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Cadmium exposure in association with history of stroke and heart failure

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Abstract

Background—It is unclear whether environmental cadmium exposure is associated with cardiovascular disease, although recent data suggest associations with myocardial infarction and peripheral arterial disease.

Objective—The objective of this study was to evaluate the association of measured cadmium exposure with stroke and heart failure (HF) in the general population.

Methods—We analyzed data from 12,049 participants, aged 30 years and older, in the 1999–2006 National Health and Nutrition Examination Survey (NHANES) for whom information was available on body mass index, smoking status, blood cotinine level, alcohol consumption, and socio-demographic characteristics.

Results—At their interviews, 492 persons reported a history of stroke, and 471 a history of HF. After adjusting for demographic and cardiovascular risk factors, a 50% increase in *blood* cadmium corresponded to a 35% increased odds of prevalent stroke [OR: 1.35; 95% confidence interval (CI): 1.12–1.65] and a 50% increase in *urinary* cadmium corresponded to a 9% increase in prevalent stroke [OR: 1.09; 95% CI: 1.00–1.19]. This association was higher among women [OR: 1.38 95% CI: 1.11–1.72] than men [OR: 1.30; 95% CI: 0.93–1.79] (p-value for interaction=0.05). A 50% increase in blood cadmium corresponded to a 48% increased odds of prevalent HF [OR: 1.48; 95% CI: 1.17–1.87] and a 50% increase in urinary cadmium corresponded to a 12% increase in prevalent HF [OR: 1.12; 95% CI: 1.03–1.20], with no difference in sex-specific associations.

Conclusions—Environmental exposure to cadmium was associated with significantly increased stroke and heart failure prevalence. Cadmium exposure may increase these important manifestations of cardiovascular disease.

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Keywords

cadmium; heart failure; stroke; cardiovascular disease; heavy metal

Introduction

There has been increasing interest in the potential adverse cardiovascular effects of environmental exposures, including heavy metals (Bhatnagar 2006; Houston 2007; Weinhold 2004). Cadmium is a ubiquitous environmental toxin which may plausibly contribute to cardiovascular disease (CVD), although existing literature is limited. The major known sources of exposure for the U.S. general population are emissions from industrial activity and waste management operations, intake of certain foods (e.g. leafy vegetables, grains, organ meats, and crustaceans) and exposure to cigarette smoke. Previous studies found an association between blood cadmium and peripheral arterial disease (Navas-Acien et al. 2004) and between urinary cadmium and peripheral arterial disease and myocardial infarction (Everett and Frithsen 2008; Navas-Acien et al. 2005). Blood cadmium is thought to be a marker of current exposure but also appears to reflect body burden from long-term retention of cadmium in the liver and kidney; urinary cadmium is thought to more specifically be a marker of cumulative exposure (ATSDR 2008; Olsson et al. 2002). Cadmium may exert its adverse cardiovascular effects by promoting atherosclerosis and by inducing disadvantageous cardiac functional and metabolic changes (Houtman 1993; Kopp et al. 1983). We sought to examine the association of community-level cadmium exposure with two aspects of CVD for which there is little to no information: stroke and heart failure (HF).

Stroke is the third leading cause of death in the U.S., and a leading cause of adult disability. The data addressing the association of cadmium with stroke is rather limited. In the English village of Shipham, where soil levels and dietary intake of cadmium were very high, researchers found no evidence of adverse effects on blood pressure and hepatic, renal and skeletal systems (Morgan and Simms 1988; Strehlow and Barltrop 1988). However, in research based in the same geographical area, a 40-year cohort study found significant excess mortality from stroke, and a follow-up ecological study reported borderline significant excess stroke mortality (Elliott et al. 2000; Inskip et al. 1982). HF is a disabling and deadly disease whose prevalence continues to rise in the U.S. despite a decline in general cardiovascular disease morbidity and mortality (Bahrami et al. 2008). To our knowledge, the possible association of cadmium exposure with HF has not been examined. Associations between cadmium exposure and these outcomes would potentially be important, because cadmium exposure is *pervasive* but *modifiable*, and stroke and HF are important sources of morbidity and mortality.

Materials and Methods

Study population

We conducted cross-sectional analyses of the relation of cadmium to a reported history of stroke and HF using data from National Health and Nutrition Examination Survey (NHANES) 1999–2006. NHANES is a publicly-available dataset established by the U.S. National Center for Health Statistics (NCHS) and is based on a complex, multistage sampling design used to obtain a representative sample of the civilian non-institutionalized U.S. population. For our analyses of blood cadmium concentration and stroke, we used data from the 12,049 adult participants aged 30 years and older, who were not pregnant and for whom information was available on blood cadmium concentration, stroke history and other important covariates (i.e., age, sex, race/ethnicity, body mass index (BMI), education,

poverty income ratio, alcohol consumption, and smoking status). Among these 12,049 participants, 12,005 also had information on HF history. NHANES measured urinary cadmium concentrations in a sub-sample of NHANES participants (i.e., one-third of the participants). Of the 12,049 participants in our analyses of blood cadmium and stroke, 3,909 had urinary cadmium and creatinine measurements and were included in our analysis of urinary cadmium and stroke. Likewise, 3,898 of the 12,005 participants were in our analyses of urinary cadmium and HF. NHANES was approved by the NCHS Institutional Review Board and informed consent was obtained from all participants.

Blood and urine cadmium measures

Cadmium was measured in whole blood using multi-element atomic absorption spectrometry (PerkinElmer model SIMAA 6000), with Zeeman background correction. Cadmium was measured in spot urine samples by inductively coupled plasma-mass spectrometry (PerkinElmer/SCIEX model 500). Urinary cadmium levels from NHANES 1999–2002 were corrected for molybdenum oxide interference. Details of protocols and quality control measures are published elsewhere (NCHS 2004; NCHS 2005a; NCHS 2005b; NCHS 2006; NCHS 2008).

Stroke, heart failure and myocardial infarction outcomes

We defined stroke and HF as having answered ‘yes’ to the questions “Has a doctor or other health professional ever told you that you have had stroke [and as a separate question] congestive heart failure?” Since stroke and HF were self-reported, we were concerned that these outcomes were underreported. To explore the potential impact of underreporting on our findings, we conducted a parallel analysis of cadmium exposure and self-reported myocardial infarction (MI), comparing these findings with those from an earlier study that used electrocardiogram (ECG) data to investigate the cadmium and MI relationship in NHANES III (Everett and Frithsen 2008). For our study population, we similarly defined MI as having answered ‘yes’ to ever being told “you had a heart attack (also called myocardial infarction)?”

Other variables of interest

We used questionnaire responses to obtain information on age, sex, race/ethnicity, education, poverty income ratio, alcohol consumption, smoking status, and coronary heart disease (CHD) status. Poverty income ratio is the ratio of family’s income to their appropriate poverty threshold, which varies by family size and composition. We characterized cigarette smoking status as active, former, or never. We defined hypertension as self-reported physician-diagnosed hypertension, or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. We defined diabetes as self-report of physician diagnosis, taking diabetic medication or having high plasma glucose (fasting glucose ≥7.0 nmol/L or non-fasting glucose ≥11.1 nmol/L). We defined hypercholesterolemia as self-report of physician diagnosis, taking blood cholesterol-lowering medication or having fasting total cholesterol ≥240 mg/dL. We defined chronic kidney disease (CKD) as estimated glomerular filtration rate < 60 ml/min/1.73 m^2. BMI was calculated as weight (kg) divided by height squared (m^2). Serum cotinine levels were measured using an isotope dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric method (NCHS 2008). Blood lead was measured simultaneously with blood cadmium by the same technique. Urine creatinine was determined using a Jaffe rate reaction measured with a CX3 analyzer (NCHS 2007).

Statistical analysis

We performed all statistical analyses using SAS version 9.1 (SAS Institute Inc) and SAS-callable SUDAAN version 9.0.3 (Research Triangle Institute), accounting for the complex sampling design and using six-year sampling weights. For analyses of urinary cadmium, we included urinary creatinine as an independent variable (Barr et al. 2005). We log-transformed all cadmium exposure biomarkers to reduce the influence of potential outliers.

We used separate multivariable-adjusted logistic regression to estimate the prevalence odds ratios (ORs) and 95% confidence intervals (CIs) for each outcome (stroke and HF) across levels of cadmium exposure biomarker. We examined each exposure biomarker as a continuous variable and in quartiles, the latter determined based on the complex multistage sampling design. For the former, we report our results as ORs for a 50% increase in cadmium exposure biomarker [i.e., $\exp(\hat{\beta}_{\log_e[Cd]} \times \ln[1.5])$]. For the latter, we also tested for linear trend across the quartiles using the median of each quartile. We adjusted our models first for potential confounders (grouped as described in Table 1 except where indicated): age (years), sex, race/ethnicity, BMI (kg/m^3), education, poverty income ratio, alcohol consumption, smoking status and blood cotinine (ng/mL). We then additionally adjusted for medical conditions that might also be related to stroke and HF: diabetes, hypertension, hypercholesterolemia, CKD and CHD status (CHD was omitted in HF analyses). The associations of cadmium exposure with stroke and HF did not change when we adjusted for blood lead, so it was not included in the final models. We conducted similar analyses of MI.

Men and women may differ in their cadmium retention or uptake, as well as sensitivity to cadmium's toxic effects (Everett and Frithsen 2008; Vahter et al. 2007). Therefore, we also investigated the relationship by sex with and without adjusting for women's menopausal status. In addition, to further differentiate the effects of cadmium exposure from those of cigarette smoke, we estimated associations of smoking status with stroke and HF, and then the change in these associations upon the addition of cadmium biomarkers. We also investigated the associations of cadmium biomarkers separately for never smokers and ever smokers. We designated $P<0.05$ as the level of statistical significance.

Results

The overall prevalences of self-reported stroke and HF in our study population for *blood* cadmium concentration were 2.9% (492 cases) and 2.8% (471 cases), respectively. The prevalences were similar for *urinary* cadmium concentration: 3.0% (171 cases) and 3.1% (165 cases), respectively. Among the 12,031 participants who had available data on blood cadmium and MI, the prevalence of MI was 4.3%. Of the eligible participants from NHANES 1999–2002, 22.6% had blood cadmium concentrations below the lower limit of detection (LLOD: 2.7 nmol/L), and of those from NHANES 2003–2006, 16.9% had concentrations below the LLOD (1.8 nmol/L). Of the eligible participants, 4.0% had urinary cadmium concentrations below the LLOD (0.44 nmol/L). The geometric mean (GM) and (standard error of the mean (SEM)) for blood cadmium concentration was 3.8 nmol/L (0.02); the GM (SEM) for urinary cadmium concentration was 2.7 nmol/L (0.03).

GM cadmium levels were more than 30% higher among those who reported having had a stroke versus those who had not, and more than 20% higher among those who reported having had HF versus those who had not (Table 1). GM cadmium concentrations by other participant characteristics are also described in Table 1.

Association of cadmium with stroke

A 50% increase in *blood* cadmium concentration corresponded to a 35% increase in the odds of prevalent stroke after adjusting for potential confounders (Table 2: Model 1). ORs

increased progressively with each increasing quartile of blood cadmium level (p-value for trend=0.02), and those in the third and fourth quartiles of blood cadmium had significantly higher odds of stroke than those in the lowest quartile (Figure 1a). The association did not change substantially after additional adjustment for medical conditions (Table 2: Model 2).

Similarly, the prevalence of stroke also increased with increasing urinary cadmium concentration in multivariable-adjusted models that included adjustment for urinary creatinine (Table 2: Model 1). Likewise, these results changed little upon further adjustment for medical conditions (Table 2: Model 2). ORs increased slightly across increasing quartiles of urinary cadmium level, but the trend was not statistically significant (Figure 1b).

Association of cadmium with heart failure

After adjusting for potential confounders, a 50% increase in *blood* cadmium corresponded to a 48% increase in the odds of prevalent HF (Table 2: Model 1). ORs increased progressively with increasing quartiles of blood cadmium up through the third quartile, and those in the third and fourth quartiles had significantly higher odds of HF than those in the lowest quartile (p-value for trend=0.03) (Figure 2a). The association remained the same after additional adjustment for medical conditions (Table 2: Model 2).

In similar multivariable-adjusted models that also included adjustment for urinary creatinine, a 50% increase in *urinary* cadmium corresponded to a prevalence OR for HF of 1.12, which changed little after additional adjustment for medical conditions (Table 2). There was a significant trend of increased odds with increasing quartile of urinary cadmium level (p-value for trend=0.01) (Figure 2b).

Sensitivity analysis addressing impact of self-reported outcomes

While false reports of stroke and HF history are uncommon, it is possible that some participants with stroke or HF did not report these conditions. To explore the potential impact of underreporting of history of disease on our findings, we ran parallel analyses of MI – another cardiovascular outcome – and compared the results with previously reported findings on MI that entailed diagnosis via electrocardiogram. We observed that a 50% increase in *blood* cadmium was associated with a 32% increased risk of prevalent MI (OR: 1.32; 95% CI: 1.13–1.54). ORs increased progressively with each increasing quartile of blood cadmium level (p-value for trend=0.01). For a 50% increase in creatinine-corrected *urinary* cadmium, the measure used in the previously reported results, the odds ratio for MI was 1.12 (95% CI: 1.03–1.21). Compared with those in the lowest quartiles, those in the third and fourth quartiles had significantly higher ORs (OR: 1.95; 95% CI: 1.13–3.35, and OR: 1.86; 95% CI: 1.04–3.32, respectively) (p-value for trend=0.02). These results are similar to the significant association between urinary cadmium with MI determined by electrocardiogram in NHANES III (Everett and Frithsen 2008). In that study, the prevalent ORs for the highest tertile compared to the lowest tertile ranged from 1.46 (95% CI: 1.01–2.13) to 1.86 (95% CI: 1.26–2.75) depending on how covariates were included.

Associations by sex

The association between *blood* cadmium and stroke was stronger among women than among men (women OR: 1.38; 95% CI: 1.11–1.72 versus men OR: 1.30; 95% CI: 0.93–1.79; p-value for interaction=0.05). The interaction remained significant after further adjustment for medical conditions (p-value for interaction=0.04). In addition, the association did not change after further adjustment for women's menopausal status.

Cadmium exposure and smoking

In multivariable-adjusted models (not adjusted for serum cotinine level), the prevalence OR for stroke for current smokers compared with never smokers was 2.23 (95% CI: 1.59–3.11). With the addition of *blood* cadmium, the OR for current smokers dropped to 1.63 (95% CI: 1.09–2.45), and results changed little after further adjustment for medical conditions. In addition, the association between blood cadmium and stroke was substantially weaker among never smokers than in the total sample (per 50% increase in blood cadmium, OR: 1.12; 95% CI: 0.97–1.30; OR: 1.19; 95% CI: 1.02–1.37 upon further adjustment for medical conditions). However, *urinary* cadmium had little effect on the association of smoking to stroke. The association between urinary cadmium and stroke was not significant among ever smokers (per 50% increase in urinary cadmium, OR: 1.13; 95% CI: 0.97–1.31) or never smokers (per 50% increase in urinary cadmium, OR: 1.06; 95% CI: 0.93–1.21).

Similarly, the OR for prevalent HF for current smokers decreased from 2.28 (95% CI: 1.66–3.12) to 1.40 (95% CI; 0.88–2.24) with additional adjustment for *blood* cadmium level. The prevalence OR of HF per 50% increase in blood cadmium and HF among never smokers was 1.07 (95% CI: 0.93, 1.23) and 1.10 (95% CI: 0.96, 1.27) upon further adjustment for medical conditions.

The impact of adjusting for *urinary* cadmium in the association between smoking and prevalent HF was similar but less dramatic. For example, the OR for smoking was reduced from 3.28 to 2.71 with the addition of urinary cadmium. The association between urinary cadmium and HF among never smokers was 1.00 (95% CI: 0.86, 1.14) and upon further adjustment 1.02 (95% CI: 0.88, 1.18). In total, these findings are consistent with the possibility that stroke and HF risk due to smoking may be mediated in part by smoking-related exposure to cadmium. Yet these data also suggest that sources of cadmium exposure other than cigarettes smoking may be important.

Discussion

Our study makes two novel observations. The first is an association between cadmium exposure and stroke. The second is an association between cadmium exposure and heart failure. The implication is that a largely disregarded ubiquitous environmental toxin might increase the risk for two highly prevalent cardiovascular diseases with significant associated morbidity and mortality: stroke and heart failure.

In our study of adults in the U.S. general population, both blood and urinary cadmium concentrations were associated with an increase in self-reported physician-diagnosed stroke and HF. Specifically, a 50% increase in blood cadmium was associated with a 35% increase in stroke prevalence and a 48% increase in HF prevalence. A 50% increase in urinary cadmium was associated with a 9% and 12% increase in prevalent stroke and HF, respectively.

While this cross-sectional study does not address causation, there is evidence for the biological plausibility of cadmium as a risk factor for stroke and HF. Cadmium has been associated with multiple mechanisms that tend to promote vascular injury and atherosclerosis. These include the formation of reactive oxygen species, promotion of lipid peroxidation, depletion of glutathione (GSH), disruption of sulfhydryl homeostasis and down-regulation of nitric oxide (Navas-Acien et al. 2004; Tellez-Plaza et al. 2008). Available clinical data suggest that cadmium is associated not only with atherosclerosis, but also with renal dysfunction, increased blood pressure and diabetes – all risk factors for stroke and HF (Eum et al. 2008; Nordberg 2009; Schwartz et al. 2003). Cadmium also induces adverse cardiac metabolic and functional changes by producing intracellular

calcium overload (Kopp et al. 1983). However, the association of cadmium with cardiovascular disease, particularly for low-level exposures (Houston 2007; Wolf and Baynes 2007) remains controversial. For example, previous studies have reported positive associations of blood cadmium (Eum et al. 2008; Tellez-Plaza et al. 2008) but inverse associations of urinary cadmium with risk for hypertension (Schutte et al. 2008; Tellez-Plaza et al. 2008). Our study supports that low-level cadmium exposure is in fact associated with adverse consequences for cardiovascular health.

Unlike myocardial infarction, which is primarily a result of atherosclerotic coronary artery disease, stroke is a heterogeneous disorder. Stroke can be either hemorrhagic or ischemic, and the latter can be cardioembolic, atheroembolic, or of small vessel origin. The NHANES did not collect data on the type of stroke, so this study did not allow us to differentiate between stroke subtypes. Similar to stroke, heart failure is a heterogeneous disorder. It can be a consequence of abnormal cardiac structure, function, rhythm and conduction, and results primarily from MI and hypertension (McMurray and Pfeffer 2005). In our data, the association of blood cadmium with both stroke and HF met or exceeded that with MI suggesting that these associations may not be solely dependent upon a pro-atherosclerotic effect. Also, though cadmium has previously been found to be associated with hypertension, diabetes and CKD – all important risk factors for stroke and HF – our results were independent of these risk factors, suggesting that cadmium may increase risk by mechanisms not yet defined.

Cigarette smoking is an important risk factor for cardiovascular disease and a source of cadmium exposure. We found that the association between smoking and prevalent stroke was substantially attenuated by blood cadmium indicating that cadmium exposure may explain some variation in stroke outcomes in smokers. However, there are many components of cigarette smoke, in addition to cadmium, that may have adverse cardiovascular effects, such as carbon monoxide, nitrogen oxides, hydrogen cyanide, tar, zinc (Hoffmann et al. 2001) and lead (Massadeh et al. 2005). In our data, the associations of the cadmium biomarkers with stroke and HF did not change upon adjustment for blood lead. Nonetheless, further clarification is needed on cadmium's adverse cardiovascular effects above and beyond the effects of other toxins in cigarette smoke.

We observed a stronger association of cadmium with stroke in women than in men, even after additional adjustment for menopausal status. Sex differences in susceptibility to cadmium toxicity may be linked to cadmium's estrogenicity, which may have a thromboembolic effect (Vahter et al. 2007). In pre-menopausal women, cadmium uptake may be enhanced by low iron status (Vahter et al. 2007); even after menopause, cadmium's effects may continue to resonate due to its long elimination half-life (10–30 years) (Jarup et al. 1998) and the possible heightened vulnerability with age (Schutte et al. 2008). A previous study of myocardial infarction found a significant association with cadmium exposure in women and not in men (Everett and Frithsen 2008). In contrast, Menke and colleagues found an association between urinary cadmium and cardiovascular mortality in men, but not in women (Menke et al. 2009). These findings raise the issue of sex-specific survival (i.e., cadmium-related cases may be more likely to be fatal for men than women, so that in a study of non-fatal cases, the cadmium association may appear stronger in women). The reasons for this variation in cadmium association between fatal and non-fatal cases are largely undetermined, but may reflect differential co-morbidities or co-exposures.

In our study, we observed a stronger association of stroke and HF with blood cadmium than with urinary cadmium. This may be due to issues related to creatinine correction (Barr et al. 2005), and, particularly for NHANES 1999–2002, noise introduced to the urinary concentration estimates by molybdenum interference and the correction for that interference

(NCHS 2005; Suzuki et al. 2008). We considered the possibility that, by chance, the smaller associations for urinary cadmium emanated from characteristics of the one-third sub-sample of participants who were in the urinary cadmium analyses. The sub-sample ORs for blood cadmium were slightly lower (although not statistically different) than the total-sample ORs (data not shown). While this suggests that the characteristics of the sub-sample could explain the weaker ORs for urinary cadmium, differences in these two cadmium exposure measures in predicting stroke and HF requires confirmation in other studies.

Our study has additional limitations. First, this study is cross-sectional, so that assumptions about the temporal order of cadmium exposure and the outcomes cannot be made. However, the reverse order seems unlikely, especially for never and current smokers. Second, as alluded to earlier in our discussion, our results may have been affected by disease survival rate. Third, the determination of stroke and HF was by self-report of physician diagnosis; however others have found self-report of diagnoses, particularly stroke, to be accurate (Okura et al. 2004), although not specifically verified in NHANES. Underreporting these outcomes is more likely than false affirmative reports (Okura et al. 2004; Simpson et al. 2004), yet underreporting would not bias our findings if it did not vary by cadmium exposure status, conditional on the covariates in our models. Findings for another cardiovascular outcome, MI, support this possibility: we found an association between urinary cadmium and self-reported physician-diagnosed MI that was similar to the association reported with MI determined by electrocardiogram in NHANES III. Fourth, although we adjusted for numerous potential confounders, it is possible that we omitted or inadequately adjusted for important confounders, such as exposure to tobacco. For example, we were not able to adjust for pack-years of smoking because of limited data. Finally, blood cadmium levels in our population were relatively low with a number of non-detectable levels, potentially biasing our analyses of this measure as a continuous variable; however, we observed similar results when we divided blood cadmium into quartiles. An important strength of this study is that the association between environmental cadmium and stroke was determined in a representative sample of U.S. population. Also, because of the relatively large sample size, we were able to test the associations in sub-populations.

In summary, our study provides evidence of a relationship between cadmium and stroke and heart failure in the U.S. adult population. These results are consistent with and build upon animal and emerging population studies linking environmental cadmium exposure to adverse cardiovascular outcomes. Studies with verified cases and, more critically, prospective studies of both nonfatal and fatal events are needed to confirm the findings and help us better understand the mechanisms by which cadmium may increase stroke and heart failure risk.

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Abbreviations

BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease

ECG	Electrocardiogram
GM	Geometric Mean
GSH	Glutathione
HF	Heart Failure
LLOD	Lower Limit of Detection
MI	Myocardial Infarction
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
SEM	Standard Error of the Mean

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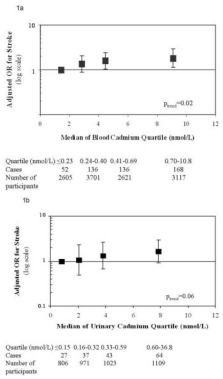
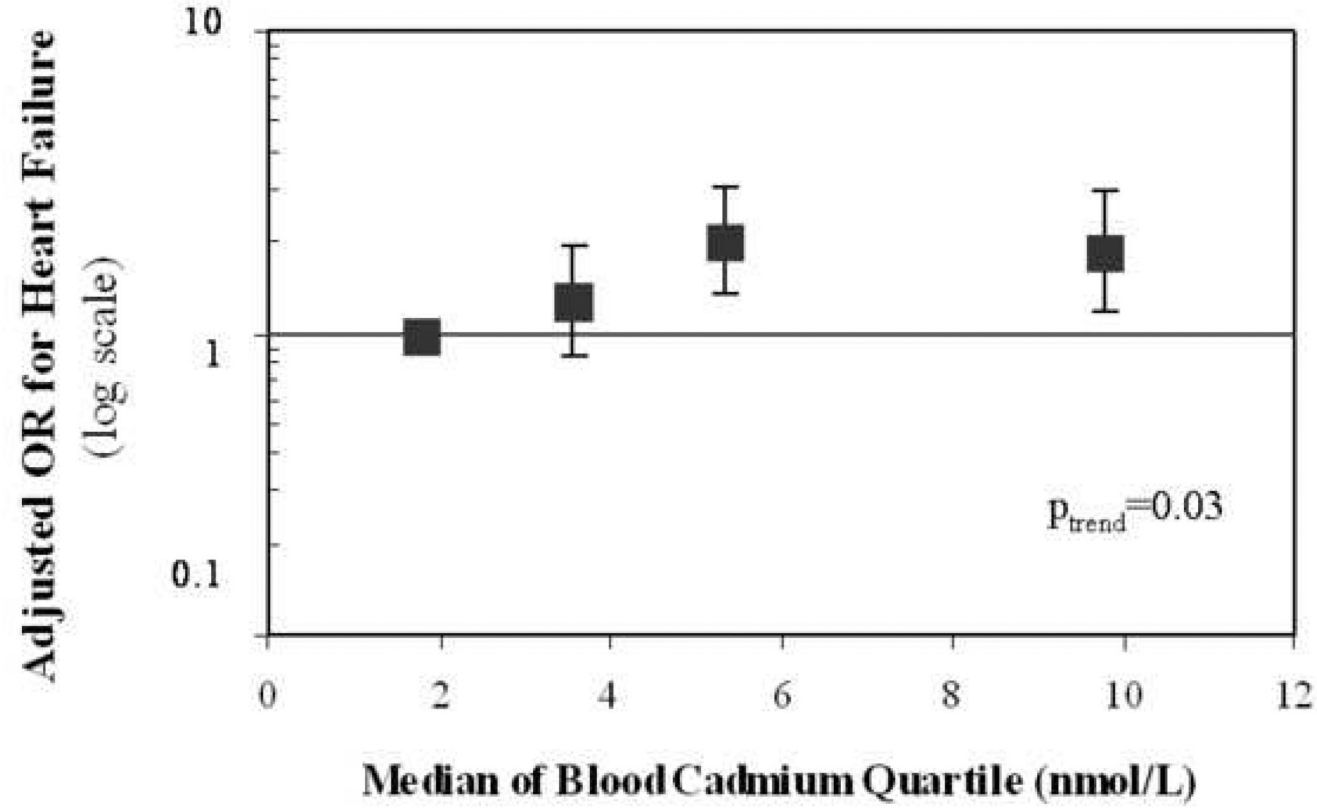


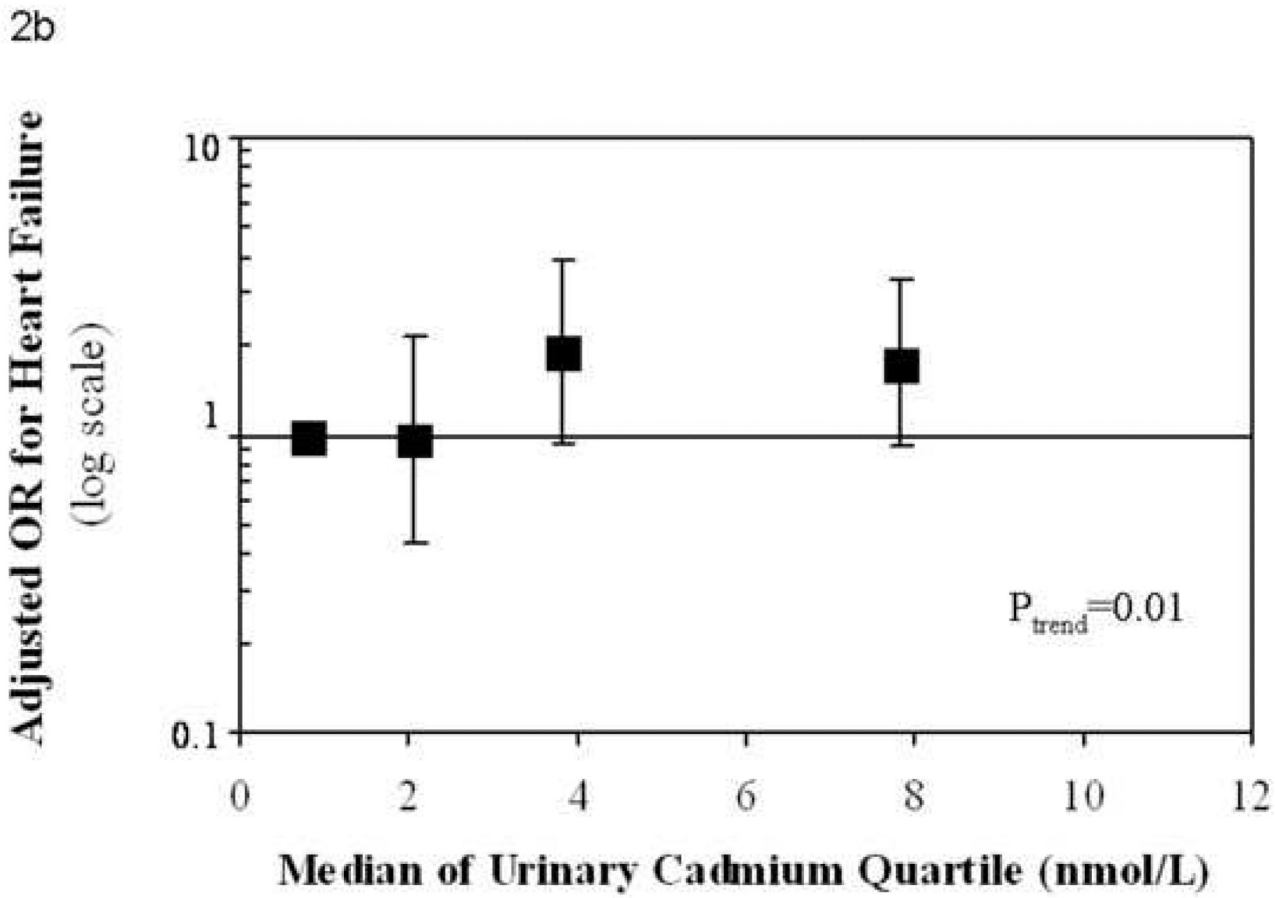
Figure 1.

The relation of quartiles of a) blood and b) urinary cadmium (with model adjusted for urinary creatinine) to the risk of prevalent stroke. Models adjusted for age, sex, race/ethnicity, poverty income ratio, education, BMI, smoking status, cotinine levels, and alcohol consumption. Urinary cadmium was collected in a subsample (n=3,909). OR = odds ratio.

2a



Quartile (nmol/L)	≤0.23	0.24-0.40	0.41-0.69	0.70-10.8
Cases	47	117	154	153
Number of participants	2605	3690	2609	3101



Quartile (nmol/L)	≤0.15	0.16-0.32	0.33-0.59	0.60-36.8
Cases	22	36	51	56
Number of participants	805	967	1021	1105

Figure 2.

The relation of quartiles of a) blood and b) urinary cadmium (with model adjusted for urinary creatinine) to the risk of prevalent heart failure. Models adjusted for age, sex, race/ethnicity, poverty income ratio, education, BMI, smoking status, cotinine levels, and alcohol consumption. Urinary cadmium was collected in a subsample (n=3,898). OR = odds ratio.

Table 1

Blood and urine cadmium geometric mean concentrations by participant characteristics.

Variable	N	Blood Cadmium nmol/L (SE)[a]	N	Urinary Cadmium[b] nmol/L (SE)[a]
Age (years)				
30–49	4725	3.4 (0.02)	1542	2.2 (0.04)
50–64	3509	4.0 (0.02)	1107	3.0 (0.04)
≥65	3815	4.3 (0.02)	1260	3.3 (0.04)
Sex				
Women	5928	4.1 (0.02)	1894	2.5 (0.03)
Men	6121	3.5 (0.02)	2015	2.8 (0.03)
Race/Ethnicity				
Mexican	2442	3.4 (0.03)	789	2.5 (0.04)
Black	2324	3.9 (0.02)	731	3.7 (0.05)
Other Hispanic	447	3.6 (0.05)	142	2.8 (0.08)
Other Race	324	4.6 (0.04)	101	3.0 (0.09)
White	6512	3.8 (0.02)	2116	2.5 (0.03)
BMI (kg/m^2)[c]				
< 25	3448	4.3 (0.02)	1105	2.6 (0.04)
25–29	4452	3.7 (0.02)	1492	2.7 (0.04)
≥30	4149	3.4 (0.02)	1312	2.7 (0.03)
Education				
<HS	3723	4.8 (0.02)	1207	3.4 (0.04)
HS/GED	2852	4.2 (0.02)	967	3.1 (0.04)
>HS	5474	3.3 (0.02)	1735	2.3 (0.03)
Poverty[d]				
Yes	1877	4.9 (0.03)	577	3.2 (0.05)
No	10172	3.7 (0.02)	3332	2.6 (0.03)
Smoke				
Never	5862	2.7 (0.02)	1890	2.0 (0.03)
Former	3638	3.5 (0.02)	1222	3.0 (0.04)
Active	2549	8.8 (0.02)	797	4.1 (0.04)
Alcohol (drinks/day)				
<1	8760	3.8 (0.02)	2835	2.8 (0.02)
1 to 4	2702	3.6 (0.02)	880	2.4 (0.04)
≥5	587	5.5 (0.05)	194	3.1 (0.11)
Stroke				
Yes	492	5.1 (0.04)	171	3.7 (0.07)
No	11557	3.8 (0.02)	3738	2.6 (0.03)
Heart Failure				
Yes	471	5.0 (0.04)	165	4.0 (0.07)
No	11534	3.8 (0.02)	3733	2.6 (0.03)

[a] SE is Standard error of the mean

[b] Subsample (1/3 of participants > 6 years old)

[c] BMI is body mass index

[d] Poverty is defined as having a poverty income ratio <1.00, where poverty income ratio is the ratio of the family income to the appropriate poverty threshold.

Table 2

Multivariable-adjusted prevalence odds ratios (95% confidence interval) for stroke and heart failure corresponding to a 50% increase in cadmium biomarker.

Variable	Cases/No.	Model 1[a]	Model 2[b]
Stroke			
Blood Cadmium	492/12049	1.35 (1.12, 1.65)	1.38 (1.14, 1.67)
Urinary Cadmium[c,d]	171/3909	1.09 (1.00, 1.19)	1.10 (1.00, 1.20)
Congestive Heart Failure			
Blood Cadmium	471/12005	1.48 (1.17, 1.87)	1.48 (1.17, 1.87)
Urinary Cadmium[c,d]	135/3898	1.12 (1.03, 1.20)	1.12 (1.04, 1.21)

[a] Model 1: Adjusted for age, sex, race/ethnicity, education, body mass index, poverty income ratio, alcohol consumption, smoking status.

[b] Model 2: Further adjusted for diabetes, hypertension, hypercholesterolemia, chronic kidney disease, and coronary heart disease (CHD); CHD was omitted in congestive heart failure analyses.

[c] Subsample (1/3 of participants > 6 years old).

[d] Also adjusted for urinary creatinine.