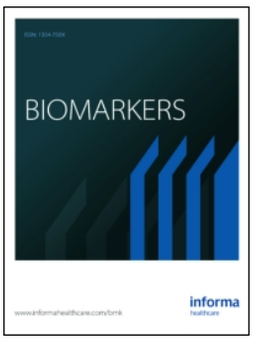

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RESEARCH ARTICLE

A cross-sectional survey of cadmium biomarkers and cigarette smoking

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ABSTRACT

Cadmium contamination of tobacco may contribute to the health hazards of cigarette smoking. The 2005–2012 United States National Health and Nutrition Examination Survey data provided a unique opportunity to conduct a cross-sectional survey of cadmium biomarkers and cigarette smoking. Among a sample of 6761 participants, we evaluated mean differences and correlations between cadmium biomarkers in the blood and urine and characteristics of never, former and current smokers. We found statistically significant differences in mean cadmium biomarker levels between never and former smokers as well as between never and current smokers. In current smokers, duration in years had a higher correlation coefficient with urinary than blood cadmium levels. In contrast, number of cigarettes smoked per day had a higher correlation coefficient with blood than urinary cadmium levels. These data suggest that blood and urine cadmium biomarker levels differ by duration and dose. These findings should be considered in evaluating any association between cadmium and smoking related diseases, especially cardiovascular disease.

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Introduction

An unintended consequence of cigarette smoking is exposure to cadmium, a metal carcinogen associated with various illnesses including lung cancer, chronic obstructive pulmonary disease, cardiovascular disease, renal dysfunction and bone disease (Jarup & Akesson, 2009).

The most common sources of human exposure to cadmium in the general population are food ingestion, cigarette smoke inhalation and occupational exposure to airborne cadmium particles (Jarup et al., 1998). Rats exposed to cadmium enriched cigarette smoke experienced significantly higher cadmium blood levels as compared to their cage control counterparts (Piascik et al., 1985). Recently, a New York City based cross-sectional heavy metal biomonitoring study of the general population found cigarette smoking to be the factor most strongly associated with increases in blood cadmium (McKelvey et al., 2007). Laboratory surveillance from the National Health and Nutrition Examination Survey (NHANES; www.cdc.gov/nchs/nhanes.htm) has also demonstrated significant increases in cadmium levels in blood and urine in smokers and former smokers (Richter et al., 2009; Tellez-Plaza et al., 2010). In a meta-analysis of non-US, cross-sectional studies, cigarette smokers had significantly higher blood levels of cadmium than non-smokers, and the amount currently smoked was highly correlated with blood cadmium levels ($r = 0.54$, $p < 0.01$) (Hecht et al., 2013).

Each cigarette contains approximately 1 μg of cadmium, 25–35% of which is absorbed into the bloodstream (Jarup et al., 1998; Nordberg & Nordberg, 1988; Travis & Haddock, 1980). Following exposure and absorption, cadmium accumulates throughout the body in different fluids and tissues including breast milk, semen, liver, kidney, lung, prostate, testicles, the optic lens and the medial layers of the aorta, where it may initiate inflammatory processes or interfere with function of other biological ions including calcium and iron (Abu-Hayyeh et al., 2001; Drasch et al., 2005; Kiziler et al., 2007; Mosad et al., 2010; Saaranen et al., 1989; Siu et al., 2009; Telisman et al., 2000). Exposure thresholds for organ toxicity have been studied in occupational settings that have evaluated proteinuria as an indicator of kidney toxicity. In this setting, it has been estimated that 50 μg/day of exposure resulting in 0.5 and 3 μg cadmium/g creatinine is a threshold that can result in adverse effects on kidney function. Toxicity thresholds in other organs and tissues in humans are less well studied but similar thresholds have been observed for effects on bone (Jarup & Akesson, 2009). Since there is no naturally occurring biological elimination pathway for cadmium, it has been estimated to have a biological half-life of 14–23 years (Friberg et al., 1985; Suwazono et al., 2009).

The most commonly used measures of cadmium exposure are urinary and blood levels (Skoczynska & Smolik, 1994). Toxico-kinetic studies performed in occupational settings, such as metallurgic factories, suggest that cadmium concentrations in blood reflect recent exposure (Jarup et al., 1988), and cadmium concentrations in urine reflect chronic exposure (Roels et al., 1999).

We explored whether blood cadmium level is associated with current smoking and whether urine cadmium level is associated with former smoking status in the general population. In addition, we explored varying smoking characteristics

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including duration of smoking in years, and dose of smoking as measured by cigarettes per day.

Methods

The NHANES is an on-going cross-sectional survey of the civilian, non-institutionalized US population. NHANES surveys are conducted annually using a complex, stratified, multistage-cluster probability sampling of a representative US sample. NHANES consists of three parts: a health interview survey, a health examination survey and a nutrition survey (www.cdc.gov/nchs/nhanes.htm). We pooled data from four NHANES cycles on 40 790 individuals from the years 2005 to 2012 of whom 6761 subjects over the age of 20 who had smoking information and the specific laboratory measures of blood and urinary cadmium were included in our analyses.

Measurement of exposure, outcome and other variables

Information on age, gender, household income, education, height, weight and smoking history was collected during the health interview. Occupational data were unavailable. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Several continuous variables were coded into categorical variables using pre-specified cutoff values. Specifically, cutoff points for age (Wildman et al., 2008) BMI (Mannino et al., 2004), education (Mannino et al., 2003), household income (Kington et al., 1998), duration of smoking (Freedman et al., 2006), dose of smoking (Caraballo et al., 1998), pack-years of smoking (Adams & Newcomb, 2014) and smoking cessation (Taylor et al., 2002) were chosen from previously peer reviewed published studies using the NHANES database.

Smoking status

Information regarding smoking status, duration, dose, and the time interval of smoking cessation was collected during the health interview. Smoking status was defined based on the response of the following two questions: "Have you smoked at least 100 cigarettes in your life?" and "Do you now smoke cigarettes?"

Cigarette smoking status was then classified as never smoker (<100 cigarettes smoked lifetime), former smoker (>100 cigarettes smoked lifetime, not currently smoking) or current smoker (>100 cigarettes smoked lifetime, and currently smoking). Smoking characteristics were further categorized for current and former smokers. The duration (years) of smoking was defined on the basis of self-reported information regarding the survey questions "How old were you when you first started to smoke cigarettes fairly regularly?" and "How old were you when you last smoked cigarettes fairly regularly?" The number of cigarettes smoked per day (dose) was ascertained on the basis of self-reported information regarding the survey question "During the past 30 days, on the days you smoked, about how many cigarettes did you smoked per day?" The combined dose-duration smoking variable, "pack-years", was defined as the average number of cigarettes smoked per day multiplied by the number of years of smoking, during a subject's lifetime and then divided by 20 (Prescott et al., 1998). The smoking cessation time period (years) was defined on the basis of self-reported information regarding the survey question, "How long has it been since you quit smoking cigarettes?" In addition, serum cotinine levels were also assessed to confirm self-reported smoking status using a cutoff value of 3 ng/ml to distinguish former smokers from current smokers, but these data were not used to define an individual's smoking status (Benowitz et al., 2009). Instead, these data were used to determine concordance with the self-reported data. Less than 2% of former smokers had serum cotinine above 3 ng/ml and re-classification of these individuals from former smokers to smokers did not have any meaningful effects on our estimates.

Laboratory values

Laboratory values (e.g. serum cotinine, blood cadmium and urinary cadmium) were obtained in the morning following an overnight fast. Detailed specimen collection and processing instructions as well as NHANES quality assurance and quality control (QA/QC) protocols are discussed in the NHANES Laboratory/Medical Technologists Procedures Manual (LPM). The NHANES QA/QC protocols met the 1988 Clinical Laboratory Improvement Act mandates, and there were no changes to equipment, lab methods or lab site over the study cycles 2005–2012 (www.cdc.gov/nchs/nhanes.htm).

Cadmium biomarker values

Urinary and blood cadmium levels were measured in a weighted subsample of participants. Blood cadmium was measured from whole blood from EDTA containing vacutainer tubes. Both biomarker specimens were processed, stored and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, and Centers for Disease Control and Prevention for analysis and levels were determined using inductively coupled plasma mass spectrometry. This multi-element analytical technique is based on quadrupole ICP-MS technology. The lower limit of detection for urine and blood cadmium was 0.03 and 0.14 μg/L, respectively. The interassay coefficients of variation for blood cadmium ranged from 2.9% to 13.7%, and the interassay coefficients of variation for urine cadmium ranged from 4.1% to 4.8% (www.cdc.gov/nchs/nhanes.htm). We imputed all individuals with undetectable levels as the undetectable cutoff point divided by the square root of 2 (Finkelstein & Verma, 2001).

Other laboratory values

Serum cotinine is measured by an isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry. Serum and urinary creatinine were measured using the Jaffe rate method (kinetic alkaline picrate) to determine their concentrations (www.cdc.gov/nchs/nhanes.htm).

Statistical analyses

Statistical analyses were performed using SAS software (v9.3; SAS Institute, Cary, NC). Survey sample weights were used in all analyses to produce estimates that were representative of the non-institutionalized civilian US population. Descriptive statistics obtained for categorical variables were presented as weighted frequency or percent. Blood and urinary cadmium biomarkers and serum cotinine values were assessed for normality assumption. Since blood and urinary cadmium levels were skewed, they were log-transformed. In order to standardize cadmium biomarker levels across age levels as well as account for varying urinary dilution, age and urinary creatinine adjusted geometric means (the natural anti-log of the mean of a set of natural log transformed data) of blood and urinary cadmium levels are presented. The geometric adjusted least square mean value of urinary cadmium was adjusted using urinary creatinine as a predictor variable in a linear regression model. We tested for linear and quadratic trends of urinary and blood cadmium adjusted geometric mean levels by duration, dose and pack-years of smoking for current and former smokers.

We used Pearson correlation coefficients to quantitate the correlations of blood and urine cadmium biomarkers with duration of smoking in years, the number of cigarettes smoked per day, and pack-years of smoking in current and former smokers. We further assessed the correlation between each cadmium biomarkers and serum cotinine.

Results

Baseline characteristics are described in Table 1. Blood and urinary cadmium levels increased with increasing age groups. Those with lower household income, and less education had higher blood and urinary cadmium levels than their higher income and educated counterparts. Blood and urinary cadmium levels declined with increased levels of BMI.

There were significant differences in adjusted geometric mean blood cadmium levels between never (0.24 μg/L) versus former (0.29 μg/L) and current (1.02 μ/L) smokers. There were also significant differences in adjusted geometric mean urinary cadmium levels between never (0.20 μg/L) versus former (0.24 μg/L) and current (0.39 μg/L) smokers.

Among current smokers, duration was linearly related to both urinary (p-trend = 0.01) and blood (p-trend = 0.04) cadmium levels. Linear dose–response relationships were also observed between smoking dose and blood (p-trend = 0.036) and urinary cadmium levels (p-trend = 0.042). Although statistically significant linear trends were seen between pack-years and urinary (p-trend = 0.032) and blood (p-trend <0.002) cadmium markers, their dose–response relationships did not appear to be linear. A nonlinear trend of blood cadmium level (but not urine cadmium level) was significant (p = 0.009) (Table 2).

In former smokers, a dose–response relationship between prior smoking duration and both cadmium biomarker levels was significant (p-trend < 0.05). A dose–response relationship

Table 1. Characteristics of study participants, National Health and Nutrition Examination Survey (2005–2012) (N = 6761).

Variables	N	Weighted sample	Weighted %	Geometric mean urinary cadmium, μg/L (CI)[a]	p Value*	Geometric mean blood cadmium, μg/L (CI)[b]	p Value*
Age, years							
20–34	1756	56 206 365	27.2	0.12 (0.11–0.13)	–	0.27 (0.26–0.29)	–
35–49	1772	62 401 417	30.1	0.22 (0.2–0.23)	<0.0001	0.32 (0.30–0.34)	<0.0001
50–64	1642	53 169 211	25.7	0.31 (0.3–0.33)	<0.0001	0.39 (0.37–0.40)	<0.0001
65–79	1170	26 900 163	13.0	0.39 (0.37–0.41)	0.0002	0.40 (0.38–0.42)	<0.0001
80+	421	8 318 841	4.0	0.43 (0.4–0.47)	<0.0001	0.48 (0.45–0.51)	<0.0001
BMI, kg/m^2							
<18.5	209	5 827 750	2.8	0.34 (0.30–0.39)	–	0.49 (0.42–0.58)	–
18.5–24.9	1896	63 441 657	30.7	0.25 (0.24–0.26)	0.0033	0.39 (0.37–0.42)	0.0022
25–29.9	2259	68 378 896	33.0	0.24 (0.22–0.25)	0.0002	0.34 (0.32–0.36)	<0.0001
≥30	2396	69 333 032	33.5	0.22 (0.21–0.23)	0.0001	0.30 (0.29–0.31)	<0.0001
Gender							
Male	3327	99 622 442	48.1	0.20 (0.19–0.21)	–	0.31 (0.30–0.32)	–
Female	3434	107 373 555	51.9	0.28 (0.26–0.29)	<0.0001	0.38 (0.36–0.39)	0.0003
Education[c]							
<High school education	1435	1 639 939	18.9	0.29 (0.27–0.30)	–	0.41 (0.38–0.44)	–
High school education or more	3628	4 727 731	81.1	0.25 (0.23–0.26)	0.0002	0.34 (0.33–0.35)	<0.0001
Household Income (US $)[d]							
<$20,000/year	1457	30 564 606	15.2	0.26 (0.24–0.28)	–	0.42 (0.39–0.45)	–
≥$20,000/year	5045	170 366 066	84.8	0.23 (0.22–0.24)	<0.0001	0.33 (0.32–0.34)	<0.0001
Race							
Mexican	1101	16 525 281	8.0	0.27 (0.26–0.28)	–	0.29 (0.28–0.31)	–
Other Hispanic	619	10 648 329	5.1	0.25 (0.23–0.27)	0.7678	0.31 (0.29–0.33)	0.0860
Non-Hispanic White	3104	143 767 148	69.5	0.22 (0.21–0.23)	0.0028	0.34 (0.32–0.35)	<0.0001
Non-Hispanic Black	1418	23 077 056	11.1	0.26 (0.24–0.27)	0.6547	0.39 (0.37–0.41)	<0.0001
Other	519	12 978 183	6.3	0.34 (0.30–0.37)	<0.0001	0.48 (0.43–0.54)	<0.0001
Smoking status							
Never	3651	111 311 288	53.8	0.20 (0.19–0.21)	–	0.24 (0.24–0.25)	–
Former	1685	4 4268 414	21.4	0.24 (0.22–0.25)	<0.0001	0.29 (0.28–0.3)	<0.0001
Current	1423	51 394 958	24.8	0.39 (0.36–0.41)	<0.0001	1.02 (0.97–1.06)	<0.0001

[a]Age and urinary creatinine adjusted.
[b]Age adjusted.
[c]One thousand six-hundred and ninety-eight missing.
[d]Two-hundred and fifty-nine missing.
*Comparison of mean to lowest category.

Table 2. Cadmium biomarker levels by smoking characteristics in current smokers ($N = 1423$).

Variables	N	Weighted Sample	Weighted %	Geometric mean urinary cadmium, µg/L (CI)	p Value*	Geometric mean blood cadmium, µg/L (CI)	p Value*
Duration of smoking (years)[a]							
<10	239	7 364 565	17.0	0.19 (0.16–0.22)	–	0.77 (0.66–0.89)	–
10–19	291	9 210 013	21.3	0.28 (0.24–0.32)	0.0338	0.79 (0.69–0.89)	0.7897
20–29	268	9 465 936	21.9	0.43 (0.38–0.48)	<0.0001	1.02 (0.91–1.13)	0.0091
≥30	588	17 169 256	39.7	0.50 (0.44–0.57)	<0.0001	1.13 (1.02–1.25)	0.0073
				p-Trend	0.011	*p*-Trend	0.043
				Nonlinear *p*-trend	0.675	Nonlinear *p*-trend	0.831
Dose (number of cigarettes per day)[b]							
<8	506	13 414 011	30.4	0.31 (0.28–0.34)	–	0.63 (0.59–0.68)	–
8–14	338	9 766 265	22.1	0.33 (0.3–0.37)	0.1503	1.01 (0.93–1.09)	<0.0001
15–24	417	15 319 297	34.7	0.41 (0.38–0.45)	0.0012	1.14 (1.07–1.22)	<0.0001
≥25	149	5 621 061	12.7	0.47 (0.41–0.55)	0.0011	1.31 (1.2–1.42)	<0.0001
				p-Trend	0.042	*p*-Trend	0.036
				Nonlinear *p*-trend	0.836	Nonlinear *p*-trend	0.333
Pack-years (duration × dose)[c]							
<5	466	13 427 365	31.2	0.27 (0.25–0.3)	–	0.63 (0.57–0.69)	–
5–9	183	5 319 895	12.3	0.36 (0.31–0.43)	0.0099	0.91 (0.79–1.05)	0.0001
10–14	153	4 484 065	10.4	0.37 (0.32–0.43)	0.0027	1.16 (1.04–1.28)	<0.0001
15–19	113	3 606 141	8.4	0.38 (0.33–0.45)	0.0012	1.11 (0.97–1.27)	<0.0001
20–24	91	3 360 228	7.8	0.43 (0.38–0.49)	0.0003	1.24 (1.05–1.47)	<0.0001
25–29	62	2 267 561	5.3	0.54 (0.44–0.65)	0.0002	1.23 (1.06–1.42)	<0.0001
30–34	67	2 187 795	5.1	0.55 (0.46–0.66)	<0.0001	1.23 (1.04–1.46)	<0.0001
35–39	58	2 103 094	4.9	0.46 (0.36–0.57)	0.0026	1.24 (1.05–1.47)	<0.0001
≥40	182	6 334 048	14.7	0.46 (0.4–0.53)	0.0007	1.34 (1.22–1.46)	<0.0001
				p-Trend	0.032	*p*-Trend	0.002
				Nonlinear *p*-trend	0.2622	Nonlinear *p*-trend	0.009

*Comparison of mean to lowest category.
[a]Thirty-seven missing.
[b]Thirteen missing.
[c]Forty-eight missing.

between prior smoking doses was significant for urinary (p-trend < 0.001) but not blood cadmium (p-trend > 0.05). The dose–response relationships between smoking pack-years and urinary (p-trend$= 0.0001$) and blood cadmium (p-trend < 0.0001) levels also did not appear linear in former smokers nor was there a quadratic, nonlinear trend. The linear trend test between years of smoking cessation and urinary (p-trend $=0.02$), and blood cadmium levels (p-trend $= 0.01$) were significant, while nonlinear tests were not significant ($p > 0.05$) (Table 3).

In current smokers, the Pearson correlation coefficient between smoking duration and urinary cadmium was higher than for blood cadmium (0.38 versus 0.23). For dose (number of cigarettes per day), the Pearson correlation coefficient was higher for blood cadmium than urinary cadmium (0.36 versus 0.19). For pack-years of smoking, the Pearson correlation coefficient was slightly higher for blood cadmium than urinary cadmium biomarkers (0.34 versus 0.30). The Pearson correlation coefficient between serum cotinine and blood cadmium was higher than for urinary cadmium (0.44 versus 0.25), and the Pearson correlation coefficient between blood and urinary cadmium biomarkers was 0.35 (Table 4).

In former smokers, the Pearson correlation coefficient between smoking duration and blood cadmium was higher than for urinary cadmium (0.47 versus 0.39). For dose (number of cigarettes per day), the Pearson correlation coefficient was poor, but similar for blood cadmium and urinary cadmium (0.10 versus 0.12). For pack-years of smoking, the Pearson correlation coefficient was slightly higher for blood cadmium than urinary cadmium biomarkers (0.31 versus 0.26). The Pearson correlation coefficient for years of smoking cessation did not demonstrate a significant correlation with urinary cadmium ($p = 0.99$) or blood cadmium ($p =0.12$). The Pearson correlation coefficient between blood and urinary cadmium biomarkers in former smokers was 0.49 (Table 4).

Discussion

In cross-sectional data from NHANES, both mean blood and urine cadmium levels were significantly higher among those who currently or previously smoke cigarettes as compared to never smokers. We further explored inter-relationships between the component parts of the commonly used, but confounded, "pack-year" measure analyzing duration (years) and dose (cigarettes per day), as separate measures. Our descriptive data contribute importantly relevant information to the formulation of the hypothesis that the inter-relationships of cadmium biomarkers with smoking are more informative when duration and dose are analyzed separately than jointly as pack-years. For example, while we found linear dose–response relationships between smoking duration and dose with both cadmium biomarkers (urine and blood) in current smokers, the relationship between pack-years and both cadmium biomarkers was not linear. This deviation from linearity maybe explained by the imprecision of using a combined duration and dose (or pack-years) as a measuring tool for smoking.

In current smokers, the correlation between smoking duration and urinary cadmium was stronger than the correlation with blood cadmium. In contrast, the correlation between smoking dose and blood cadmium was stronger than its correlation with urinary cadmium. These findings suggest that urinary cadmium levels may be more influenced by smoking duration, and blood cadmium levels may be more influenced

Table 3. Cadmium biomarker levels by smoking characteristics in former smokers ($N = 1685$).

Variables	N	Weighted	Weighted %	Geometric mean urinary cadmium, μg/L (CI)	p Value*	Geometric mean blood cadmium, μg/L (CI)	p Value*
Duration of smoking (years)[a]							
<10	385	14 005 857	32.1	0.22 (0.20–0.24)	–	0.27 (0.25–0.30)	–
10–19	358	12 558 132	28.7	0.27 (0.25–0.30)	0.0002	0.29 (0.26–0.32)	0.1675
20–29	280	7 599 143	17.4	0.33 (0.29–0.37)	<0.0001	0.35 (0.32–0.38)	0.0001
≥30	420	9 530 221	21.8	0.43 (0.40–0.47)	<0.0001	0.47 (0.44–0.51)	<0.0001
				p-Trend	0.0113	p-Trend	0.0403
				Nonlinear p-trend	0.6750	Nonlinear p-trend	0.8306
Dose[b] (number of cigarettes per day)							
<8	552	15 714 271	33.7	0.26 (0.24–0.29)	–	0.31 (0.28–0.34)	–
8–14	248	8 610 008	18.5	0.29 (0.25–0.32)	0.1763	0.34 (0.31–0.37)	0.1750
15–24	436	13 165 942	28.2	0.30 (0.27–0.33)	0.0432	0.33 (0.31–0.36)	0.2938
≥25	304	9 133 522	19.6	0.33 (0.30–0.36)	0.0150	0.34 (0.31–0.37)	0.1542
				p-Trend	0.0003	p-Trend	0.1478
				Nonlinear p-trend	0.9887	Nonlinear p-trend	0.7130
Pack-years (duration × dose)[c]							
<5	502	15 346 605	35.4	0.25 (0.22–0.28)	–	0.30 (0.28–0.33)	–
5–9	186	6 982 769	16.1	0.25 (0.22–0.28)	0.7567	0.30 (0.27–0.34)	0.8402
10–14	150	4 550 303	10.5	0.28 (0.24–0.32)	0.7757	0.30 (0.26–0.33)	0.9934
15–19	104	2 901 015	6.7	0.36 (0.27–0.46)	0.0057	0.35 (0.28–0.43)	0.0906
20–24	74	1 702 339	3.9	0.31 (0.25–0.38)	0.3294	0.36 (0.30–0.43)	0.1836
25–29	60	2 163 058	5.0	0.37 (0.29–0.46)	0.0096	0.34 (0.27–0.43)	0.3302
30–34	69	2 098 811	4.8	0.34 (0.28–0.42)	0.1096	0.36 (0.30–0.44)	0.0607
35–39	48	1 780 124	4.1	0.42 (0.34–0.51)	0.0017	0.37 (0.29–0.47)	0.1246
≥40	241	5 808 900	13.4	0.39 (0.35–0.43)	<0.0001	0.42 (0.38–0.47)	<0.0001
				p-Trend	0.0001	p-Trend	<0.0001
				Nonlinear p-trend	0.5698	Nonlinear p-trend	.0927
Smoking cessation (years)[d]							
<3	149	4 936 896	9.6	0.34 (0.29–0.40)	–	0.45 (0.38–0.52)	–
3–5	209	6 443 707	12.6	0.35 (0.30–0.40)	0.7786	0.40 (0.36–0.45)	0.1532
6–10	266	8 547 100	16.7	0.35 (0.31–0.39)	0.8913	0.41 (0.37–0.45)	0.1329
11–15	210	6 632 441	12.9	0.34 (0.30–0.39)	0.4256	0.34 (0.30–0.39)	0.0027
≥16	847	24 696 531	48.2	0.25 (0.23–0.27)	<0.0001	0.28 (0.26–0.30)	<0.0001
				p-Trend	0.022	p-Trend	0.01
				Nonlinear p-trend	0.125	Nonlinear p-trend	0.131

*Comparison of mean to lowest category.
[a]Two hundred forty-two missing.
[b]One hundred forty-five missing.
[c]Two hundred and fifty-one missing.
[d]Four missing.

Table 4. Pearson correlation coefficient of smoking characteristics and cadmium biomarkers.

	Urinary cadmium r	p Value	Blood cadmium r	p Value
Current smokers				
Duration (years)	0.38	<0.0001	0.23	<0.0001
Dose (cigarettes per day)	0.19	<0.003	0.36	<0.0001
Pack-years (duration × dose)	0.30	<0.0001	0.34	<0.0001
Urinary cadmium (μg/L)	–	–	0.35	<0.0001
Blood cadmium (μg/L)	0.35	<0.0001	–	–
Serum cotinine (ng/ml)	0.25	<0.0001	0.44	<0.0001
Former smokers				
Duration (years)	0.39	<0.0001	0.47	<0.0001
Dose (cigarettes per day)	0.12	0.005	0.10	0.005
Pack-years (duration × dose)	0.26	<0.0001	0.31	<0.0001
Smoking cessation (years)	−0.001	0.99	−0.04	0.12
Urinary cadmium (μg/L)	–	–	0.49	<0.0001
Blood cadmium (μg/L)	0.49	<0.0001	–	–

by smoking dose in current smokers. This finding is consistent with the observation that cadmium concentrations in blood reflect recent exposure (Jarup et al., 1988), and cadmium concentrations in urine reflect chronic exposure (Roels et al., 1999).

In former smokers, a direct dose–response relationship and moderately strong correlation existed between prior smoking duration with both cadmium biomarkers (urine and blood) with the correlation between smoking duration and blood cadmium stronger than its correlation with urinary cadmium. In contrast, the correlation between smoking dose and both cadmium biomarkers was weak. These findings suggest that blood and urinary cadmium levels in former smokers are influenced by smoking duration, but not prior smoking dose.

In comparison to a correlation coefficient reported by Olsson et al. (2002) between urinary and blood cadmium levels of 0.64, we found a moderate correlation between urinary cadmium and blood cadmium levels in both current (0.35) and former (0.49) smokers. The Olson study, however, observed only 105 farmers from Southern Sweden, 70% of whom were never smokers (Olsson et al., 2002). In comparison

to this prior report of moderately high correlation, our data suggest that blood and urine cadmium levels are not that highly correlated. Our study, however, is comprised 54% who self report never smoking. In future analyses, investigators should attempt to determine which biomarker is a better measure for assessing the risk of cadmium induced smoking related diseases.

The chief limitation of these cross-sectional data is the lack of knowledge of the time sequence between the exposures and outcomes. Additional limitations include the possibility of measurement and misclassification error of self-reported smoking characteristics as well as a single measure of blood and urinary cadmium from each subject. The effect of non-differential misclassification errors likely underestimates the results. In addition, time dependent variables including duration of smoking and smoking cessation were measured at a single point in time; inferences made from these observations are hypothesis generating and require confirmation in studies that measure individual variable data over time. The strengths of these analyses include that NHANES data are collected using extensive quality control measures and by technicians trained and certified in all aspects of data collection. Findings from studies using NHANES sub-group data are representative of the US non-institutionalized civilian population when appropriate statistical methods are used (www.cdc.gov/nchs/nhanes.htm). Finally, the large NHANES sample size provides more precise estimates of effect.

We believe these data contribute important and relevant information regarding the inter-relationships of cadmium biomarkers with specific smoking characteristics. Cadmium is highly toxic, so a better understanding as to how to best measure it among those who are mostly liked to be exposed, is important for future analytic studies designed a priori to test hypotheses.

Author contributions

E.H. conceived, researched and wrote the manuscript. K.A., D.L., C.H. and W.W.H. provided guidance and support and made substantial contributions to conception, design, analysis and interpretation of data as well as revising the manuscript and making critically important contributions. All authors have given final approval of the version to be published; and agree to be accountable for all aspects of the work.

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