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Temporal stability of urinary cadmium in samples collected several years apart in a population of older persons

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ABSTRACT

Objectives: There is growing evidence that urine cadmium is a temporally stable biomarker indicative of long-term cadmium exposure; however questions remain with regard to generalizability to older persons, the impact of changes in smoking behavior, and the degree of temporal stability when repeat sample collection spans years instead of weeks or months.

Methods: Using archived samples from cohorts of older men (Osteoporotic Fractures in Men (MrOS-US)) and women (Study of Osteoporotic Fractures (SOF)) (mean age = 80 at study visit 2), we analyzed two morning urine samples each from 39 men and 18 women with a diverse self-reported smoking history. For MrOS, samples were collected approximately 6 years apart, and 4 years apart for SOF. Intra-class correlations were computed to assess temporal stability, and adjusted for age and body mass index.

Results: The median creatinine-adjusted urinary cadmium levels (0.39 μg/g for men, 0.89 μg/g for women) were similar to levels expected for these age/sex groups in the US according to the National Health and Nutrition Examination Survey. The overall intra-class correlation was high (ICC = 0.85; 95% CI: 0.76–0.91) and similar between cohorts (MrOS: ICC = 0.74; 95% CI: 0.58–0.86; SOF: ICC = 0.81; 95% CI: 0.59–0.93), but slightly lower among those who stopped smoking between visits of sample collection (ICC = 0.64; 95% CI: 0.31–0.87) or among former smokers who quit prior to the first sample collection (ICC = 0.68; 95% CI: 0.25–0.93).

Conclusions: We report good-to-excellent reproducibility of urine cadmium using morning urine samples collected 4–6 years apart from older men and women, but slightly lower correlations among those with a history of smoking. Single measures of urine cadmium are a reliable biomarker in older men and women.

1. Introduction

Cadmium is a natural element heavily used in industrial activities that is also often found in phosphate-based fertilizers (ATSDR, 2012). Cadmium is a known risk factor for kidney disease and lung cancer, among other outcomes (ATSDR, 2012). Human exposure to cadmium has increased over the past several hundred years; for example, levels in human bones from the 20th century are about 10 times above pre-industrial levels (Jaworowski et al., 1985). Most common pathways of human exposure are via inhalation of cigarette smoke, and ingestion of a wide range of foods, including leafy vegetables, rice, meats, and organs (Egan et al., 2007; Olsson et al., 2005). Following exposure, much of the cadmium accumulates in the kidney, and levels in urine have been shown to be proportional to levels in the kidney (Nordberg, 2009). Therefore, urinary cadmium (U−Cd) levels are often considered to be an indicator of long-term exposure (Nordberg, 2009). In the realm of environmental exposure biomarkers, an easy-to-collect biomarker that is indicative of long-term exposure is rare and merits careful scrutiny.

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We recently reviewed the U−Cd biomarker (Vacchi-Suzzi et al., 2016) and reported an intraclass correlation coefficient (ICC) for creatinine corrected U−Cd (U-Cd_{cr}) of 0.66–0.81 in studies which indicated use of interference correction strategies in the analytical method (Akerstrom et al., 2014; Arisawa et al., 1997; Sanchez-Rodriguez et al., 2015; Smolders et al., 2014; Vacchi-Suzzi et al., 2017). While there was no clear difference whether the samples in those studies were spot urines, from first morning voids, or from different time intervals ranging from weeks to months to 3 years, these studies did not include older persons where changes in kidney function may be more likely to impact temporal stability of urine biomarkers. Furthermore, no studies have accounted for changes in habits such as smoking behaviors that could affect the measurement. Therefore, consideration of temporal stability of U-Cd_{cr} in subsets of the population is merited, along with an assessment of the stability when samples are collected more than three years apart.

Two recent ecologic studies suggest U-Cd_{cr} may decrease after ceasing smoking, although individual-level data were not available. Sanchez-Rodriguez et al. (2015) report that a year after a public smoking ban went into effect, non-smokers exhibited a median drop in U-Cd_{cr} of 0.07 μg/g, with 76% of participants showing a drop in U-Cd_{cr}. Adams and Newcomb (2014) modeled cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) and estimated that U−Cd drops 23% in the first year after quitting smoking among 55 year old men with 20 pack years of smoking history.

In this small study of 57 individuals aged 65 and older from two cohorts (MrOS (Osteoporotic Fractures in Men) and SOF (Study of Osteoporotic Fractures)), we examine temporal stability of UCd_{cr} across and within four groups: current smokers, former smokers, never smokers, and those who stopped smoking between visits of data collection. Average duration between visits was 6 years for the MrOS samples, and 4 years for the SOF samples.

2. Methods

Participants were randomly selected from the MrOS and SOF cohorts based upon having available urine samples and history of smoking behaviors. The parent study protocols were approved by the institutional review boards at each study site, and written informed consent was obtained from all participants. This study received approval from the Stony Brook University institutional review board.

2.1. MrOS sample

The Osteoporotic Fractures in Men (MrOS) prospective cohort study follows ambulatory men ≥ 65 years of age (n = 5994) at six U.S. clinics (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA) (For detailed information see the MrOS website: http://mrosdata.sfcc-cpmc.net). Enrollment in MrOS took place from March 2000 through April 2002, at which time men had to be 65 years of age or older. Between 2003 and 2005, 3135 of the MrOS participants were recruited to participate in an ancillary study on sleep (MrOS Sleep) and from 2009 to 2012, 1055 participants returned for a second sleep visit. More information on the MrOS parent study (Blank et al., 2005; Orwoll et al., 2005) and details of the inclusion/exclusion criteria for sleep visits (Blackwell et al., 2011; Smagula et al., 2017) have been published previously. Participants from both sleep visits completed questionnaires on demographic factors and smoking history (including cigarettes, cigars, and pipes), and provided first morning urine samples following overnight fasting that we use in this study (Devore et al., 2016). Among those with urine samples from both sleep visits, we randomly selected 10 current smokers, 10 former smokers, 10 never smokers, and all 9 individuals who had stopped smoking between visits.

2.2. SOF sample

Ambulatory women were enrolled in the Study of Osteoporotic Fractures (SOF), a multicenter, prospective cohort study of primarily Caucasian, community-dwelling women aged 65 years and older from 4 geographic areas (Portland, OR; Minneapolis, MN; Pittsburgh, PA; Baltimore, MD) from 1986 to 1988 (For detailed information see the SOF website: https://sofonline.epi-ucsf.org/interface/). The 9704 participants comprising the original cohort were subsequently invited to participate in 9 principal follow-up visits with high rates of participation among survivors (> 95%). A detailed description of this study was published previously (Cummings et al., 1993; Ensrud et al., 2007). The current study included women participating in SOF visit 4 (1992–1994) and SOF visit 6 (1997–1998). Participants from both visits completed questionnaires on demographic factors and smoking history (including cigarettes, cigars, and pipes), and provided morning urine samples following overnight fasting that we use in this study. Visit 4 samples included first morning voids or morning spot urine samples; visit 6 samples included timed morning samples which are comprised of an aggregate of all urine collected over a 2 h window. Among those who provided urine at both visits, we randomly selected 10 current smokers, 15 former smokers, 10 never smokers, and 15 individuals who stopped smoking between visits. However, because of challenges in locating untreated urine from some participants from visit 4, we report data on 5 current, 6 former, 6 never, and 1 woman who stopped smoking between visits.

2.3. Cadmium and creatinine measurement

Once collected, all urine samples were stored at −80 °C until the time of study. U−Cd was measured by inductively coupled plasma mass spectrometry (ICP-MS) by the Trace Inorganics Laboratory at RTI International (RTP, NC) as described previously (Vacchi-Suzzi et al., 2017). In brief, urine samples were prepared for analysis on a graphite heating block digestion with high purity nitric and hydrochloric acids (Thermo Fisher Scientific, Waltham, MA). Measurements were performed on a Thermo iCAP Q ICP-MS equipped with a Peltier-cooled cyclonic spray chamber and collision cell technology (CCT) with He gas to allow exclusion of analytical interferences. Throughout the processing of each analytical batch, acid-matrix matched quality control samples were analyzed to monitor continued instrument stability. QC sets were considered to be passing if the measured concentration for all elements was found to be within ± 15% of the nominal concentration (0.25 ng/mL for Cd). The National Institute of Standards and Technology (NIST) standard reference material (SRM) 2668 (Toxic Elements in Frozen Human Urine) was prepared with each analytical batch and analyzed for all elements at high level concentrations. The certified concentration of cadmium in the high level SRM is 16.40 ng/mL (1.640 in the digested samples) to provide an indicator of method performance. Over several batches analyzed on different days, the average percent recovery of the SRM was 105%. These results indicate strong recovery of standard reference material samples and accurate analytical results for cadmium.

U−Cd limit of detection (LOD) ranged between 0.002 and 0.003 μg/L across analytic batches, and the limit of quantification (LOQ) was 0.125 μg/L. U−Cd was above the LOD in all samples. In 21% of the samples from MrOS and 6% of the samples from SOF U−Cd was measured below the level of quantification (LOQ). Because all samples were above the LOD, all values below the LOQ were included as reported in the analysis.

To help correct for differences in urine concentration, urinary creatinine concentrations were quantified using a Cayman Chemicals Creatinine Assay Kit No. 500701 (Cayman Chemicals, Ann Arbor, MI, USA) with UV-VIS measurement at 500 nm employing a Beckman Coulter DU800 UV/VIS Spectrometer (Beckman Instruments Inc., Brea, CA, USA).

Nineteen percent of samples were randomly selected from all batches and re-tested for Cd, and all samples were retested for creatinine to verify the accuracy of analytical results. Average percent difference between re-tested samples was 3.5% for Cd and 7.7% for creatinine, with the vast majority within 10%.

Two women had creatinine levels (118 mg/L, 119 mg/L) that fell outside the 2.5–97.5% percentile ranges measured in a 45,000 person cohort (129–2690 mg/L); no men had creatinine levels outside this range (Arndt, 2009). Analyses were run with and without these two female participants and results remained essentially unchanged.

2.4. Statistical analysis

The difference in U-Cd_{cr} between visits was expressed using the mean change and interquartile range (IQR) in U-Cd_{cr} between visits. A paired T-test was used to compare means across visits within the same cohort. ICC was calculated according to Shrout and Fleiss (1979), with ICC defined as in eq. (1), where σ_b^2 and σ_w^2 are the between-individual variance and the within-individual variance, respectively.

$$ICC = \frac{\sigma_b^2}{\sigma_b^2 + \sigma_w^2} \quad (1)$$

ICC was calculated across the repeat samples for all 57 participants, adjusted for age and body mass index, as well as stratified by sex, smoking history, and change in time of day of urine collection. In accordance with the criteria presented by Rosner (2002), we considered the reproducibility to be good when $0.40 \leq ICC < 0.75$, and excellent when $ICC \geq 0.75$. All statistical analyses were performed using SAS 9 (Cary, NC). To calculate ICC, we used a SAS 9 macro that allows for covariate adjustment (Hertzmark, 2010).

3. Results

Demographic characteristics are summarized in Table 1 for the 39 men from MrOS and 18 women from SOF. Both cohorts had a mean age of 80 at the time the second urine sample was collected. Levels of U−Cd fall in the expected range for this age group per NHANES [12]. Mean U-Cd_{cr} did not differ between visits (p = 0.43 for MrOS, p = 0.90 for SOF) but the mean U-CD_{cr} was more than twice as high for SOF women (0.89–0.90) as for MrOS men (0.37–0.39) in both visits. For MrOS the SD of U-Cd_{cr} was 0.26, and the range was from 0.04 to 1.21 μg/g for both visits combined; for SOF, the SD was 0.51 with a range from 0.25 to 2.20 μg/g for both visits combined.

Table 1
Demographic characteristics. Sample size, means and standard deviations are reported unless otherwise noted.

	Men (MrOS)	Women (SOF)
N	39	18
Smoking history		
Never	10	6
Former	10	6
Current	10	5
Stopped between Study Visits 1 and 2	9	1
Age at Study Visit 2 [years (min.-max.)]	80 (75–90)	80 (75–87)
Study Visit 1		
U−Cd (μg/L) ± SD	0.41 ± 0.33	0.40 ± 0.29
Creatinine (g/L) ± SD	1035 ± 482	530 ± 332
U-Cd_{cr} (μg/g) ± SD	0.39 ± 0.26	0.89 ± 0.51
Body Mass Index (kg/m^2) ± SD	27.6 ± 3.9	26.6 ± 7.0
Study Visit 2		
U−Cd (μg/L) ± SD	0.37 ± 0.33	0.42 ± 0.29
Creatinine (g/L) ± SD	1013 ± 480	541 ± 331
U-Cd_{cr} (μg/g) ± SD	0.37 ± 0.26	0.90 ± 0.51
Body Mass Index (kg/m^2) ± SD	27.6 ± 3.9	26.6 ± 6.4

For MrOS, Study Visit 1 took place 2003–2005 and Study Visit 2 2009–2012. For SOF, Study Visit 1 took place 1992–1994 and Study Visit 2, 1997–1998.

Table 2
Median change in U-Cd_{cr} between visits and intra-class correlation coefficient (ICC, 95% confidence interval (CI)) overall and for different strata. All ICC models were adjusted for body mass index and age at the time of visit.

	N	Median change in U-Cd_{cr} (μg/g) (IQR)	ICC (95% CI)
All	57	−0.02 (−0.10, 0.06)	0.85 (0.76–0.91)
Sex			
Males (MrOS)	39	−0.02 (−0.05, 0.03)	0.74 (0.58–0.86)
Females (SOF)	18	+0.04 (−0.18, 0.28)	0.81 (0.59–0.93)
Smoking History			
Never Smokers	16	−0.03 (−0.05, 0.00)	0.82 (0.61–0.93)
Former Smokers	16	+0.00 (−0.09, 0.07)	0.64 (0.31–0.87)
Current Smokers	15	+0.03 (−0.14, 0.18)	0.89 (0.74–0.96)
Stopped Smoking Between Visits	10	−0.02 (−0.16, 0.04)	0.68 (0.25–0.93)
Difference in Time of Day of Sample Collection Between Visits[a]			
≤ ½ hr	14	−0.00 (−0.10, 0.02)	0.81 (0.57–0.94)
½ hr – 2 h	15	+0.01 (−0.05, 0.07)	0.61 (0.30–0.86)
2–3 h	9	−0.03 (−0.05, 0.00)	0.90 (0.69–0.97)

Study Visits are approximately 6 years apart for MrOS (males) and 4 years apart for SOF (females).

[a] Only available for MrOS (Males), one sample was missing data. All samples were collected in the morning.

Table 2 summarizes the differences in U-Cd_{cr} across study visits 1 and 2 overall and stratified by smoking history or change in time of day of sample collection between visits. Median and IQR differences across visits are small and not statistically significant. Also listed are ICCs for U-Cd_{cr} across repeat visits. Overall ICC = 0.85, with ICC = 0.74 for men and ICC = 0.81 for women. ICC ranged from 0.64 to 0.89 across strata of smoking histories with confidence intervals overlapping for the four smoking groups:. ICC = 0.64 (95% CI: 0.31–0.87) for former smokers, ICC = 0.68 (95% CI: 0.25–0.93) for those who stopped smoking between visits, ICC = 0.82 (95% CI: 0.61–0.93) for never smokers, and ICC = 0.89 (95% CI: 0.74–0.96) for current smokers at both visits. For MrOS, time of day of sample collection was also recorded, and there were some differences in ICC depending on the amount of change in the time of day of sample collection between visits (ICCs ranged 0.61–0.90) although again with overlapping confidence intervals. Even for the group with the smallest ICC = 0.61 (with changes in the time of sample collection between ½ to 2 h), the paired *t*-test across the two study visits yields t = 0.08 and p = 0.94, indicating there is only a small difference in U-Cd_{cr} across the two study visits.

4. Discussion

We report small changes in creatinine corrected urinary cadmium levels in older men from MrOS sampled approximately six years apart, and in older women from SOF sampled roughly four years apart. The overall median change in U-Cd_{cr} was −0.02 μg/g with an IQR from −0.10 to 0.06, with similar small changes in the median U-Cd_{cr} in strata defined by sex, smoking history, or time of day of sample collection. Similarly, the ICC was good-to-excellent for all strata, which is even more notable given the samples are from two separate cohorts collected 10–15 years apart. This indicates a one-time measure of U-Cd_{cr} is a stable measure in older men and women, with only small differences based on smoking history.

Women tend to have higher levels of U-Cd_{cr} than men, both because of lower creatinine levels in women, and because iron deficiency, which is more common in women during their child-bearing years, contributes to greater absorption of cadmium into the blood and accumulation into the kidneys (Berglund et al., 1994; Kippler et al., 2007). Mean U-Cd_{cr} was more than twice as high in SOF women compared with MrOS men in our study. The median change in U-Cd_{cr} between visits was small, −0.02 for MrOS men and +0.04 for SOF women, but the IQR was much wider for women (−0.18, 0.28) than for men (−0.05, 0.03).

Nonetheless, the ICC was high for both men (0.75) and women (0.81). Thus, even though the U-Cd_{cr} levels were quite different between MrOS men and SOF women, the changes in values between visits were quite small and ICCs were near excellent for both groups.

With respect to smoking history, however, the story is a little different. All smoking strata showed small changes in U-Cd_{cr} between visits, with the ICC being strongest among current smokers (0.89) and never smokers (0.82), and lower among former smokers (0.64) and those who stopped smoking between visits (0.68), although all confidence intervals overlapped. As would be expected, never smokers had the lowest levels (0.41 μg/g) followed by former smokers (0.60 μg/g) and then those who stopped smoking between visits (0.65 μg/g), and finally current smokers (0.67 μg/g). A recent ecologic study suggested that non-smokers showed a median drop in U-Cd_{cr} of 0.07 μg/g a year after a public smoking ban went into effect (Sanchez-Rodriguez et al., 2015); Adams and Newcomb (2014) modeled cross-sectional NHANES data and estimated that U−Cd drops 23% in the first year after quitting smoking among 55 year old men with 20 pack years of smoking history. In our study, for those who stopped smoking between visits, we observed a mean drop of 0.02 μg/g and a median drop of 0.03 μg/g, yet 40% of the individuals displayed a small increase in U-Cd_{cr}. The increase could be a reflection of former smokers who may not have completely quit smoking. Overall however, our data suggest that U-Cd_{cr} levels may drop slightly after stopping smoking and it is plausible that the rate of decline of U-Cd_{cr} in older persons might be expected to be slower than that observed in younger individuals who generally stop smoking after a shorter smoking history. However, we did not observe a large change in U-Cd_{cr} and the ICC is still good (0.68) among these individuals and comparable to that among former smokers (0.64).

To our knowledge there are seven studies (Akerstrom et al., 2014; Arisawa et al., 1997; Gunier et al., 2013; Sanchez-Rodriguez et al., 2015; Smolders et al., 2014; Vacchi-Suzzi et al., 2017; Wang et al., 2015) that have examined the temporal stability of U-Cd_{cr}, and they reported intra class correlation (ICC) coefficients which ranged from 0.42 to 0.89. One potential difference between studies was whether or not they corrected for prevalent interferences by molybdenum oxide or tin (Jarrett et al., 2008). When we only included those studies that specified an attempted correction of polyatomic interferences when it may have been a concern, the range of ICC values narrows to 0.66–0.89, with no clear difference whether the samples were spot urine or first morning void or whether the time interval between samples was months or a few years (Akerstrom et al., 2014; Arisawa et al., 1997; Sanchez-Rodriguez et al., 2015; Vacchi-Suzzi et al., 2017). In this study we report a range of ICCs from 0.61 to 0.90, consistent with the range seen in the literature, indicating that samples collected up to 6 years apart in older individuals with varied smoking histories and varied urine collection protocols are similarly stable. Given that Cd levels in urine are proportional to levels that have accumulated in the kidney and U−Cd is considered to be an indicator of long-term exposure (Nordberg, 2009), these studies show this biomarker to be quite useful for environmental epidemiologic studies, even at levels of exposure quite common in the population at large.

This study has distinct strengths and a few limitations. Samples were collected from 2 separate populations of older men and women across different decades. The levels of U-Cd_{cr} are within the range expected for the general population indicating that observations from this study have wide generalizability. The laboratory analysis was performed with consumables that were screened to minimize potential contamination and the analysis method included numerous quality control samples to provide confidence in the accuracy of results both within and between analytical batches. Despite those strengths, there are also some potential areas for future optimization. First, we were unable to measure markers of kidney function (such as glomerular filtration rate or low-molecular protein excretion) or directly determine levels of Cd accumulated in the kidneys. Changes in urinary function (urinary flow rate with or without body weight adjustment) or kidney function can influence biomarker concentrations such as urinary cadmium concentration (Hays et al., 2015; Weaver et al., 2011). It is possible that these factors may contribute to the observed temporal variability in the U-Cd_{cr} levels of some individuals, although creatinine correction should help mitigate this concern; also the small degree of temporal variability suggests this is not a major limitation here. Sample size was small in some of the stratified analysis and this factor may also have contributed to some of the variability in the ICC values. It was also not possible to collect a 24 h urine sample to compare with the urine samples available. However, few epidemiologic cohorts include 24 h urine samples in their biobanks, justifying our focus on first morning void, morning spot, or 2 h timed urine samples.

In conclusion, we report good-to-excellent reproducibility of urine cadmium using morning urine samples collected 4–6 years apart from older men and women. Slightly lower reproducibility was observed among those with a history of smoking and those results merit additional investigation. Single measures of urine cadmium are a reliable biomarker in older men and women.

Conflicts of interest

Authors declare no conflicts of interest, financial or otherwise.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2018.10.005.

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