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Associations between cadmium levels in blood and urine, blood pressure and hypertension among Canadian adults

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ABSTRACT

Background: Cadmium has been inconsistently related to blood pressure and hypertension. The present study seeks to clarify the relationship between cadmium levels found in blood and urine, blood pressure and hypertension in a large sample of adults.

Methods: The study sample included participants ages 20 through 79 from multiple cycles of the Canadian Health Measures Survey (2007 through 2013) with measured blood cadmium (n=10,099) and urinary cadmium (n=6988). Linear regression models examined the association between natural logarithm transformed cadmium levels and blood pressure (separate models for systolic and diastolic blood pressure) after controlling for known covariates. Logistic regression models were used to examine the association between cadmium and hypertension. Models were run separately by sex, smoking status, and body mass index category.

Results: Men had higher mean systolic (114.8 vs. 110.8 mmHg, $p < 0.01$) and diastolic (74.0 vs. 69.6 mmHg, $p < 0.01$) blood pressure compared to women. Although, geometric mean blood (0.46 vs. 0.38 μg/L, $p < 0.01$) and creatinine-adjusted standardized urinary cadmium levels (0.48 vs. 0.38 μg/L, $p < 0.01$) were higher among those with hypertension, these differences were no longer significant after adjustment for age, sex and smoking status. In overall regression models, increases in blood cadmium were associated with increased systolic (0.70 mmHg, 95% confidence interval [CI]=0.25–1.16, $p < 0.01$) and diastolic blood pressure (0.74 mmHg, 95% CI=0.30–1.19, $p < 0.01$). The associations between urinary cadmium, blood pressure and hypertension were not significant in overall models. Model stratification revealed significant and negative associations between urinary cadmium and hypertension among current smokers (OR=0.61, 95% CI=0.44–0.85, $p < 0.01$), particularly female current smokers (OR=0.52, 95% CI=0.32–0.85, p=0.01).

Conclusion: This study provides evidence of a significant association between cadmium levels, blood pressure and hypertension. However, the significance and direction of this association differs by sex, smoking status, and body mass index category.

1. Introduction

Cadmium is a heavy metal that occurs naturally in the environment. Whereas certain occupational subgroups are at elevated risk of cadmium exposure, including sawmill and wood preservation workers, auto repair workers, and welders (CAREX Canada, 2014), non-occupational exposure to cadmium is generally the result of cigarette smoking and ingestion of cadmium-high foods (CAREX Canada, 2015; Garner and Levallois, 2016). The International Agency for Research on Cancer considers there to be sufficient evidence of the carcinogenic effect of cadmium and its compounds among humans (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2009). Furthermore, other evidence indicates that prolonged or increased exposure to cadmium could have significant health consequences, including kidney dysfunction, skeletal damage, and possible cardiovascular effects (Järup et al., 1998; United Nations Environment Programme, 2010). Blood levels of cadmium are valid markers of recent exposure (Järup and Åkesson, 2009; Järup, 2003). However, even after exposure cessation, cadmium levels in the blood can remain elevated, and are therefore also reflective of long-term exposure (Järup et al., 1998). Urinary cadmium levels reflect long-term (cumulative) exposure as well as cadmium levels in the kidney (Centers for Disease Control and Prevention, 2009, p. 202; Järup, 2003).

Animal model studies have demonstrated that higher levels of

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cadmium are associated with increased blood pressure and hypertension (Perry and Erlanger, 1974; Perry et al., 1977, 1979; United Nations Environment Programme, 2010). Observational studies, however, have found mixed results. Studies vary in the direction or significance that cadmium body stores have on blood pressure or hypertension, with results seeming to vary by type of cadmium biomonitoring sample (blood vs urine), sex, smoking status, ethnicity and medication levels (Tellez-Plaza et al., 2008; Whittemore et al., 1991; Agarwal et al., 2011; Scinicariello et al., 2011; Lee and Kim, 2012; Lee et al., 2016). In their recent systematic review and meta-analysis of the associations between blood and urine cadmium, blood pressure and hypertension, Gallagher and Meliker (2010) concluded that there was evidence of a positive association between blood cadmium (BCd) and blood pressure among women, but not among men. Furthermore, their analysis indicated that there was an inverse relationship between urinary cadmium (UCd) and the likelihood of hypertension. However, Gallagher and Meliker pointed out that few studies included representative, population-based samples of never smokers, and that previous studies have varied in their outcome definitions, thereby limiting interpretation of meta-analysis findings (Gallagher and Meliker, 2010).

The present study seeks to add to the existing literature by examining the association between cadmium levels of adult Canadians and measurements of blood pressure and the presence of hypertension. This study will examine the association of cadmium levels in both blood and urine, and will also examine whether the significance or magnitude of any association between cadmium and blood pressure differs according to sex or smoking status.

2. Materials and methods

2.1. Data source

Data for the present study were drawn from multiple cycles of the Canadian Health Measures Survey (CHMS), which collects both survey-based information as well as direct physical health measures for Canadians. The present study pools information from Cycle 1 (2007–2009) and Cycle 2 (2009–2011) for analyses concerning UCd measures, and further includes Cycle 3 (2012–2013) data for analyses concerning BCd measures: UCd was not measured in Cycle 3 of the CHMS. The CHMS includes the population ages 3 through 79 (6 through 79 in Cycle 1) living in the ten provinces, but excludes the following individuals: persons living in the three territories; persons living on reserves and other Aboriginal settlements in the provinces; full-time members of the Canadian Forces; the institutionalized population and residents of certain remote regions. These exclusions are thought to represent approximately 4% of the target population (Statistics Canada, 2015a).

The study sample was limited to respondents 20–79 years of age, and excluded pregnant women (n=106) and those who were missing relevant measures of cadmium (blood, urine) or blood pressure. This left a final sample of 10,099 respondents for BCd analyses, and 6988 respondents for UCd analyses.

2.1.1. Ethics approval for the CHMS

All processes of the CHMS were reviewed and approved by the Research Ethics Boards of two federal agencies (Health Canada, Public Health Agency of Canada) to ensure that internationally recognized ethical standards for human research were met and maintained. In addition, protocols were developed through extensive consultation with recognized experts and were performed by accredited health professionals in conformance with universal precautions.

2.2. Measures

2.2.1. Cadmium measures

Blood and urine samples were collected from all eligible respondents at the mobile examination clinic. Blood samples were collected by a phlebotomist using a standardized venipuncture technique. These were subsequently centrifuged and aliquoted into smaller tubes. Respondent-provided urine samples were also aliquoted into smaller tubes. Urine samples were collected using the first catch urine in cycle 2, as opposed to the mid-stream urine collected in cycle 1. Cycle 2 respondents were also asked to abstain from urinating two hours prior to their appointment. This may have resulted in a shift in creatinine levels when multiple cycles are compared. This, in turn, could affect creatinine-adjusted levels of cadmium. Blood and urine sample tubes were placed in shipping trays and stored in the mobile examination clinic laboratory's refrigerator or freezer, depending on the test. All specimens were stored as soon as processing was complete to ensure the quality of the samples' integrity, which was achieved within two hours from the time of collection for most samples: a four hour ceiling from the point of collection was placed on the time for blood samples to be processed and stored (Statistics Canada, 2015a).

The limit of detection (LOD) for BCd was 0.045 μg/L (0.4 nmol/L) in cycles 1 and 2, and 0.080 μg/L (0.71 nmol/L) in cycle 3. The LOD for UCd was 0.09 μg/L (0.8 nmol/L) for cycle 1 and 0.07 μg/L (0.6 nmol/L) for cycle 2. Consistent with others who suggest excluding urine samples that are too dilute (Alessio et al., 1985), urine samples with creatinine levels below the LOD (0.31 mmol/L for cycle 1, 0.44 mmol/L for cycle 2) were excluded from analyses (n=10). For remaining samples, observations below the LOD for the particular measure were imputed with values at half the LOD. When the LOD for a particular test differed between cycles, the highest LOD was used (BCd, 0.08 μg/L; UCd, 0.09 μg/L). All values were rounded to two significant digits (Statistics Canada, 2015b), and were converted from Système International units to conventional units for the study.

For UCd analyses, it was necessary to take into account the dilution level of the urine sample. This is generally accomplished by adjusting for urinary creatinine levels. Greater attention is being paid to the method used to adjust urinary biomarkers for creatinine, and the analytic impact that adjustment has. The present study used creatinine-adjusted standardization, an adjustment technique recommended by O'Brien et al. (2016). First, a model was fit for the natural logarithm of creatinine as a function of age, sex, body mass index (BMI) category, use of anti-hypertensive medication, diabetes diagnosis, presence of chronic kidney disease, and CHMS cycle. Next, the observed creatinine level was divided by the predicted creatinine level (exponentiated to yield the original metric) to generate a creatinine ratio. Finally, the observed UCd level was divided by this creatinine ratio to yield a creatinine-adjusted standardized UCd measure (CAS-UCd).

2.2.2. Blood pressure and hypertension

A series of blood pressure readings were taken at one-minute intervals for each respondent, with the last five readings being averaged to determine systolic (SBP) and diastolic blood pressure (DBP) measures. Respondents with any of the following characteristics were classified as hypertensive: (i) SBP≥140 mmHg; (ii) DBP≥90 mmHg; (iii) self-reported doctor-diagnosed high blood pressure; or (iv) use of anti-hypertensive medications, which was determined based on the Anatomical Therapeutic Chemical (ATC) code assigned to respondents' medications. Based on previous work with CHMS data (Bushnik et al., 2014; Wilkins et al., 2012), codes indicative of anti-hypertensive medications were: beta blockers (ATC codes C07, excluding C07AA07, C07AA12 and C07AG02); agents acting on the renin-angiotensin system (ATC codes C09); thiazide diuretics (ATC codes C03, excluding C03BA08 and C03CA01); calcium channel antagonists (ATC codes C08); and miscellaneous anti-hypertensives (ATC codes C02, excluding C02KX01).