risk of developing early clinical signs of kidney disease than those with these health conditions who did have elevated kidney biomarkers (*40*). Thus, associations between these preclinical biomarkers and low-level environmental cadmium exposures may be particularly relevant for certain susceptible populations.

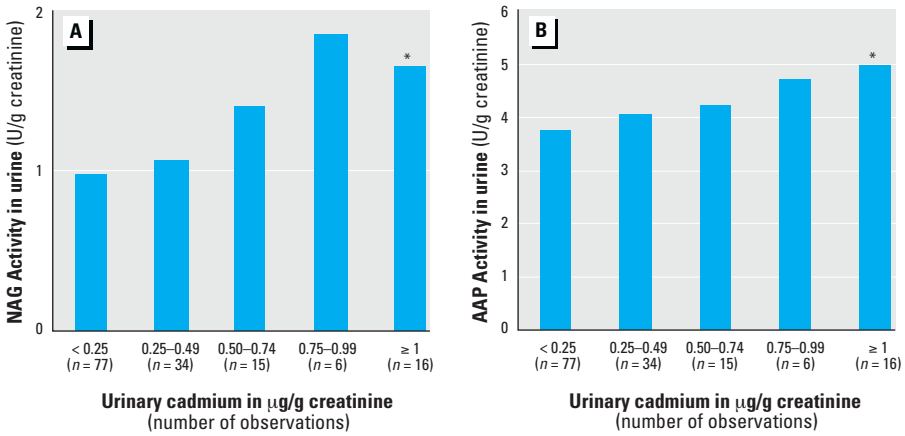

Figure 1. Least-squares mean concentrations (adjusted for age, sex, smoking, and self-reported diabetes or thyroid disease) of urinary NAG (U/g creatinine) (*A*) and AAP (U/g creatinine) (*B*) among adult participants, summarized by five categories of creatinine-adjusted urinary cadmium.
*$p < 0.05$ compared to the lowest exposure group (< 0.25 µg cadmium/g creatinine).

In this study, we evaluated renal biomarkers among a population exposed to levels of cadmium that are similar to those of the U.S. general population. Whether the observed changes in excreted enzymes reflects early, irreversible tubular damage or an overly sensitive indication of subclinical effects that will never progress to actual renal dysfunction will require continued follow-up of low-exposure populations such as these.

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