Environmental Pollution xxx (2017) 1–8

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Blood and urine cadmium concentrations and walking speed in middle-aged and older U.S. adults☆

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ARTICLE INFO

Article history:
Received 16 December 2016
Received in revised form
21 March 2017
Accepted 3 September 2017
Available online xxx

Keywords:
Cadmium exposure
Environmental exposure
Physical function
Walking speed
Epidemiology

ABSTRACT

Reduced physical performance is an important feature of aging, and walking speed is a valid measure of physical performance and mobility in older adults. Previous epidemiological studies suggest that cadmium exposure, even at low environmental levels, may contribute to vascular, musculoskeletal, and cognitive dysfunction, which may all be associated with reductions in physical performance. To this end, we investigated the associations of blood and urine cadmium concentrations with walking speed in middle-aged and older adults in the U.S. general population. We studied U.S. adults from the National Health and Nutrition Examination Survey 1999 to 2002 who were ≥50 years of age, who had determinations of cadmium in blood or in urine, and who had measurements of the time taken to walk 20 feet. Walking speed (ft/sec) was computed as walked distance (20 ft) divided by measured time to walk (in seconds). The weighted geometric means of blood and urine cadmium were 0.49 [95% confidence interval (CI): 0.47, 0.52] μg/L and 0.37 (95% CI: 0.34, 0.42) ng/mL, respectively. After adjusting for sociodemographic, anthropometric, health-related behavioral, and clinical risk factors and inflammation markers, the highest (vs. lowest) quintile of blood cadmium was associated with a 0.18 (95% CI: 0.10, 0.25) ft/sec reduction in walking speed (*p*-Trend <0.001). No association was observed for urine cadmium levels with walking speed. Cadmium concentrations in blood, but not in urine, were associated with slower gait speed. Our findings add to the growing volume of evidence supporting cadmium's toxicity even at low levels of exposure.

1. Introduction

A decline in physical performance is an important characteristic of aging. Walking speed is a reliable measure of physical performance and mobility in older adults and has been recommended as a practical and informative "vital sign" for assessing functional status and overall health (Middleton et al., 2015). Previous studies have reported that slow walking speed may be associated with increased mortality (Studenski et al., 2011), disability (Kuo et al., 2006), hospital admissions (Penninx et al., 2000), and poor quality of life in older adults (Ekstrom et al., 2011). Identifying and reducing the risk factors that contribute to a decline in walking speed is therefore important for healthy aging, yet few epidemiological studies have been conducted on the association between environmental toxicants (lead and cobalt) and walking speed (Ji et al., 2013; Lang et al., 2009).

Cadmium is a ubiquitous environmental toxicant, with exposure primarily through cigarette smoke, dietary sources (mainly shellfish, offal, and vegetables) and ambient air in urban or industrial

Abbreviations: Cr, Creatinine; CVD, Cardiovascular disease; DSST, Digit Symbol Substitution Test; GFR, Glomerular Filtration Rate; LOD, Limit of Detection; MEC, Mobile Examination Center; METs, Metabolic Equivalent; NHANES, National Health and Nutrition Examination Survey.

☆ This paper has been recommended for acceptance by David Carpenter.

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http://dx.doi.org/10.1016/j.envpol.2017.09.022
0269-7491/

areas (Järup et al., 1998; Olmedo et al., 2016). Cadmium is known to be cardiotoxic and carcinogenic after inhalation, and its accumulation in the body results in the development of chronic disease (IARC, 1993; Nordberg et al., 2007). In this sense, there is epidemiologic evidence that environmental exposures to cadmium, even at low levels, contribute to the development of hypertension (Tellez-Plaza et al., 2008), cardiovascular disease (Tellez-Plaza et al., 2013), peripheral arterial disease (Fagerberg et al., 2013), diabetes (Schwartz et al., 2003), kidney disease (Navas-Acien et al., 2009), osteoporosis (Gallagher et al., 2008), and hearing loss (Choi et al., 2012). In addition, a recent study suggests a putative adverse relationship between urine cadmium at high exposure levels and frailty in U.S. older adults (Garcia-Esquinas et al., 2015). Given the ubiquitous exposure of cadmium and its cardiotoxic and musculoskeletal effects, which are themselves associated with motor dysfunction (Dumurgier et al., 2010; Hausdorff et al., 2005), we hypothesized that exposure to cadmium may be a risk factor affecting poor physical performance in older adults. Both blood and urine cadmium are biomarkers of ongoing and long-term exposure, although blood cadmium more readily reflects biologically active cadmium (recent exposure) than does urine cadmium (Nordberg et al., 2007). We therefore examined the association of blood and urine cadmium concentrations with walking speed in a representative U.S. sample of middle-aged and older adults who participated in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2002, while controlling for important potential confounding factors including demographic, anthropometric, behavioral, and clinical factors and inflammation markers.

2. Methods

2.1. Study population

NHANES is an ongoing cross-sectional survey of a nationally representative U.S. population conducted by the CDC's National Center for Health Statistics. The survey includes an initial extensive interview at home with a subsequent physical examination and additional interviews at a mobile examination center (MEC) (CDC, 2000).

The present analysis used data from NHANES 1999–2002 with the time to walk 20 feet measured in participants 50 years or older. Survey participants who were not able to walk alone without holding onto someone, were excluded from the timed walk component, or who had a history of chest or abdominal surgery within the prior three weeks, myocardial infarction within the prior six weeks, knee surgery, severe back pain, or a history of brain aneurysm or stroke (CDC, 2002); the initial sample eligible for a timed walk examination was 4449 participants. From these, we excluded participants with unavailable measures on walking speed ($n = 489$), as well as those who used assistive devices during walking speed measures ($n = 169$), or who had unreliable high walking speed of >6 ft/s ($n = 4$), yielding 3787 participants. Of those 3787 adults eligible for evaluation of walking time, 3671 and 1157 adults had cadmium measures in blood and urine, respectively. After further excluding participants with missing data for covariates listed in Table 1, a total of 3226 and 1003 adults were eligible for analyses of blood and urine cadmium, respectively.

2.2. Walking speed

Time to complete a 20-ft walk test was measured by certified health technicians intensively trained in NHANES examination protocols (CDC, 2002, 2004). Participants were asked to walk 20 feet at their usual pace, and the time to walk was recorded using a hand-held stopwatch. Timing begun when the participant's foot first touched the floor beyond the start line; stop time was obtained when the foot first touched the floor beyond the 20-ft finish line (CDC, 2000). This method of measuring walking speed was previously proved to have test-retest reliability (Studenski et al., 2003). We computed walking speed (ft/sec) by dividing the walked distance (20 ft) by measured time to walk (seconds).

2.3. Cadmium concentrations in blood and urine

Whole blood and spot urine specimens were processed, were frozen at −20 °C, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, CDC (Atlanta, GA, USA) for analysis (CDC, 2001). Blood cadmium concentrations were measured using a simultaneous multi-element atomic absorption spectrometer (model SIMMA 6000; PerkinElmer, Norwalk, CT, USA) with Zeeman background correction. The limit of detection (LOD) for blood cadmium concentrations was 0.3 μg/L (CDC, 2015); blood cadmium concentrations were below the LOD in 14.07% of the study participants. The interassay coefficients of variation ranged between 4.1% and 9.4%. Urine cadmium concentrations were measured using inductively coupled plasma mass spectrometry (model PerkinElmer/SCIEX 500, PerkinElmer, Norwalk, Connecticut) (CDC, 2003). The LOD for urine cadmium concentrations was 0.06 ng/mL; urine cadmium concentrations were below the LOD in 3.78% of the study participants. The interassay coefficients of variation ranged between 1.2% and 4.7%. For blood and urine cadmium levels below the LOD, NHANES reported a value equal to the $LOD/\sqrt{2}$.

2.4. Other covariates

We used a number of variables as confounding factors: demographic information (age, sex, race/ethnicity, and education level), anthropometric measurements (height and weight), health-related behaviors (physical activity, alcohol consumption, and cumulative cigarette smoke), clinical factors (hypertension, diabetes, arthritis, and cardiovascular disease (CVD)), and serum biomarkers of inflammation (C-reactive protein and homocysteine).

Race/ethnicity was categorized as Non-Hispanic White, Non-Hispanic Black, Mexican American, and Other. Education level was categorized as <high school, high school, and >high school. Cumulative cigarette smoke was categorized as never, <20 and ≥20 cumulative cigarette pack-years. Alcohol consumption was categorized as never, <1 and ≥1 day per week. Physical activity was self-reported for moderate-to-vigorous leisure-time activities performed over the previous 30 days; metabolic equivalents per week (METs-hours/week) were computed based on the total volume of physical activity intensity and frequency (Ainsworth et al., 1993). Physical activity was categorized as <7.5, 7.5–21, and >21 METs-hours/week (Haskell et al., 2007; US Institute of Medicine, 2002). Definition of hypertension was based on a self-reported physician diagnosis, current use of anti-hypertensive medication, or a clinical blood pressure reading ≥140/≥90 mmHg. Definition of type 2 diabetes mellitus was based on a self-reported physician diagnosis or current use of anti-hyperglycemia medication (Bainbridge et al., 2008). Arthritis was defined as self-reported physician diagnosis. CVD was defined as a self-reported presence in any one of following diseases: coronary heart disease, congestive heart failure, heart attack, or angina/angina pectoris. Because of their reported association with lower walking speed, we controlled our analyses for plasma concentrations of C-reactive protein and homocysteine (Kuo et al., 2007). Because walking speed may be directly affected by height through a long stride, we controlled for measured height

Please cite this article in press as: Kim, J., et al., Blood and urine cadmium concentrations and walking speed in middle-aged and older U.S. adults, Environmental Pollution (2017), http://dx.doi.org/10.1016/j.envpol.2017.09.022