Environmental Research 147 (2016) 356–364

Contents lists available at ScienceDirect

Environmental Research

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

Metal mixtures in urban and rural populations in the US: The Multi-Ethnic Study of Atherosclerosis and the Strong Heart Study ☆

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ARTICLE INFO

Article history:
Received 28 December 2015
Received in revised form
22 February 2016
Accepted 24 February 2016

Keywords:
Metals
Urine
Biomarker
Statistical methods
Exposure sources

ABSTRACT

Background: Natural and anthropogenic sources of metal exposure differ for urban and rural residents. We searched to identify patterns of metal mixtures which could suggest common environmental sources and/or metabolic pathways of different urinary metals, and compared metal-mixtures in two population-based studies from urban/sub-urban and rural/town areas in the US: the Multi-Ethnic Study of Atherosclerosis (MESA) and the Strong Heart Study (SHS).
Methods: We studied a random sample of 308 White, Black, Chinese-American, and Hispanic participants in MESA (2000–2002) and 277 American Indian participants in SHS (1998–2003). We used principal component analysis (PCA), cluster analysis (CA), and linear discriminant analysis (LDA) to evaluate nine urinary metals (antimony [Sb], arsenic [As], cadmium [Cd], lead [Pb], molybdenum [Mo], selenium [Se], tungsten [W], uranium [U] and zinc [Zn]). For arsenic, we used the sum of inorganic and methylated species (∑As).
Results: All nine urinary metals were higher in SHS compared to MESA participants. PCA and CA revealed the same patterns in SHS, suggesting 4 distinct principal components (PC) or clusters (∑As-U-W, Pb-Sb, Cd-Zn, Mo-Se). In MESA, CA showed 2 large clusters (∑As-Mo-Sb-U-W, Cd-Pb-Se-Zn), while PCA showed 4 PCs (Sb-U-W, Pb-Se-Zn, Cd-Mo, ∑As). LDA indicated that ∑As, U, W, and Zn were the most discriminant variables distinguishing MESA and SHS participants.
Conclusions: In SHS, the ∑As-U-W cluster and PC might reflect groundwater contamination in rural areas, and the Cd-Zn cluster and PC could reflect common sources from meat products or metabolic

Abbreviations: ∑As, the sum of inorganic and methylated species; As, arsenic; CA, cluster analysis; Cd, cadmium; CKD-EPI, the Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ICPMS, inductively coupled plasma mass spectrometry; LDA, linear discriminant analysis; LOD, limits of detection; MESA, the Multi-Ethnic Study of Atherosclerosis; Mo, molybdenum; Pb, lead; PC, principal component; PCA, principal component analysis; Sb, antimony; Se, selenium; SHS, the Strong Heart Study; Zn, zinc; U, uranium; W, tungsten

☆MESA was supported by contracts N01-HC- 95159 through N01-HC-95167, N01-HC-95169, and R01-HL077612 from the National Heart, Lung, and Blood Institute (NHLBI). SHS was supported by grants HL41642, HL41652, HL41654 and HL65521 from NHLBI. Metal analyses in SHS and MESA were supported by R01HL090863 from NHLBI and by R01ES021367 from the National Institute of Environmental Health Sciences. M. R. Jones was supported by a National Cancer Institute (NCI) National Research Service Award (T32CA009314).The MESA study protocols were approved by each field center's institutional review board. The Strong Heart Study protocol was approved by the Institutional and Indian Health Service Review Boards and the participating American Indian communities.

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http://dx.doi.org/10.1016/j.envres.2016.02.032
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interactions. Among the metals assayed, ∑As, U, W and Zn differed the most between MESA and SHS, possibly reflecting disproportionate exposure from drinking water and perhaps food in rural Native communities compared to urban communities around the US.

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1. Introduction

Exposure to metals is widespread in the environment. Experimental and epidemiologic evidence support a role for low-to-moderate chronic exposure to certain toxic metals in the development of cardiovascular disease, kidney disease, morbid neurocognitive outcomes and some cancers (Hu, 2000; Navas-Acien et al., 2005, 2009a). Urinary biomarkers are commonly used to assess metal exposure and internal dose as they integrate multiple exposure sources including air, water and food (Aitio et al., 2007). Metals in urine might be related to each other due to common environmental sources or to similarities in metabolism. Multivariate analysis, including principal component analysis (PCA) and cluster analysis (CA), is widely used in environmental research to identify metal sources in air, soil and water (Lee et al., 2006; Loska and Wiechuła, 2003; Yongming et al., 2006) and to describe underlying patterns of metal biomarkers (Basu et al. 2011; Nowak, 1998; Wang et al., 2009). By reducing the initial dimension of the variables (Everitt et al. 2011; Hotelling, 1933), these methods can facilitate interpretation and identification of common sources and metabolic pathways for urinary metals.

Few studies have evaluated common sources of metal exposures in general populations, as most studies on metal-mixtures have focused on occupationally-exposed populations or populations living in contaminated areas (Basu et al. 2011; Nowak, 1998; Wang et al., 2009). Urban or rural residency might be an important source of variation in metal exposures as natural and anthropogenic sources could differ. While it is often assumed that urban areas are more contaminated than rural areas due to the high number of potential sources (Davis et al., 2009; Diamond and Hodge, 2007), some rural communities can sometimes be affected by important contamination (Carpenter, 2014; Hoover et al., 2012). Compared with urban areas, groundwater sources contaminated with naturally occurring metals are more commonly used for drinking water in rural and sub-urban areas [U.S. Environmental Protection Agency (USEPA, 2015)]. Sociocultural factors could also influence differences in metal exposure across different communities and ethnic/racial groups.

Our study population was drawn from two separate cohorts, American Indian participants in the Strong Heart Study (SHS) residing in rural areas and towns of Arizona, Oklahoma, and North/South Dakota, and White, Black, Hispanic, and Chinese-American participants in the Multi-Ethnic Study of Atherosclerosis (MESA) residing in urban and sub-urban areas of Baltimore, MD; Chicago, IL; Los Angeles, CA; New York, NY; St. Paul, MN; and Winston-Salem, NC. Both studies are funded by the National Heart, Lung, and Blood Institute. The communities and ethnic groups included in the study were selected with their main goal of evaluating cardiovascular disease and its risk factors in diverse populations around the United States.

Our objective was to characterize metal-mixtures in urine and identify patterns of metal mixtures which could suggest common environmental sources and/or metabolic pathways of different urinary metals in MESA and SHS. In addition to PCA and CA, we used linear discriminant analysis (LDA) to determine which metal(s) differed the most between MESA and SHS, as well as between different US regions and race/ethnic groups. To evaluate the consistency of the metal patterns across different communities, we compared the principal component (PC) score levels in each study area. We specifically hypothesized that arsenic, uranium and tungsten would cluster together due to common exposure from contaminated groundwater in the Southwestern and Midwestern States (McMahon et al., 2015; Salinas and Ingram, 2005). Understanding patterns of metal-mixtures in US communities could help to identify sources of metal exposures and to guide future assessment of the health implications of metal-mixtures.

2. Methods

2.1. Study population

MESA is a population-based cohort study evaluating cardiovascular disease and its risk factors in participants aged 45–84 years who were free of cardiovascular disease at baseline (2000–2002) in 6 urban and sub-urban communities in the United States (Bild et al., 2002). We recently measured baseline urinary metal concentrations in an overall sample of 310 participants from the 6 study sites (90 White, 75 Black, 75 Hispanic, and 70 Chinese American participants). These 310 participants were selected using random stratification by site and race group with a predetermined distribution of participants per race and site to ensure sufficient numbers for stratified analyses. The selected sample size was also based on funding available. We excluded 2 participants with abnormal levels of tungsten in urine (37.5 and 230.0 times higher than the 90th percentile), leaving a total of 308 participants for this analysis.

The SHS is a population-based cohort study of cardiovascular disease and its risk factors in 13 rural American-Indian communities (reservations and small towns) from Arizona, Oklahoma, and North/South Dakota that started in 1989–1991 (North et al., 2003). The names of the tribes are not provided following the desire of the communities. In 1998–2003, relatives of the original SHS participants were recruited into a family study that included 96 extended families (Arizona, 33; Oklahoma, 36; and North/South Dakota, 27) totaling 3665 participants from all three centers ranging in age from 14 to 93 years. Urinary metals were measured in 2456 of these participants as part of an ancillary study to evaluate gene-environment interactions for diabetes and the metabolic syndrome. Among them, we randomly sampled three individuals from each family within the same age range as MESA participants. Urinary metals were measured in 95 of 96 families. One family had only one individual within the MESA participant age range and six additional families had only two participants, resulting in a total of 277 participants for this analysis. The rationale for selecting up to three family members per family was to obtain a balanced sample size between SHS and MESA. Sensitivity analyses were conducted to confirm similar results by selecting one single family member per family.

The MESA study protocols were approved by each field center's institutional review board. The Strong Heart Study protocol was approved by the Institutional and Indian Health Service Review Boards and the participating American Indian communities. All the participants provided oral and written informed consent.

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