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Low-level cadmium exposure and cardiovascular outcomes in elderly Australian women: A cohort study

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ABSTRACT

Background: Cadmium has been associated with increased risk of cardiovascular disease (CVD) in observational studies, however there has been a limited focus on this relationship in women.
Objectives: This study investigated the association of urinary cadmium (UCd) concentrations with CVD outcomes and all-cause mortality in elderly Western Australian (WA) women.
Methods: UCd excretion was measured at baseline in 1359 women, mean age 75.2 ± 2.7 years and 14.5 years of atherosclerotic vascular disease (ASVD) hospitalisations and deaths, including both the principle cause of death and all associated causes of death. Health outcome data were retrieved from the Western Australian Data Linkage System. Cox regression analysis was used to estimate hazard ratios of ASVD and all-cause mortality. UCd was ln-transformed and models were adjusted for demographic and CVD risk factors.
Results: Median (IQR) concentration of UCd was 0.18 (0.09–0.32) μg/L. In multivariable-adjusted analyses per ln unit (equivalent to ~2.7 fold) increase in UCd, there was a 36% increase in the risk of death from heart failure and 17% increase in the risk of a heart failure event, respectively (HR = 1.36, 95% CI 1.11–1.67; HR = 1.17, 95% CI 1.01–1.35). When analyses were restricted to never smokers the relationship between UCd and death from heart failure remained (HR 1.29, 95% CI 1.01–1.63).
Conclusions: This study suggests that even at low levels of exposure cadmium may be associated with heart failure hospitalisations and deaths in older women, however given the dilute nature of these urine samples, the results must be interpreted with caution.

1. Introduction

Cadmium is a widespread heavy metal released in industrial and agricultural processes and has been associated with many serious chronic diseases (Nawrot et al., 2010). Environmental exposure to cadmium is mainly due to exposure to tobacco smoke and diet, with diet being the main source of cadmium in non-smokers (Nawrot et al., 2010). Low environmental exposure to cadmium has been found to increase the risk of adverse health outcomes including decreased bone mineral density (Gallagher et al., 2008), impaired kidney function (Olsson et al., 2002) and various cancers (Åkesson et al., 2012; McElroy et al., 2006). An Australian study by Hinwood et al. (2013), examined exposure in 173 pregnant women and reported that one third had urinary cadmium concentrations ≥1 μg/g creatinine, which indicated an increased risk of health effects in this population. In older Australian women lower concentrations of urinary cadmium were reported, however, an association between urinary cadmium and decreased bone mineral density was still present at this low level of exposure (Callan et al., 2015).

A limited number of longitudinal studies of cadmium exposure, all-cause mortality and cardiovascular disease have been conducted, with most studied cohorts residing in the United States (Menke et al., 2009; Tellez-Plaza et al., 2013a; Tellez-Plaza et al., 2013b; Tellez-Plaza et al., 2012) or Japan (Nakagawa et al., 2006; Suwazono et al., 2014).

A recent *meta*-analysis calculated overall HRs for all-cause mortality (6 studies) and CVD mortality (5 studies) associated with increased urinary cadmium to be 1.44 (95% CI 1.25, 1.64) and 1.57 (95% CI 1.27, 1.95), respectively (Larsson and Wolk, 2015). When the analysis was

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restricted to the four studies that had undertaken subgroup analysis by sex, the HR for all-cause mortality for women in the highest vs lowest category of urinary cadmium concentration was 1.50 (95% CI 1.08, 2.08) (Larsson and Wolk, 2015). A US study using the NHANES cohort concluded that cadmium exposure was associated with an increased risk of all-cause and cardiovascular disease mortality among men, but not women (Menke et al., 2009). An analysis of the 1999–2004 NHANES cohort found no differences in the association between cadmium exposure all-cause and CVD mortality by sex (Tellez-Plaza et al., 2012). A more recent systematic review of populations with low to moderate levels of cadmium exposure, however, found similar associations between cadmium exposure and cardiovascular disease between men and women, but the relationship was not significant for women (Tellez-Plaza et al., 2013c). Conversely, a longitudinal study conducted in a cadmium contaminated area of Japan suggested that high levels of exposure to cadmium led to excess risk of mortality among women but not in men (Uetani et al., 2007). Whilst sex specific risk was suggested in these studies the results were inconsistent and the differential associations by sex may represent chance findings. Barregard et al. (2016) investigated the relationship between blood cadmium and incident cardiovascular disease (CVD) in men and women in Sweden and found increased hazard ratios for all CVD events for participants in the highest exposure quartile.

Mechanistically, cadmium exposure has been shown to elicit endothelial damage both in vitro and in murine models, with accelerated plaque formation observed (Knoflach et al., 2011; Messner et al., 2009). Cadmium exposure was found to be associated with the development of atherosclerotic plaques in 64 year old Swedish women after a 5 year follow up (Fagerberg et al., 2012), thus providing evidence of the pro-atherogenic potential effects of cadmium exposure.

Longitudinal studies of cadmium exposure and mortality are scarce, particularly in those with low levels of exposure. Given that women are known to have higher levels of cadmium exposure (Vahter et al., 2007) the contradictory results regarding the association between cadmium exposure and all-cause and CVD mortality in women, suggests that more studies focussed on women are warranted, especially older women. Furthermore, there have been limited studies on the relationship between cadmium exposure and non-fatal cardiovascular events.

CVD remains the number one cause of mortality in Australia and globally (Australian Bureau of Statistics, 2014; World Health Organization, 2013). Therefore, it is important to identify factors that increase the risk of developing CVD. The objective of this study was to examine the association between cadmium exposure and the incidence of mortality, cardiovascular mortality and (non-fatal) cardiovascular events in 14.5 year follow up of 1359 elderly Western Australian women. Coronary heart disease (CHD), stroke or cerebrovascular accident (CVA), heart failure (HF) and peripheral arterial disease (PAD), collectively known as atherosclerotic vascular disease (ASVD), were examined, as well as all-cause mortality.

2. Methods

2.1. Study population

Participants of this study (n = 1500) were women randomly recruited in the Perth metropolitan region from the Australian electoral roll in 1998. They were initially randomised into a 5-year, double-blinded, placebo-controlled calcium intervention trial of 1.2 g of elemental calcium in the form of two tablets of calcium carbonate taken daily, or an identical placebo (Prince et al., 2006). Participants were aged ≥70 years, ambulant and expected survival of at least 5-years. Participants were then followed for an additional 10-year observational extension study using the WA Data Linkage System (WADLS). At baseline written informed consent was obtained from all participants for the study and access to electronic health records. The Human Research Ethics Committee of the University of Western Australia approved the study protocol and consent form (approval number 05/06/004/H50). The Human Research Ethics Committee of the Western Australian Department of Health (DOHWA HREC) also approved the data linkage study (approval number #2009/24) and Edith Cowan University approved the current analysis (project number 12120).

2.2. Biochemistry

Baseline second morning void urine samples were collected in 1998 from 1359 participants, frozen and stored at −20 °C and available for analysis. These samples were collected when participants attended a clinic appointment. Participants had all been advised to be well hydrated prior to the appointment. In 2014, samples were thawed and prepared for metals analysis at Edith Cowan University, Joondalup, Western Australia. Metal free polypropylene tubes and pipette tips were used during sample preparation. Four hundred microlitres of urine was diluted 1 in 10 in 2% nitric Acid (Suprapur, Merck). Seven standards were prepared over the range of 0.02–500 mg/L in 2% nitric acid from stock standards containing elements of interest. An internal standard (containing Sc, Ge, Y, Rh, Te), was also prepared along with certified reference material (urine ClinChek level I and II, Recipe). The standards and controls were then diluted as per samples. Simultaneously, verification standards ICP-MS-E (High Purity Standards) of 2, 50, 100 mg/L were prepared in 2% nitric acid. The samples were analysed on a Thermo Fisher iCAP Q ICP-MS using an autosampler (Thermo Scientific Inc., New York, United States). New peristaltic pump tubing was used with each batch and the rinse solution used was Merck Nitric acid 2% Suprapur with 50 mL/L of Triton X (Merck). Calibration checks were run every 20 samples; if check samples outside calibrations, new calibration was performed. New calibration curves were run routinely every 60 samples.

Urinary creatinine was measured by the Jaffe reaction using an Abbott Architect c16000 auto analyser (Abbott Laboratories, Illinois, USA). Urine specific gravity was measured using an Atago Master Refractometer (Atago Co., Tokyo, Japan), at the School of Medical and Health Sciences, Edith Cowan University.

A Hitachi 917 auto analyser (Roche Diagnostics, Mannheim, Germany) was used to measure total cholesterol, high-density lipoprotein cholesterol (HDLC) and serum triglyceride concentrations. Low-density lipoprotein cholesterol (LDLC) was calculated using Friedewald's method (Friedewald et al., 1972). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate estimated glomerular filtration rate (eGFR) using serum creatinine (Levey et al., 2009).

2.3. Baseline assessment

Smoking status was coded as non-smoker (i.e. never smoked) or former/current smoker (ever smoked) if they had consumed more than 1 cigarette per day for more than 3 months at any time in their life. Sixty women with a history of smoking provided incomplete smoking history records and were given a value of median pack years from the whole cohort. Body weight (kg) was measured using electronic scales (August Sauter GmbH D-7470 Albstadt 1 Ebingen) to the nearest 0.1 kg with participants wearing light clothes and no shoes. Height (m) was measured using a wall-mounted stadiometer (Holtain Limited, Crymych, Dyfed, Britain) to the nearest 0.1 cm without socks or shoes. Body mass index (BMI) was calculated using the following equation = weight (kg)/[height (m)]^2. Prevalent diabetes and hypertension, and the use of cardiovascular medications (anti-hypertensive agents, statins and low dose aspirin) were available from the demographic questionnaire. Systolic (SBP) and diastolic blood pressure (DBP) were measured using the right arm, after the subject had been reclined and rested for 5 min, using a mercury column manometer.

Prevalent atherosclerotic vascular disease at baseline was determined retrospectively from hospital discharge data 1980–1998 using