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Urinary cadmium concentrations and metabolic syndrome in U.S. adults: The National Health and Nutrition Examination Survey 2001–2014

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ABSTRACT

Background: Low to moderate acute cadmium exposure has been associated with increased risk of chronic diseases, such as cardiovascular and kidney disease. Little is known about the association between urinary cadmium levels—an indicator of longer-term exposure—and metabolic syndrome (MetS).

Methods: We analysed data from 3982 participants aged 20– < 80 years of the National Health and Nutrition Examination Survey 2001–2014. Urinary cadmium levels were measured and adjusted for creatinine using spot urine samples. Cadmium levels were evaluated in quintiles (Q). MetS was defined by National Cholesterol Education Program's Adult Treatment Panel III report criteria. Prevalence odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable logistic regression accounting for complex survey design, while adjusting for potential confounders and stratifying by sex and smoking status.

Results: In the overall study population, there was a marginal inverse association between urinary cadmium and MetS (adj. OR for Q5 versus Q1: 0.7; 95% CI: 0.5–1.0). Sex stratified models were similar. When examining individual components of MetS, participants with higher levels of urinary cadmium had decreased odds of abdominal obesity (adj. OR for Q5 versus Q1 0.4; 95% CI: 0.3–0.6), but increased odds for low HDL (adj. OR for Q5 versus Q1 2.1; 95% CI: 1.4–3.1). Among current smokers, higher urinary cadmium was associated with increased odds of MetS, hypertension, and low HDL even after accounting for serum cotinine—a marker of smoking intensity.

Conclusions: Higher levels of urinary cadmium, a marker of long term exposure, were not associated with an increased risk of MetS in the overall study population. However, higher urine cadmium was associated with altered MetS components. Current smokers were the most vulnerable group, with higher long-term cadmium exposure being associated with increased risk of MetS, low HDL, and hypertension.

1. Background

Metabolic syndrome (MetS) affects over one-third of adults living in the United States (Aguilar et al., 2015). As a cluster of interrelated metabolic anomalies, MetS includes central obesity, hypertriglyceridemia, reduced HDL cholesterol, hypertension and hyperglycemia (DeFronzo and Ferrannini, 1991). Importantly, individuals who meet the criteria for MetS are at a two-fold increased risk of cardiovascular disease (Borne et al., 2014). MetS varies in the U.S. population, differing by sex, potentially owing to differences in hormone-mediated pathways and underlying pathophysiology (Beigh and Jain, 2012; Nishijo et al., 2004). Additionally, MetS differs by race/ethnicity and socioeconomic status (Beigh and Jain, 2012).

While lifestyle and genetic factors largely determine the risk for MetS, a growing body of evidence suggests that environmental factors, including heavy metals exposures, are associated with an increased risk of this syndrome (Kaur, 2014; Tellez-Plaza et al., 2008; Moon, 2014). Specifically, lead and mercury have been shown to be positively

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associated with MetS and its individual components (Mendez et al., 2016; Park et al., 2006; Wang et al., 2007). Arsenic is also associated with an increased risk of MetS (Wang et al., 2007). However, other commonly occurring metals and metalloids have been less well studied.

Cadmium is a ubiquitously occurring toxic metal (Faroon et al., 2012; Jaishankar et al., 2014), which has several major sources of exposure, including cigarette smoking, diet (e.g. whole grains, fish, and green leafy vegetables), occupational exposures, as well as living near an industrial area that is more likely to be polluted with this metal (McElroy et al., 2007; Staessen et al., 1999; Tellez-Plaza et al., 2013a; Järup et al., 1998). Cadmium may affect glucose and lipid metabolism through a variety of pathways, including hormonal and cellular differentiation mechanisms (Borne et al., 2014; Edwards and Prozialeck, 2009; Ithakissios et al., 1975; Kawakami et al., 2010; Schwartz et al., 2003). While some epidemiological studies have shown associations between cadmium and adverse health outcomes, such as cardiovascular disease (Tellez-Plaza et al., 2013a; Navas-Acien et al., 2004; Tellez-Plaza et al., 2010), chronic kidney disease (Hellstrom et al., 2001; Orr and Bridges, 2017), and all-cause mortality (Tellez-Plaza et al., 2012), others have been less conclusive due to differences in cadmium measurements. For example, the association between cadmium and hypertension depended on whether urine or blood cadmium levels were evaluated (Tellez-Plaza et al., 2008; Lee and Kim, 2012; Gallagher and Meliker, 2010). These differences may be attributed to differences in half-life based on biospecimen measurement, with blood representing shorter-term exposure to cadmium, while urine represents longer-term exposure (Tellez-Plaza et al., 2008; Schwartz et al., 2003; Gallagher and Meliker, 2010).

In the current investigation, we conducted one of the first population-based studies on the association between urinary cadmium levels and MetS in the National Health and Nutrition Examination Survey (NHANES 2001–2014). We evaluated effect modification by sex and age for the association between long-term cadmium exposure and MetS. Finally, given that smoking is a source of cadmium and a risk factor for cardiovascular disease, we conducted a restricted analysis to evaluate urinary cadmium exposure and MetS risk by smoking status.

2. Methods

2.1. Study population

This study utilized data from NHANES, an on-going cross-sectional survey conducted by the U.S. National Center for Health Statistics that consists of a representative sample of the U.S. civilian population. Employing a complex multistage cluster probability sampling strategy reported in 2-year cycles (CDC, 2013), participants are recruited into the study and information is collected on sociodemographic, behavioral, and nutrition factors from questionnaires, as well as examinations and laboratory data to assess a variety of health outcomes, including anthropometry and biomarker data.

Data were merged from 7 biannual NHANES cycles, from the years 2001–2014, resulting in a pooled sample size of 35,881 participants, aged 20– < 80 years. Of these, 11,573 individuals had data on urinary cadmium. Among this subset, 5984 individuals did not have information on high density lipoprotein (HDL), low density lipoprotein (LDL) and glucose levels, which left 5589 participants with data on all five components of the MetS. Among the 5589 participants with cadmium and MetS data, we excluded pregnant and/or lactating women (n = 179) and people with fasting time < 8 h (n = 506). We also excluded subjects with self-reported cardiovascular disease (CVD) (n = 239), as well as those with chronic kidney disease, assessed as glomerular filtration rate < 60 (CKD) (n = 259), as this condition can affect urine cadmium concentrations (Hellstrom et al., 2001). Finally, there were about 424 participants with missing covariate information. These exclusions resulted in a final sample size of 3982 adults aged 20– < 80 years for whom complete data was available on urine cadmium, MetS and its components, as well as all covariates of interest.

2.2. Urinary cadmium

Cadmium levels were measured in spot urine samples in a random one-third sample of the overall study population (CDC (Centers for Disease Control and Prevention), 2005). Analyses of urinary cadmium levels occurred at the Environmental Health Sciences Laboratory of the Centers for Disease Control and Prevention's National Center for Environmental Health. A detailed protocol on NHANES specimen collection, processing, quality control is provided in the NHANES *Laboratory/Medical Technologists Procedures Manual* (CDC, 2016). Briefly, urinary cadmium levels were measured using inductively coupled plasma-mass spectrometry multi-element analytical technique. In NHANES survey cycles 2001 to 2004, the LOD for urinary cadmium was 0.042 μg/L; for 2005 to 2010, the LOD was 0.030 μg/L; for 2011–2012 the LOD was 0.056 μg/L and finally for 2013–2014 the LOD was 0.036. For study participants who had measurements of urine cadmium concentrations that were below the limit of detection (LOD: 0.056 μg/L), (CDC, 2009a) a level equal to LOD divided by the square root of 2 was imputed (CDC, 2011). A total of 212 (4.8%) of all participants in this analysis were at or below the urinary cadmium LOD. Urine dilution was accounted for by adjusting for urine creatinine.

2.3. Metabolic syndrome

MetS was defined using the National Cholesterol Education Program's Adult Treatment Panel III report (NCEP/ATPIII) (Grundy et al., 2004). In accordance with this definition, individuals were classified as having MetS if they met at least 3 of the following 5 criteria: 1) waist circumference ≥102 cm in men or ≥88 cm in women; 2) triglycerides ≥150 mg/dL; 3) high density lipid (HDL) cholesterol < 40 mg/dL in men or < 50 mg/dL in women; 4) blood pressure ≥130/85 mm Hg or treatment for hypertension; and 5) fasting blood glucose ≥100 mg/dL or treatment for diabetes. Blood pressure levels for each participant were taken as the average of four blood pressure measurements. Data on blood pressure, as well as waist circumference, were collected by a trained examiner in the mobile examination center (CDC, 2009b). Detailed information on methods used to collect information on fasting glucose, HDL cholesterol and triglyceride levels has been described in the *NHANES Laboratory/Medical Technologists Procedures Manual* (CDC, 2016).

2.4. Covariates

The following variables were identified as potential confounders: age, sex, race/ethnicity, physical activity, smoking status, education, poverty status, alcohol use, and BMI. The latter variable was included in all models, except for the model with central adiposity as the main outcome. We also adjusted for estimated glomerular filtration rate, given that kidney function can impact urinary cadmium concentrations. This information was collected via self-reported questionnaires. Age was examined as a continuous variable, as well as dichotomized at 60 years of age, given that urinary cadmium concentrations differed for those who were < 60 years of age compared to those ≥60 years of age. Individuals < 20 years of age or those 80 years of age and over were excluded. The latter exclusion was done due to NHANES' classification of participants age ≥80 years as 80 or 85 in certain surveys for the purpose of anonymity. Race/ethnicity was categorized as non-Hispanic white (referent), non-Hispanic black, Mexican-American and others. Physical activity was classified as having vigorous, moderate or no physical exercise (referent). Smoking status was coded as current, past or never smoker (referent). Education was classified as high school graduate or less, some college, or college-graduate or higher (referent). An income-to-poverty ratio was used to infer poverty status; if ratio < 1, individuals were classified as below poverty level based on