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Associations between blood cadmium concentration and kidney function in the U.S. population: impact of sex, diabetes and hypertension

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Abstract

Background: Exposure to cadmium has been associated with nephropathy and implicated in the development of diabetes and hypertension. The role of environmental metal exposure may be an underexplored risk factor for decreased kidney function among people with diabetes and/or hypertension. The objective of this study was to examine the association of blood concentration of cadmium with kidney function parameters and evaluate sex, diabetes, and hypertension as effect modifiers of the association.

Methods: This study used data from 12,577 adult participants in the National Health and Nutrition Examination Survey (NHANES) 2007–2012 cycles. We used multivariable linear and logistic regression models to conduct a cross-sectional analysis of the association between cadmium exposure quartiles and estimated glomerular filtration rate (eGFR), urine albumin to creatinine ratio (UACR), low eGFR (defined as eGFR <60 mL/minute/1.73m^2), and albuminuria (defined as UACR ≥ 30 mg/g). Models were adjusted for confounders and interaction terms were evaluated for cadmium concentration and sex, diabetes, and hypertension. Final models were stratified by sex and indices of existing diabetes and hypertension status.

Results: The mean eGFR was 94.3 mL/minute/1.73 m^2 (SD 21.5) and the geometric mean of UACR was 7.9 mg/g (95% CI 7.6 to 8.2 mg/g). Blood cadmium concentration was inversely associated with eGFR and positively associated with UACR. We found significant effect modification of the association of eGFR with cadmium, predominantly for sex and hypertension. The strength of the association between cadmium quartiles and eGFR was more pronounced among females compared to males. Among females with hypertension and diabetes, eGFR was lower on average by 4.9 mL/minute/1.73 m^2 (95% CI −10.1 to 0.29) in the highest versus lowest

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cadmium quartile, and in females with hypertension alone, eGFR was lower on average by 5.8 mL/minute/1.73 m^2 (95% CI −8.2 to −3.3) in the highest versus lowest cadmium quartile. Among those in the highest exposure quartile, higher mean UACR was observed among participants with hypertension compared to those without.

Conclusions: Our results confirm that cadmium exposure is associated with decreased glomerular filtration and increased urine protein excretion, and provide evidence that the magnitude of these associations differ by sex and may vary based on preexisting diabetes and hypertension. Future prospective sex-specific investigations are necessary to address concerns of reverse causality and efforts should be made to reduce smoking and environmental contamination from cadmium to protect human health.

Keywords

cadmium; kidney function; diabetes; hypertension; sex differences; NHANES

Background

In the United States (U.S.) chronic kidney disease (CKD) affects approximately 14.8% of the population and the proportion of CKD patients who progress to end-stage renal disease (ESRD) increases each year (Saran et al., 2017). Diabetes and hypertension are major risk factors for CKD. Nearly 29 million people in the U.S. have diabetes and one in three persons with diabetes will develop ESRD, accounting for nearly 44% of new cases (de Boer et al., 2011; Prevention., 2014). High blood pressure is the second leading cause of ESRD in the U.S. after diabetes (Haroun et al., 2003; Lea and Nicholas, 2002; Maschio et al., 2000). An estimated 34% of U.S. adults over 20 years of age have hypertension, representing nearly 86 million people (Benjamin et al., 2017; Go et al., 2014). Given that advances in medical care and access to standard treatment for diabetes and hypertension is not slowing the development of CKD, identification of other modifiable risk factors for CKD is critical.

Environmental exposure to cadmium is known to be nephrotoxic (Madden and Fowler, 2000; Soderland et al., 2010). Cadmium exposure at high levels, generally observed in occupational settings, can lead to accumulation in the proximal tubules of the kidney, resulting in tubular dysfunction and decreased reabsorption of protein (Johri et al., 2010). In the general population, cigarette smoke is a dominant source of cadmium exposure (Hecht et al., 2016a; Hecht et al., 2016b; Richter et al., 2009) and in non-smokers exposure predominantly occurs from dietary sources (Satarug et al., 2017). Blood cadmium concentration has consistently been associated with kidney function parameters in U.S. adults, with studies using NHANES data controlling for prevalent diabetes and hypertension (Buser et al., 2016; Navas-Acien et al., 2009). Blood cadmium concentration has been associated with hypertension (Oliver-Williams et al., 2018; Tellez-Plaza et al., 2008), but associations with diabetes have been inconsistent (Moon, 2013; Tinkov et al., 2017). Although the mechanisms of action have not been fully elucidated, diabetes and hypertension may be in the causal pathway between cadmium exposure and kidney disease. In addition, cadmium has been associated with changes in levels of sex hormones suggesting that effects on hormonally-related diseases may differ by sex (Ali et al., 2014; Bochud et al., 2017; Kresovich et al., 2015; Nagata et al., 2016).

To our knowledge, no study has focused on assessment of diabetes or hypertension as effect modifiers of the association between blood cadmium concentration and kidney function using continuous measures, nor have sex-specific analyses been conducted. As such, the role of environmental exposures may be an underexplored topic for decreased kidney function among males and females with diabetes and/or hypertension. The objective of the current study was to examine the association of blood cadmium concentration with continuous measures of kidney function and evaluate sex, diabetes and hypertension as modifiers of the association in a nationally representative sample of U.S. adults.

Methods

Study population

The NHANES is a national survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention using a complex sampling frame to attain a sample representative of the U.S. population. The NHANES study protocols are approved by the Institutional Review Board of the NCHS, and participants provided written informed consent (National Center for Health Statistics, 2017). We obtained publicly available cross-sectional data from 30,442 participants over three survey cycles spanning 2007–2012. All participants aged 20 years and older with measurements of blood cadmium, urine and blood creatinine, and urine albumin were included in the analysis. At the time of the exam, females between 20 and 44 years of age were asked if they are pregnant and given a pregnancy test. Females with a positive lab pregnancy test, self-reported pregnancy, or those for whom pregnancy status was not obtained were excluded (n=393). Participants were asked to report medication use; individuals using immunosuppression medications (n=30) were excluded. Approximately 1,089 participants had zero values for the sample weights and 12,729 were under 20 years old. Numerous individuals were missing data on measures of cadmium (n=1,554), creatinine (n=1,827), albumin (n=1,060), glycohemoglobin (n=1,585), systolic or diastolic blood pressure (n=2,000), cotinine (n=1733), or body mass index (n=875), and excluded from the analysis (numbers with missing data for each variable are not mutually exclusive). The final analytic sample consisted of 12,577 individuals.

Outcome measurements

We estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) glomerular filtration rate equation that incorporates participant measures of serum creatinine, age, race, and sex (Levey et al., 2009). Serum creatinine was measured using the Jaffe rate method with the Beckman Synchron LX20 and Beckman UniCel® DxC800 Synchron. The three NHANES cycles provided serum creatinine measures traceable to an isotope dilution mass spectrometry (IDMS) method. CKD is commonly defined as decreased kidney function for more than three months (Stevens and Levin, 2013). Since this study was based on single measurements, we defined an estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m^2 as low eGFR, not as CKD, when using eGFR as a dichotomous outcome.

A secondary outcome was urine albumin to creatinine ratio (UACR) (urine albumin concentration in mg/dL divided by urine creatinine concentration in g/dL). Clinical

recommendations specify the measurement of UACR from random spot urine samples (Stevens and Levin, 2013). Urinary albumin was measured from a spot sample using a solid-phase fluorescent immunoassay. Urinary creatinine was measured using a Roche/Hitachi Modular P Chemistry Analyzer using an enzymatic (creatinase) method immunoassay. Albuminuria was defined as UACR ≥ 30.0 mg/g (Stevens and Levin, 2013).

Exposure measurements

Cadmium concentration in μg/L was measured from whole blood using inductively coupled plasma mass spectrometry at the Division of Laboratory Sciences within the Centers for Disease Control and Prevention National Center for Environmental Health (National Center for Health Statistics, 2017). There were no changes to equipment, lab methods, or lab site during the 2007–2012 cycles. Any sample below the detection limit (0.20 μg/L in 2007–2010; 0.16 μg/L in 2011–2012) was set as the limit of detection divided by the square root of two. We categorized cadmium concentration into quartiles based on the distribution of cadmium exposure in the study sample. The first exposure quartile included the proportion of individuals with cadmium concentrations below the limit of detection and was considered the referent group in all categorical analyses.

Covariates

Participant information on age (continuous; years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), education level (less than high school, high school graduate, some college, or college graduate/added education beyond college), sex (male/female), and alcohol consumption [never/rare (less than 12 drinks per year) or moderate (≤ one drink per day for females and ≤ two drinks per day for males)] was self-reported via interview questionnaires. History of cigarette smoking was self-reported in the interview as never, former, infrequent current use of cigarettes, or daily use. For former smokers, time elapsed since quitting smoking was dichotomized as less than or equal and greater than five years. In addition to smoking history, recent smoke exposure was quantified using serum cotinine. Serum cotinine levels (ng/mL) were measured using an isotope dilution-high performance liquid chromatography / atmospheric pressure chemical ionization tandem mass spectrometry method. Cotinine levels below 10 ng/mL were considered low exposure and levels 10 ng/mL or higher were considered high exposure to tobacco smoke for descriptive purposes (Pirkle et al., 1996). Continuous cotinine level was used for adjustment in multivariable models. Body mass index (BMI) was used as a continuous variable and categorized into normal (BMI <25), overweight (BMI 25–30), or obese (BMI >30) after dividing measured weight in kilograms by measured height in meters squared. Self-reported weak kidneys (yes/no) was defined using a questionnaire item that asked if the respondent had even been told by a doctor or other health professional that he or she had weak or failing kidneys. Hypertension (yes/no) was defined using self-reported diagnosis by a physician, or any antihypertensive medication use (angiotensin converting enzyme inhibitors, angiotensin II inhibitors, renin inhibitors, beta-adrenergic blocking agents, calcium channel blocking agents, diuretics, vasodilators or peripheral vasodilators), or a systolic blood pressure reading greater than or equal to 140 mmHg or a diastolic blood pressure reading greater than or equal to 90 mmHg. Diabetes status (non-diabetic or diabetic) was ascertained from self-reported questionnaire items, or any antidiabetic medication use (antidiabetic agents), or

using the percentage of glycohemoglobin (Hemoglobin A1c [HbA1c]) present in blood samples. Participants who did not self-report that they had diabetes, but who had HbA1c values of 6.5 or greater were classified as having diabetes. HbA1c was measured using the A1c G7 HPLC Glycohemoglobin Analyzer. A four-category index of diabetes and hypertension disease status was created by combining the individual variables into categories of no disease, diabetes only, hypertension only, and diabetes and hypertension combined.

Statistical analysis

All analyses utilized the sample exam weights, strata, and primary sampling units to account for the complex NHANES sampling design and nonresponse using SAS 9.4 (SAS Institute, Cary, NC) survey procedures. The distribution of UACR was right skewed and the natural log transformation was applied. Cadmium was right skewed, and was natural log transformed for bivariate analyses and categorized for use in multivariable models. Weighted arithmetic (eGFR) and geometric (UACR, cadmium exposure) means and 95% confidence intervals (95% CIs) were calculated for normally distributed and skewed variables, respectively, by covariate. T-tests were used to evaluate if levels of each continuous outcome or exposure differed by levels of covariate categories. The percentages of participants with low eGFR and albuminuria were estimated for all covariates. The Rao-Scott modified Chi-square test was used to determine if the proportions differed by covariate categories.

Linear regression models were built for continuous outcomes (eGFR and log transformed UACR) and logistic regression models were built for dichotomous outcomes (low eGFR and albuminuria) using a forward approach beginning with a crude model of cadmium quartiles to allow for non-linear dose responses. We also modeled cadmium concentration as an ordinal variable to test for linear trend. Models were initially adjusted for age (continuous), sex, race/ethnicity (non-Hispanic white, non-Hispanic African-American, Hispanic, or other), body mass index (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), cotinine level (continuous), and alcohol use. Estimates did not substantially change when diabetes and hypertension status were added to the model. Interaction terms between categorized cadmium concentration, and diabetes, hypertension, and sex variables were added to the adjusted model one at a time, and in combination to assess if effect modification was present. Lower order terms were included in the model when interaction terms were added. We used three-way interaction terms to evaluate effect modification when multiple two-way interaction terms were statistically significant. For significant interactions, sex-stratified models were used to estimate the association between cadmium concentration and the outcome of interest using an interaction term between cadmium and the four-category index of diabetes and hypertension disease status. We considered a p-value less than 0.05 statistically significant when interpreting interaction terms. Sensitivity analyses were conducted to investigate if the observed associations persisted within strata of smoking status, and among participants with high eGFR or low UACR (eGFR ≥ 60 or UACR < 30).

Results

In our sample of 12,577 participants, the mean eGFR was 94.3 mL/minute/1.73 m^2 (SD 21.5) and the geometric mean of UACR was 7.9 mg/g (95% CI 7.6 to 8.2 mg/g). After weighting, approximately 6.5% (95% CI 5.8–7.1%) of the sample had low eGFR as indicated by an eGFR less than 60 mL/minute/1.73 m^2, 8.7% (95% CI 8.0–9.4%) had albuminuria (UACR ≥ 30 mg/g creatinine), and 1.8% (95% CI 1.6–2.1%) had both low eGFR and albuminuria. As shown in Table 1, eGFR varied by race, decreased with age and was lower among participants with diabetes, high blood pressure, and higher BMI. Former smokers who had stopped smoking five or more years before their health interview had lower mean eGFR values compared to never or current smokers. UACR increased with age and was higher among females and participants with diabetes or hypertension. Low eGFR and albuminuria were more common among participants with diabetes or hypertension, and among females compared to males.

Levels of blood cadmium ranged from undetectable (limit of detection (LOD) = 0.20 μg/L in 2007–2010; LOD=0.16 μg/L in 2011–2012) to 9.3 μg/L, with a geometric mean of 0.35 μg/L (95% CI 0.34 to 0.36). Approximately 2,195 (17.5%) of participants in our sample had cadmium levels below the LOD. As shown in Table 2, geometric mean levels of cadmium exposure increased with age, and varied by sex, educational attainment, race, body mass index, and smoking status. Geometric mean cadmium levels were lower at higher BMI levels. Participants with hypertension had higher mean levels of exposure compared to participants without hypertension, but absolute differences were small. Among the 4,400 participants with self-reported hypertension who provided information on duration, mean levels of cadmium concentration did not differ by hypertension duration (p=0.36; data not shown). Cadmium levels did not differ by self-reported diabetes status, nor did mean cadmium levels vary by diabetes duration among the 1,518 participants who provided information on the duration of their diabetes (p=0.28; data not shown). Current daily smokers had higher mean levels of cadmium exposure compared to participants who reported never having smoked or who reported being former smokers. Participants with low eGFR or albuminuria had higher mean levels of blood cadmium concentration compared to those without low eGFR or albuminuria.

Adjusted associations between blood cadmium and kidney function parameters and modification by diabetes, hypertension, and sex

The adjusted estimates for the associations of blood cadmium quartiles with kidney function parameters are presented in Table 3. Blood cadmium was inversely associated with continuous eGFR (p for trend=0.005) (Table 3). When interaction terms between exposure and (1) diabetes, (2) hypertension, and (3) sex were individually added to the adjusted model for continuous eGFR, the association of cadmium with eGFR was stronger in females (p-value <0.0001), participants with diabetes (p=0.04), and participants with hypertension (p=0.02) (data not shown). When all three two-way interaction terms were added to the same model, only the interaction between exposure and sex remained significant (p<0.0001). When three-way interaction terms were included in the model, the interactions between

cadmium and sex (p=0.007) and cadmium, hypertension, and sex were significant (p=0.03) (data not shown).

Blood cadmium was also associated with increased odds of low eGFR (p for trend=0.0001). The odds of low eGFR in the highest exposure quartile (Q4) were 1.8 times greater (95% CI 1.2, 2.6) compared to the lowest exposure quartile (Q1) (Table 3). We observed a significant interaction between blood cadmium concentration and sex (p=0.006) and cadmium concentration and hypertension (p=0.05) (data not shown). No interaction was observed between blood cadmium concentration and diabetes (p=0.21) (data not shown). Among females, cadmium concentration was associated with an increase in the odds of low eGFR [OR for Q4 vs. Q1 = 2.1 (95% CI 1.3 to 3.2)]. The odds of low eGFR among those with hypertension were higher [OR for Q4 vs. Q1=1.9 (95% CI 1.3 to 2.9)] compared to those without hypertension [OR for Q4 vs. Q1= 1.3 (95% CI 0.71 to 2.4)]. When all three interaction terms were added to the same model, the interaction terms between blood cadmium concentration and sex (p=0.009) and hypertension (p=0.05) remained significant (data not shown). When three-way interaction terms were included in the model, the interactions between cadmium and hypertension (p=0.05) and cadmium, hypertension, and diabetes were significant (p=0.05) (data not shown).

Blood cadmium quartiles were associated with continuous log transformed UACR (p for trend=0.0001) (Table 3). A significant interaction was observed between blood cadmium quartiles and hypertension (p=0.003) (data not shown). The adjusted geometric mean UACR for normotensive participants in Q4 was 10.6 mg/g (95% CI 9.8, 11.5) and for hypertensive patients was 15.6 mg/g (95% CI 14.2, 17.0). The interaction persisted when all three interaction terms were added to the same model (p=0.003) (data not shown). No interaction was observed between blood cadmium concentration and sex (p=0.42) or diabetes (p=0.41). Blood cadmium was associated with increased odds of albuminuria (p for trend=0.0004) and the odds of albuminuria in Q4 was 1.6 times greater (95% CI 1.3, 2.1) compared with Q1. In the fully adjusted logistic regression model for albuminuria, we did not observe any interactions between blood cadmium concentration and sex (p=0.55), diabetes (p=0.42), or hypertension (p=0.24) (data not shown).

Sex-stratified models

To further investigate effect modification due to the presence of significant two- and three-way interaction terms in the multivariable adjusted models for eGFR, sex-specific associations between blood cadmium quartiles and continuous eGFR were assessed using sex-stratified multivariable models (Table 4) that included interaction terms between blood cadmium quartiles and the diabetes and hypertension index variable. Increasing cadmium concentration was associated with lower average values of eGFR among females. For females with diabetes and hypertension, mean eGFR for Q4 was 5 mL/minute/1.73m^2 lower relative to Q1 [β for Q4 vs. Q1 −4.9 (95% CI −10.1, 0.29) p=0.06]. For females with preexisting hypertension alone, the average eGFR for Q4 was 6 mL/minute/1.73m^2 lower relative to Q1 [β for Q4 vs. Q1 −5.7 (95% CI - 8.2, −3.3) p<0.0001]. Overall, cadmium concentration was not associated with eGFR among males. For males with prevalent

diabetes alone, mean eGFR for Q4 was 7 mL/minute/1.73m^2 lower relative to Q1 [β for Q4 vs. Q1 −7.4 (95% CI −13.5, −1.4) p=0.02].

Sensitivity analyses

Estimates of associations did not substantially change when education level was added to the model as a proxy for socioeconomic status, nor when continuous HbA1c, systolic, or diastolic blood pressure measurements were added to adjusted models to control for severity of prevalent diabetes and/or hypertension. Associations among participants with hypertension did not differ when hypertension was defined as physician-diagnosed hypertension. Estimates of associations did not substantially change when cotinine concentration was removed from the model which also included self-reported smoking history (not shown). In a linear regression model, self-reported smoking status was highly associated with measured log transformed cotinine concentration (r-square=0.71; p<0.0001). In the model for continuous eGFR, the interaction term between smoking status and cadmium was significant (p=0.02) (data not shown). Within strata of smoking level, the inverse association between cadmium and eGFR was strongest among former smokers who quit five or more years ago [β for Q4 vs. Q1 −6.4 (95% CI −8.8, −3.9) p <0.0001], whereas no association was observed among current daily smokers [β for Q4 vs. Q1 2.0 (95% CI −8.5, 12.6) p=0.70]. Results were similar for the model for low eGFR. In the model for continuous UACR, the interaction term between smoking status and cadmium was significant (p=0.05) but absolute differences between stratum specific estimates were small. The association between cadmium and albuminuria did not appear to differ by smoking status (p for interaction=0.08).

After restricting the sample to participants with eGFR ≥ 60 or UACR < 30, blood cadmium concentration was not associated with continuous eGFR overall (data not shown). A positive association between blood cadmium concentration and UACR [β for Q4 vs Q1 1.07 (95% CI 1.01, 1.12); p for trend=0.04] was observed in the restricted sample.

Discussion

In this study, we found that blood cadmium concentrations were inversely associated with eGFR and positively associated with higher urine albumin excretion. The strength of the association between blood cadmium concentration and impaired kidney function was more pronounced among females compared to males, and differed by common risk factors for kidney disease, primarily hypertension. We observed a significant association between higher cadmium concentrations and lower eGFR in females, and the magnitude was greatest in females with hypertension only or both hypertension and diabetes. Similar patterns were observed when using 60 ml/min/1.73m^2 as the threshold for low eGFR. Aside from a negative association between cadmium concentration and eGFR among males with diabetes, we did not observe strong overall evidence of an association between cadmium and eGFR among males. If the association between cadmium concentration and GFR does differ by sex, published reports of pooled associations may not be as informative as previously thought. Examination of UACR did not produce evidence of sex-specific associations, but we did observe evidence of effect modification by hypertension status. We observed higher

levels of UACR (more protein excretion) with higher cadmium levels among participants with hypertension compared to those without. For albuminuria, we observed a positive association with blood cadmium concentration overall, but did not find evidence of effect modification by sex, or prevalent diabetes or hypertension. The magnitude of the associations in our study were small, but for selected subpopulations that we identified, such as females with hypertension, our findings may be clinically relevant. Prospective studies are needed to fully understand if cadmium exposure is associated with a clinically meaningful decline in kidney function. We are unable to estimate an annual change in kidney function with our data, but prior studies have found that declines in kidney function as small as 3 mL/min/1.73 m^2 per year may be associated with increased risk of cardiovascular disease and all-cause mortality in adults (Rifkin et al., 2008; Shlipak et al., 2009).

To our knowledge, this is the first study to look at the association of blood cadmium concentration with kidney function stratified by sex or by indices of diabetes and hypertension status using data from the U.S. NHANES. One previous study using the Korean NHANES investigated associations between blood cadmium quartiles and eGFR <60 mL/min per 1.73 m^2 by sex, and observed a trend for higher odds of low eGFR among females in the highest cadmium exposure quartile relative to the lowest quartile. No trend was observed among males with similar exposure (Myong et al., 2012). Though not sex-specific, Kim et al. demonstrated 1.5 times increased odds of CKD (defined as eGFR <60 mL/min/1.73 m^2 or UACR ≥30 mg/g) for each unit increase in cadmium exposure among participants with hypertension using the Korean NHANES. They also observed 1.9 times increased odds of CKD for each unit increase in blood cadmium concentration among participants with diabetes, but no association among those without hypertension or without diabetes (Kim et al., 2015). Our findings are consistent with these results.

Previous studies evaluating associations of kidney function parameters in relation to blood cadmium concentration using U.S. NHANES data have found inverse associations between eGFR and cadmium concentration and positive associations between UACR values ≥ 30 mg/g and cadmium concentration; however, none of these studies have aimed to evaluate effect modification specifically. In a study using the 2007–2012 U.S. NHANES data restricted to participants with both blood and urine measurements of cadmium concentration, blood cadmium concentration was inversely associated with eGFR calculated using the CKD-EPI equation and positively associated with albuminuria. Interaction terms between natural log transformed cadmium concentration and covariates were included in models, but the only statistically significant interaction was with age (Buser et al., 2016). Using 1999–2006 NHANES cycles, Navas-Acien and colleagues calculated eGFR using the Modification of Diet in Renal Disease Study formula and observed increased odds of CKD and albuminuria when comparing the highest to the lowest blood cadmium quartiles with effect modification by hypertension status (p=0.03 for the interaction between hypertension and log-transformed blood cadmium concentration) (Navas-Acien et al., 2009). They did not observe interaction by sex (interaction term p-values 0.41 and 0.26 for albuminuria and CKD, respectively), whereas we observed strong interactions by sex when assessing the relationship between exposure quartiles and both continuous and low eGFR (p=0.0001). Differences between studies may be due to differences in sample restrictions or use of different equations to estimate GFR.

Our results did not strongly suggest that diabetes is an effect modifier of the association between blood cadmium concentration and parameters of kidney function. The interaction term for cadmium and diabetes was significant in our multivariable model for eGFR, but was no longer significant after adjustment for all interaction terms simultaneously or when three-way interaction terms were used. This suggests that the finding among men with diabetes from the sex-stratified models should be interpreted cautiously. Other studies have investigated the association between cadmium, diabetes, and kidney function with varying results. In a study comparing blood cadmium levels in participants with and without diabetes, a lower concentration of blood cadmium was observed in diabetic compared to non-diabetic participants but no association was observed between cadmium concentration and either eGFR or UACR (Anetor et al., 2016). One small Swedish study of females with diabetes reported a positive association between blood concentration of cadmium > 0.56 μg/L and protein excretion, but did not observe any association between cadmium concentration and eGFR (Barregard et al., 2014). A study of Korean adults found blood cadmium concentration to be associated with higher odds of CKD in adults with diabetes, but not associated with CKD in adults without diabetes (Kim et al., 2015).

Blood levels of cadmium have been positivity associated with hypertension and blood pressure in prior studies (Lee and Kim, 2012; Scinicariello et al., 2011). We found blood cadmium concentration to be associated with lower estimated eGFR among females with hypertension than in normotensive females. Daily exposure to cadmium through foods such as rice, cereals, potatoes, and root vegetables (Nordberg et al., 2012) can lead to oxidative stress and reduction of antioxidants by unbound cadmium ions (Nair et al., 2015). This may induce changes in sodium transport, impacting blood pressure, in addition to damaging tubule proteins and altering gene expression within the kidney (Baker et al., 2005; Garrett et al., 2011).

In the present study, the association between blood cadmium concentration and low levels of kidney function was significant, even after robust control for smoking. Smoking is a potential confounder in our analysis. A relationship between smoking and kidney disease has been suggested (Bleyer et al., 2000; Fox et al., 2004), with evidence indicating that exposure to cadmium (Richter et al., 2009) and other toxicants in cigarettes such as nicotine (Jain and Jaimes, 2013) may have deleterious effects on the kidney. Endothelial damage from long-term smoking may be a mechanism of action, especially among people who are already undergoing endothelial damage due to diabetes or hypertension (Messner and Bernhard, 2010). Additionally, long-term smoking may result in increased oxidative stress, another mechanism of kidney damage shared by cadmium exposure, diabetes, and hypertension (Tucker et al., 2015). In our study, associations with cadmium exposure persisted despite tight control for smoking exposure using a five-category index of smoking history that took duration of smoking into account, as well as additional adjustment using cotinine levels.

For non-smokers, diet is a primary route of exposure to cadmium (Perez et al., 2017). Foods with known high levels of cadmium include breads, rice, lentils, and fish (Bosch et al., 2016; Marti-Cid et al., 2008). Diet may be an area susceptible to intervention, as a previous study showed that reduced consumption of cadmium-contaminated rice resulted in an overall

decrease in urinary albumin excretion over an 8-year follow up period (Liang et al., 2012). This highlights the importance of policies to prevent cadmium from entering the environment, most importantly waterways and ecosystems where food is grown (Agency for Toxic Substances and Disease Registry (ATSDR), 2012; He et al., 2005). A recent review of the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) updated the tolerable intake guideline for cadmium and decided to express the tolerable weekly intake (TWI) as a tolerable monthly intake (TMI) to account for the long half-life of cadmium (World Health Organization (WHO), 2011). The established TMI was 25 μg/kg body weight per month, which corresponds to 58 μg/day for a 70 kg person. This is in contrast to the TWI of 2.5 μg/kg body weight for cadmium set by the European Food Safety Authority (EFSA), the other major international body on food safety (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011). The EFSA TWI is equivalent to 25 μg/day for a 70 kg person, which is less than half of that recommended by JECFA.

Overall, the impact of cadmium exposure appeared to be more severe among females compared to males, adding to the literature on sex differences in the toxic health effects of metal exposure (Vahter et al., 2007). Differences may be due to physiological variances in the kidney (Cobo et al., 2016; Okada et al., 2014) itself or the regulation of blood pressure (Hilliard et al., 2013). Cadmium can bind to the same cellular transporters as essential elements like zinc, calcium, and iron, indicating that low levels of essential nutrients could provide an opportunity for cadmium to accumulate in the body (Jenkitkasemwong et al., 2012; Lin et al., 2014; Vance and Chun, 2015). Low levels of iron in females may provide cadmium ions with a binding site in the intestine, leading to increased blood and urine cadmium concentrations among females (Akesson et al., 2005; Berglund et al., 1994; Vahter et al., 2002). Cadmium has been shown to be associated with sex hormones in males and females (Ali et al., 2014; Bochud et al., 2017; Kresovich et al., 2015; Nagata et al., 2016) and as such the associations we observed may also be acting through hormonal pathways.

There are several limitations to our study. Our study relies on a single, cross-sectional sample to estimate kidney function using multiple parameters, and these measurements may vary over time. In particular, eGFR may be subject to extreme intra-individual variability due to intrinsic renal disease or extrinsic factors such as diet and exercise (Stevens et al., 2006). However, in a study with repeat sampling of serum creatinine the within-person coefficient of variation was 7.6%, demonstrating relatively low variability despite a 44% and 8% prevalence of hypertension and diabetes, respectively, among those in the study population (Selvin et al., 2013). Similar to the findings of Buser et al. 2016, we cannot rule out the possibility that associations were due to reverse causation. We did not observe an association between cadmium concentration and eGFR when we restricted our sample to participants with eGFR ≥60 mL/min/1.73 m^2, which may be consistent with the hypothesis of reserve causation. Several studies have evaluated urinary cadmium as a biomarker, suggesting that associations between urinary cadmium and parameters of kidney function should be interpreted cautiously (Akerstrom et al., 2013b; Chaumont et al., 2012; Haddam et al., 2011; Wallin et al., 2014). Continued research to identify the mechanisms involved in reverse causality when studying the association between low-level cadmium exposure and kidney function has led to considerable debate about the most appropriate biomarker of

cadmium exposure, particularly in the context of cross-sectional studies. Recent investigations of cadmium concentration in kidney tissue have suggested that blood cadmium concentration is a valid biomarker of cadmium exposure (Akerstrom et al., 2013a). Given our interest in measures of kidney function, which may influence the urinary excretion of cadmium, we chose to use cadmium concentration as measured in blood. Blood cadmium concentration may be a useful indicator of longer-term exposure (Jarup et al., 1997; Wallin et al., 2014); however, we cannot rule out that concentrations in blood were higher among individuals with decreased glomerular filtration due to defects in urinary cadmium excretion. We did not observe differences in mean cadmium levels by duration of diabetes or hypertension, nor did associations change when we further controlled for disease severity using continuous systolic and diastolic blood pressure measurements and continuous HbA1c. The fact that cadmium exposure level does not appear to be substantively different by the duration of comorbidities, decreases the possibility of reverse causality. Other environmental exposures, however, may have confounded the analysis. Despite an overall large sample size, we may have had limited power to precisely estimate stratum specific measures of association. Our cross-sectional study design is useful for exploratory and hypothesis generating analyses, but prospective study of repeat measurements of kidney function parameters in relation to cadmium concentration is needed to validate our findings before any discussion on causality can take place. Mechanistic study of the association between cadmium exposure and kidney function using animal models may provide insights into differences by sex, hypertension, or diabetes status that our cross-sectional study cannot provide. Although we assessed the association between cadmium concentration and low eGFR, a diagnosis of CKD requires multiple assessments of kidney function over weeks or months, further highlighting the need to replicate these findings in cohorts with multiple measures of kidney function over time. We cannot draw conclusions about the temporality of cadmium exposure and kidney function, nor the temporality of diabetes or hypertensive status with kidney function. Strengths of our study include use of objective laboratory measurements in the evaluation of kidney function by eGFR as calculated using the CKD-EPI equation. NHANES also provides self-reported information on diagnosis of diabetes and hypertension, which was supplemented using measures of HbA1c, systolic and diastolic blood pressure, and medication use.

Conclusion

In conclusion, we reconfirmed previous studies indicating that increased cadmium exposure is associated with decreased kidney function and demonstrated that the degree of this association differs by sex and may vary based on preexisting diabetes and hypertension status. Our findings support future prospective research in this area that is sex-specific, in addition to the need to take individual lifestyle and environmental characteristics into account when assessing risk for disease development, especially among individuals with preexisting conditions that may contribute to the development and progression of kidney dysfunction. It is imperative to strengthen anti-smoking efforts and prevent environmental exposures from increasing in magnitude in order to protect human health.

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ER-18–1190R1 Highlights

- Environmental exposure to cadmium is a risk factor for decreased kidney function.
- The magnitude of the association between cadmium exposure and kidney function may differ by sex and preexisting diabetes and hypertension status.
- The strength of the association between cadmium quartiles and estimated glomerular filtration rate was more pronounced among females compared to males.
- The inverse association between cadmium quartiles and estimated glomerular filtration rate was largest among females with hypertension and females with both hypertension and diabetes.

Table 1.

Weighted demographic and clinical characteristics of NHANES 2007–2012 participants overall, and by outcome (n=12,577).

	Overall	Continuous eGFR (mL/minute/1.73 m^2)		Low eGFR (eGFR < 60)		Urine Albumin to Creatinine Ratio (mg/g)		Albuminuria (UACR ≥ 30 mg/g)	
	n (%)	Mean (95% CI)	p-value	% (95% CI)	p-value	GM (95% CI)	p-value	% (95% CI)	p-value
Age in years									
20–39	4135 (35.7)	110.3 (109.5–111.1)		0.23 (0.05–0.41)		6.4 (6.2–6.6)		5.1 (4.4–5.8)	
40–59	4172 (39.1)	93.0 (92.1–93.8)	<0.0001	2.3 (1.6–3.1)	<0.0001	7.4 (7.1–7.8)	<0.0001	6.9 (5.9–7.9)	<0.0001
60+	4270 (25.2)	73.6 (72.9–74.3)		21.8 (20.3–23.2)		11.5 (10.8–12.3)		16.4 (14.8–18.0)	
Sex									
Female	6135 (49.7)	94.2 (93.1–95.3)	0.74	7.8 (6.9–8.7)	<0.0001	9.0 (8.7–9.4)	<0.0001	9.3 (8.3–10.3)	0.03
Male	6442 (50.3)	94.3 (93.4–95.3)		5.2 (4.5–6.0)		6.9 (6.6–7.2)		8.1 (7.3–8.9)	
Race/ethnicity									
African-American, nH	2520 (10.1)	101.7 (100.5–103.0)		6.2 (5.2–7.2)		8.2 (7.7–8.7)		11.9 (10.5–13.4)	
White, nH	5939 (70.9)	90.9 (89.9–91.8)	<0.0001	7.5 (6.6–8.3)	<0.0001	7.7 (7.4–8.0)	0.02	7.8 (7.0–8.7)	<0.0001
Hispanic	3186 (13.0)	104.9 (103.6–106.1)		2.8 (2.3–3.3)		8.6 (8.1–9.2)		10.2 (8.6–11.7)	
Other	932 (6.0)	98.9 (96.8–100.9)		3.5 (2.1–4.9)		8.2 (7.4–9.1)		9.5 (7.0–12.1)	
Education									
< High school	3327 (17.5)	94.8 (93.3–96.2)		9.3 (8.0–10.6)		9.5 (8.9–10.2)		13.6 (11.9–15.3)	
High school graduate	2895 (22.6)	93.7 (92.5–94.8)	0.29	7.5 (6.5–8.5)	<0.0001	8.3 (7.8–8.8)	<0.0001	9.5 (8.0–10.9)	<0.0001
Some college	3581 (31.0)	95.5 (94.1–96.9)		5.6 (4.5–6.7)		7.6 (7.3–8.0)		7.8 (6.9–8.8)	
≥ College graduate	2774 (28.9)	93.1 (91.7–94.5)		4.9 (3.6–6.2)		7.0 (6.7–7.3)		5.9 (4.9–7.0)	
Body mass index, kg/m^2									
Normal	3607 (30.4)	97.3 (96.1–98.6)		5.4 (4.5–6.3)		8.0 (7.7–8.2)		8.0 (6.9–9.1)	
Overweight	4263 (34.4)	92.4 (91.5–93.4)	<0.0001	6.7 (5.9–7.4)	0.002	7.2 (6.9–7.5)	0.004	6.6 (5.7–7.5)	<0.0001
Obese	4707 (35.2)	93.4 (92.4–94.5)		7.2 (6.2–8.2)		8.5 (8.1–9.0)		11.3 (9.9–12.6)	
Hypertension									
Hypertensive	5651 (39.2)	84.8 (83.9–85.7)	<0.0001	13.3 (12.2–14.4)	<0.0001	10.5 (9.9–11.1)	<0.0001	14.7 (13.5–15.9)	<0.0001
Nonhypertensive	6926 (60.8)	100.4 (99.4–101.3)		2.1 (1.5–2.7)		6.5 (6.3–6.7)		4.8 (4.1–5.5)	
Diabetes									
Diabetic	1951 (10.9)	84.2 (82.9–85.5)	<0.0001	17.4 (15.5–19.3)	<0.0001	16.8 (15.4–18.3)	<0.0001	26.6 (24.0–29.2)	<0.0001
Non-diabetic	10626 (89.1)	95.5 (94.5–96.5)		5.1 (4.5–5.8)		7.2 (6.9–7.4)		6.5 (5.9–7.0)	
Weak kidneys									
Yes	336 (2.1)	69.5 (65.2–73.8)	<0.0001	40.3 (33.8–46.9)	<0.0001	26.6 (20.9–33.7)	<0.0001	36.9 (30.3–43.5)	<0.0001
No	12241 (97.9)	94.8 (93.9–95.7)		5.8 (5.2–6.4)		7.7 (7.4–7.9)		8.1 (7.3–8.8)	
Alcohol use									
Rare/never	7355 (51.7)	92.7 (91.7–93.7)	<0.0001	8.7 (7.9–9.5)	<0.0001	8.8 (8.4–9.2)	<0.0001	11.0 (10.0–12.0)	<0.0001
Moderate	5222 (48.3)	96.0 (94.9–97.0)		4.1 (3.2–5.0)		7.0 (6.7–7.2)		6.2 (5.3–7.0)	
Smoking status									
Never	6714 (53.7)	95.1 (93.7–95.9)	<0.0001	6.0 (5.3–6.8)	<0.0001	7.6 (7.3–7.9)	0.09	7.8 (6.8–8.7)	0.0002
Former (5+ years)	2488 (19.3)	84.9 (83.5–86.2)		11.9 (10.5–13.5)		8.6 (8.1–9.1)		11.0 (9.7–12.4)	

	Overall	Continuous eGFR (mL/minute/1.73 m^2)		Low eGFR (eGFR < 60)		Urine Albumin to Creatinine Ratio (mg/g)		Albuminuria (UACR ≥ 30 mg/g)	
	n (%)	Mean (95% CI)	p-value	% (95% CI)	p-value	GM (95% CI)	p-value	% (95% CI)	p-value
Former (<5 years)	649 (5.9)	96.8 (94.7–98.8)		5.2 (3.1–7.2)		7.5 (6.7–8.3)		8.1 (5.4–10.7)	
Current (infrequent)	465 (3.4)	104.6 (102.0–107.2)		2.5 (0.01–5.0)		7.0 (6.3–7.8)		6.9 (4.0–9.8)	
Current (infrequent)	465 (3.4)	104.6 (102.0–107.2)		2.5 (0.01–5.0)		7.0 (6.3–7.8)		6.9 (4.0–9.8)	
Current (daily)	2261 (17.7)	99.1 (97.9–100.2)		3.1 (2.4–3.9)		8.1 (7.8–8.5)		9.4 (8.1–10.7)	
Cotinine level									
< 10 ng/ml	9388 (74.8)	92.6 (91.5–93.7)	<0.0001	7.6 (6.9–8.4)	<0.0001	7.9 (7.6–8.2)	0.32	8.6 (7.8–9.4)	0.71
≥ 10 ng/ml	3189 (25.2)	99.2 (98.2–100.2)		3.1 (2.3–3.9)		7.7 (7.4–8.1)		8.9 (7.5–10.2)	
Blood cadmium concentration (range)									
Q1 (0.11–0.21 μg/L)	3068 (28.3)	99.0 (97.8–100.2)		2.9 (2.2–3.6)		6.8 (6.5–7.1)		6.3 (5.4–7.3)	
Q2 (0.22–0.34 μg/L)	3289 (27.0)	94.3 (93.1–95.6)	<0.0001	4.8 (39–5.7)	<0.0001	7.4 (7.0–7.7)	<0.0001	7.2 (6.3–8.2)	<0.0001
Q3 (0.35–0.60 μg/L)	3054 (21.8)	88.9 (87.4–90.6)		11.3 (9.6–12.9)		8.7 (8.2–9.2)		9.9 (8.5–11.3)	
Q4 (0.61–9.3 μg/L)	3166 (22.9)	93.4 (92.2–94.5)		8.3 (6.8–9.8)		9.3 (8.9–9.7)		12.0 (10.7–13.4)	
Survey year									
2007–2008	4376 (33.6)	95.0 (93.2–96.7)		6.3 (5.3–7.2)		8.4 (7.9–8.9)		9.8 (8.710.9)	
2009–2010	4416 (32.6)	94.0 (92.4–95.5)	0.32	6.3 (5.2–7.4)	0.71	7.1 (6.6–7.7)	0.40	7.5 (6.2–8.7)	0.03
2011–2012	3785 (33.8)	93.8 (92.4–95.3)		6.9 (5.5–8.2)		8.2 (7.9–8.5)		8.7 (7.4–10.0)	

eGFR: estimated glomerular filtration rate; UACR: urine albumin to creatinine ratio; GM=geometric mean; CI=confidence interval; nH=non-Hispanic; Q1: Quartile 1; Q2: Quartile 2; Q3: Quartile 3; Q4: Quartile 4

Table 2.

Bivariate associations of geometric mean and 95% confidence intervals (95% CI) for blood cadmium with covariates and outcomes in NHANES 2007–2012 participants (n=12,577).

	Blood cadium concentration, µg/L		
	GM	**(95% CI)**	**p-value**
Age in years			
20–39	0.30	(0.29–0.31)	
40–59	0.37	(0.36–0.39)	<0.0001
60+	0.40	(0.39–0.42)	
Sex			
Female	0.39	(0.37–0.40)	<0.0001
Male	0.32	(0.31–0.34)	
Race/ethnicity			
African-American, nH	0.40	(0.39–0.42)	<0.0001
White, nH	0.35	(0.34–0.36)	
Hispanic	0.29	(0.28–0.31)	
Other	0.45	(0.42–0.49)	
Education			
<High school	0.46	(0.43–0.48)	
High school graduate	0.40	(0.38–0.42)	<0.0001
Some college	0.35	(0.33–0.36)	
≥ College graduate	0.28	(0.27–0.29)	
Body mass index, kg/m^2			
Normal	0.40	(0.38–0.43)	
Overweight	0.34	(0.33–0.36)	<0.0001
Obese	0.32	(0.32–0.33)	
Hypertension			
Non-hypertensive	0.34	(0.32–0.35)	<0.0001
Hypertensive	0.38	(0.37–0.39)	
Diabetes			
Non-diabetic	0.35	(0.34–0.36)	0.65
Diabetic	0.36	(0.34–0.38)	
Weak kidneys			
Yes	0.48	(0.42–0.55)	<0.0001
No	0.35	(0.34–0.36)	
Alcohol use			
Rare/never	0.36	(0.35–0.37)	0.10
Moderate	0.35	(0.33–0.36)	
Smoking status			
Never	0.25	(0.24–0.25)	
Former (5+ years)	0.32	(0.31–0.33)	<0.0001
Former (<5 years)	0.36	(0.34–0.39)	

	Blood cadium concentration, µg/L		
	GM	**(95% CI)**	**p-value**
Current (infrequent)	0.47	(0.43–0.53)	
Current (daily)	1.09	(1.05–1.13)	
Cotinine level			
< 10 ng/ml	0.27	(0.26–0.27)	<0.0001
≥ 10 ng/ml	0.82	(0.78–0.85)	
eGFR < 60			
Yes	0.46	(0.43–0.49)	<0.0001
No	0.35	(0.34–0.36)	
Albuminuria			
Yes	0.43	(0.40–0.46)	<0.0001
No	0.35	(0.34–0.36)	
Blood cadmium concentration			
Q1	0.15	(0.14–0.15)	
Q2	0.27	(0.27–0.27)	<0.0001
Q3	0.45	(0.44–0.45)	
Q4	1.14	(1.11–1.17)	
Survey year			
2007–2008	0.37	(0.35–0.39)	
2009–2010	0.35	(0.34–0.36)	0.01
2011–2012	0.34	(0.32–0.35)	

GM=geometric mean; CI=confidence interval; nH=non-Hispanic; eGFR: estimated glomerular filtration rate; Q1: Quartile 1; Q2: Quartile 2; Q3: Quartile 3; Q4: Quartile 4

Table 3.

Multivariable adjusted[a] associations between cadmium exposure quartiles and kidney function parameters in NHANES 2007–2012 participants.

Blood cadmium concentrations Quartile (Range)	Continuous eGFR (mL/minute/1.73 m^2) β (95% CI)	Low eGFR (eGFR <60 vs. ≥60) OR (95% CI)	Continuous log UACR (mg/g) β (95% CI)	Albuminuria (UACR ≥ 30 vs. <30) OR (95% CI)
Q1 (0.11–0.21 μg/L)	ref	ref	ref	ref
Q2 (0.22–0.34 μg/L)	0.13 (−1.05, 1.32)	0.85 (0.60, 1.22)	−0.03 (−0.08, 0.03)	0.93 (0.78, 1.11)
Q3 (0.35–0.60 μg/L)	−1.06 (−2.36, 0.23)	1.39 (1.03, 1.89)[b]	0.05 (−0.01, 0.11)	1.12 (0.92, 1.36)
Q4 (0.61–9.3 μg/L)	−1.63 (−2.68, −0.59)[b]	1.80 (1.23, 2.65)[b]	0.19 (0.10, 0.28)[b]	1.61 (1.25, 2.07)[b]
p for trend	0.005	0.0001	0.0001	0.0004

[a]Model adjusts for age (continuous), sex, race/ethnicity (non-Hispanic white, non-Hispanic AfricanAmerican, Hispanic, or other), serum cotinine level (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), alcohol use (yes/no), body mass index (continuous), hypertension (yes/no), and diabetes (yes/no)

[b]Statistically significant ($p<0.05$)

Q1: Quartile 1; Q2: Quartile 2; Q3: Quartile 3; Q4: Quartile 4; eGFR: estimated glomerular filtration rate; UACR: urine albumin to creatinine ratio

Table 4.

Multivariable adjusted associations between cadmium exposure quartiles and estimated glomerular filtration rate (eGFR) overall by sex, and by prevalent diabetes and hypertension status among NHANES 2007–2012 participants.

Blood cadmium concentrations	Continuous eGFR (mL/minute/1.73 m^2)
Females[a]	**Adjusted mean difference (95% CI)**
Q1	ref
Q2	−0.18 (−1.62, 1.26)
Q3	−1.81 (−3.16, −0.46)[b]
Q4	−3.61 (−4.85, −2.36)[b]
p for trend	0.0003
Females *Q4 vs. Q1 (ref)*[c]	
Diabetes and hypertension	−4.91 (−10.12, 0.29)
Diabetes only	4.28 (−4.04, 13.15)
Hypertension only	−5.77 (−8.20, −3.34)[b]
No diabetes or hypertension	−0.64 (−2.21, 0.93)
Males[a]	
Q1	ref
Q2	0.08 (−1.16, 1.32)
Q3	−0.62 (−2.63, 1.39)
Q4	0.56 (−0.99, 2.12)
p for trend	0.09
Males *Q4 vs. Q1 (ref)*[c]	
Diabetes and hypertension	−2.41 (−7.71, 2.90)
Diabetes only	−7.45 (−13.52, −1.38)[b]
Hypertension only	−0.76 (−3.24, 1.72)
No diabetes or hypertension	−1.51 (−3.51, 0.49)

[a]Model adjusts for age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic AfricanAmerican, Hispanic, or other), serum cotinine level (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), alcohol use (yes/no), body mass index (continuous), hypertension (yes/no), and diabetes (yes/no)

[b]Statistically significant ($p<0.05$)

[c]Model adjusts for age (continuous), race/ethnicity (nonHispanic white, non-Hispanic African-American, Hispanic, or other), serum cotinine level (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), alcohol use (yes/no), and body mass index (continuous);