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Blood Cadmium by Race/Hispanic origin: The Role of Smoking

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Abstract

Background—There have been increasing concerns over health effects of low level exposure to cadmium, especially those on bones and kidneys.

Objective—To explore how age-adjusted geometric means of blood cadmium in adults varied by race/Hispanic origin, sex, and smoking status among U.S. adults and the extent to which the difference in blood cadmium by race/Hispanic origin and sex may be explained by intensity of smoking, a known major source of cadmium exposure.

Methods—Our sample included 7,368 adults from National Health and Nutrition Examination Survey (NHANES) 2011-2014. With direct age adjustment, geometric means of blood cadmium and number of cigarettes smoked per day were estimated for subgroups defined by race/Hispanic origin, smoking status, and sex using interval regression, which allows mean estimation in the presence of left- and right-censoring.

Results—Among never and former smoking men and women, blood cadmium tended to be higher for non-Hispanic Asian adults than adults of other race/Hispanic origin. Among current smokers, who generally had higher blood cadmium than never and former smokers, non-Hispanic white, black, and Asian adults had similarly elevated blood cadmium compared to Hispanic adults. A separate analysis revealed that non-Hispanic white adults tended to have the highest smoking intensity regardless of sex, than adults of the other race/Hispanic origin groups.

Conclusions—The observed pattern provided evidence for smoking as a major source of cadmium exposure, yet factors other than smoking also appeared to contribute to higher blood cadmium of non-Hispanic Asian adults.

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Keywords

Blood cadmium; race/Hispanic origin; Asians; smoking; NHANES

1. Introduction

Cadmium at high doses can decrease bone mineral density and cause kidney dysfunction (Satarug et al., 2010). Cadmium has been determined to be a human carcinogen, causing lung cancers and associated with kidney and prostate cancer (IARC, 1993; Ju-Kun et al., 2016). An association between high level exposure to cadmium and breast cancer has also been reported in multiple studies (Larsson et al., 2015). An important source of cadmium exposure is cigarette smoking, but foods such as potatoes, rice, wheat, soybean, shellfish and organ meat also are sources (ATSDR, 2012). In the United States, characteristics such as Asian ancestry (CDC, 2015), female sex, smoking status, and older age (Adams and Newcomb, 2014; CDC, 2015; Mortensen et al., 2011) are associated with higher cadmium body burdens. Differences in blood cadmium between Asians and other racial groups in the U.S. have been reported scarcely (CDC, 2015; McKelvey et al., 2007). Additional knowledge on racial difference in cadmium exposure may facilitate further research on the avoidable sources of exposure to cadmium, thereby contributing to the efforts to prevent adverse health effects induced by cadmium. We explored sex-specific differences in blood cadmium between race/Hispanic origin groups by smoking status and examined the extent to which the difference may be explained by smoking intensity.

2. Methods

2.1 Data Source and Measurements

We used data on race/Hispanic origin, sex, age at screening, blood cadmium, and self-reported smoking status and intensity from the National Health and Nutrition Examination Survey (NHANES) 2011-2014. The final response rates for the exam component for adults were 64.5% and 63.7% for 2011-12 and 2013-2014, respectively (CDC, 2012; CDC, 2014). The entire sample from 2011-12 and a 1/2 subsample from 2013-14 of adults, both of which were selected to be representative of the adult U.S. population in terms of race/Hispanic origin, sex, age, and income levels through a multistage probability design (Johnson et al., 2014), were targeted for blood cadmium measurements. Eligible for inclusion were 8,123 non-Hispanic white, non-Hispanic black, non-Hispanic Asian and Hispanic adults aged 20 and over, of whom 755 had missing data. Missing data were: 622 for blood cadmium; 151 for number of cigarette smoked (former and current smokers); and 9 missing smoking status (the total exceeds 755 because some participants were missing more than one variable). The remaining adults with complete data (n=7,368) formed the analytic sample.

2.2 Variables

Blood cadmium was measured using inductively coupled plasma mass spectrometry, with limits of detection (LODs) 0.16 and 0.10 μg/L in 2011-12 and 2013-14, respectively, by the Environmental Health laboratory at CDC (CDC, 2012; CDC, 2014). We used three mutually-exclusive smoking status categories: never (reported <100 cigarettes smoked during one's lifetime); former (do not currently smoke); or current (currently smoke some or all days). Self-reported average number of cigarettes smoked per day before quitting for former smokers or in the last 30 days for current smokers was used as a measure of smoking intensity. Serum cotinine was used to assess the validity of self-reported smoking status for NHANES 2011-2012; serum cotinine data were not available for NHANES 2013-2014. A serum cotinine > 10 ng/mL was taken as biochemical evidence of recent active smoking (during the last 5 days prior to examination) (Pirkle et al., 1996): 4.0% of self-reported never smokers; 8.6% of self-reported former smokers; and 92.2% of self-reported current smokers had serum cotinine > 10 ng/mL.

2.3. Statistical Methods

Age-adjusted geometric means of blood cadmium and number of cigarettes smoked for subgroups defined by race/Hispanic origin, smoking status, and sex, were estimated with direct age adjustment in the following 4 steps: 1, log-transformation; 2, estimation of within-subgroup age-specific means, i.e., three age group-specific means (age groups of 20-39, 40-59, 60 and over) (Klein and Schoenborn, 2001) within each subgroup; 3, estimation of subgroup means with direct age adjustment; 4, back-transformation of subgroup specific means. There were: 72 within-subgroup age-specific means and 24 subgroup means for blood cadmium; 48 within-subgroup age-specific means and 16 subgroup means for number of cigarettes smoked, which was reported by former and current smokers only. Both blood cadmium and number of cigarettes smoked were right skewed (which justified log-transformation) and censored (blood cadmium values below the LOD were left-censored, and number of cigarettes smoked reported as ≤ 1 or ≥ 95 were left- and right-censored, respectively). To properly handle the censoring, interval regression (Conroy, 2005) was used in step 2. A single interval regression model, weighted with examination weights for 2011-2012 and 1/2 sub-sample special weights for 2013-2014, was fit to the entire analytic sample to estimate within-subgroup age-specific means. In step 3, an age-adjusted mean for each subgroup was calculated as a linear combination of coefficients from step 2 with standard proportions for 3 age groups (Klein and Schoenborn, 2001) used as scalars. In step 4, the age-adjusted means from step 3 were back-transformed to obtain age-adjusted geometric means (referred to as “means” hereafter). Results obtained in step 3 were used for pairwise comparisons by Wald test at significance level of 0.05. We used “svy” estimation of Stata 13 (StataCorp, 2013), allowing variance estimation suitable for complex survey design.

2.4. Sensitivity Analysis

We performed a sensitivity analysis, in which reported age-adjusted subgroup mean and standard error estimates of blood cadmium were compared with the corresponding estimates based on an alternative approach that ignored left-censoring (i.e., using the data with < LOD values substituted with LOD/(√2) and fitting linear regression model in place of interval regression). Additionally, for each of the 72 pairwise comparisons of age-adjusted means we performed, reported statistical significance (as well as relative difference in the two estimated geometric means, calculated as “higher estimate” divided by “lower estimate) was compared with the counterpart based on the alternative approach. These pairwise comparisons include: 36 sex and smoking status-specific comparisons by race/Hispanic origin; 12 race/Hispanic origin and smoking status-specific comparison by sex; and 24 sex and race/Hispanic origin comparisons by smoking status.

3. Results

Age-adjusted blood cadmium means by race/Hispanic origin, smoking status, and sex ranged from 0.16 µg/L (95% confidence interval [CI]: 0.15, 0.17) to 1.10 µg/L (95% CI: 0.98, 1.23) (Figure 1 and Table 1). All subgroup means had satisfactory precision of relative standard errors < 30% (data not shown in tabular form). Within each sex-race/Hispanic origin group, current smokers had 2-4 times higher mean blood cadmium than former smokers, who in turn had up to 60% higher mean blood cadmium than never smokers. Among current smokers, Hispanic adults tended to have lower mean blood cadmium than adults of the other race/Hispanic origin, and there were no differences between non-Hispanic white, non-Hispanic black and non-Hispanic Asian adults. Among never and former smokers of the same sex, however, mean blood cadmium was almost always higher in non-Hispanic Asian adults compared to adults of other three race/Hispanic origin groups ($p < 0.001$ for all pairwise comparisons except for non-Hispanic Asian vs. non-Hispanic black formerly-smoking males with $p = 0.7$). Within most smoking status-race/Hispanic origin groups, women had higher mean blood cadmium levels than men.

Non-Hispanic white former and current smokers tended to smoke the most among men. Among currently smoking women, non-Hispanic white women also had the highest mean number of cigarettes smoked. Among formerly smoking women, non-Hispanic white, non-Hispanic black and non-Hispanic Asian women had similar mean number of cigarettes smoked, and Hispanic women had fewer cigarettes than non-Hispanic white and black women. Among former smokers, women tended to have smoked fewer cigarettes than men, but no consistent difference by sex was seen among current smokers.

We used a sensitivity analysis with the aim to document discrepancies between the blood cadmium results based on the approach used and the alternative approach, in which values below LOD were substituted with LOD/($\sqrt{2}$), ignoring censoring. We found that the non-Hispanic white male never smoker subgroup, which had the highest < LOD proportion, had the most pronounced discrepancies in estimation of an age-adjusted mean and its standard error; the highest ratio of alternative to reported mean, 1.27; and the lowest ratio of alternative to reported standard errors, 0.53. Figure 2 is a graphical depiction of these results as a plot of "alternative-reported" relative differences of point estimates for each sex, race/Hispanic origin vs. < LOD proportion. These "alternative to reported" ratios tended to get closer to 1 as the < LOD proportion decreased. The ratio were exactly 1 (i.e., no discrepancy) for the subgroups with no < LOD observations. The rankings by race/Hispanic origin within each sex-smoking status subgroup were similar between the alternative and reported results. The alternative approach detected a statistically significant difference for the same pairwise comparisons that we reported as significant except for two pairs: non-Hispanic black vs. Hispanic among male never smokers; never vs. former smokers among Hispanic women. The alternative approach underestimated the magnitude of relative difference in most (63 out of 72) of pairwise comparisons performed. In the remaining pairwise comparisons: the relative difference was overestimated (by up to about 2%) in 5 pairwise comparisons; and no "alternative vs. reported" discrepancy was seen in 4 pairwise comparisons where neither of the two comparison subgroups involved below LOD observations. "Alternative vs. reported" discrepancies tended to be more pronounced for the pairwise comparisons with higher relative differences. The most pronounced discrepancy in pairwise relative difference was for the comparison of never vs. current smokers among non-Hispanic males, where the relative difference was underestimated by 21.5% in the alternative approach. This pairwise comparison had the highest observed relative difference of 5.77, which was estimated to be 4.54 using the alternative approach.

4. Discussion

Our findings at the national level parallel previous reports, showing that Asians had higher blood cadmium levels than other race/Hispanic origin groups (CDC, 2015; McKelvey et al., 2007), and most prominently current smokers had higher blood cadmium (Adams and Newcomb, 2014; CDC, 2015; Mortensen et al., 2011). However, our analysis goes further and investigates the effects of smoking status and amount smoked on race/Hispanic differences in blood cadmium. Among never smokers, non-Hispanic Asians still had higher blood cadmium levels indicating that factors other than smoking were responsible for the higher levels. In addition, amount smoked did not explain the higher levels in the non-Hispanic Asian group among former smokers as non-Hispanic white former smokers tended to smoke the largest number of cigarettes. Among current smokers, non-Hispanic white adults smoked the most, yet non-Hispanic white, non-Hispanic black, and non-Hispanic Asian adults had similar mean blood cadmium. Taken together, the pattern observed in never smokers and the mismatched rankings for smoking intensity and blood cadmium reinforced the notion that factors other than smoking (such as, possibly, a diet rich in rice, shellfish, and soybean) contributed to the differences in blood cadmium across race/Hispanic origin groups. High consumption of rice among Asians is well documented at national level (Batres-Marquez et al., 2009) and in select sub-populations, e.g., nurses (Zhang et al., 2016). To our knowledge, there has been no published national-level estimates of shellfish and soybean (or soy-based food) consumption rates for Asians in the U.S. However, one of the highest shellfish consumption rates for a racial subgroup in the U.S. has been reported for a largely Asian group in King County, Washington (Picot et al., 2011). Furthermore, adults with Asian cultural background were found to consume more soybean-based food than adults of other cultural backgrounds in Canada (Mudryj et al., 2015) as expected, given that soybean-based food are a part of traditional diet in some Asian countries (Messina et al., 2006).

At the relatively low cadmium exposure typical of the general population, blood cadmium reflects largely recent exposure in the past few months (Lauwerys et al., 1994), yet a portion of blood cadmium also reflects body burden from past exposure, which resulted from accumulation of cadmium in tissues such as kidney and liver. Tissue cadmium stores can be slowly released back to blood over years (Lauwerys et al., 1994); thus, some levels of blood cadmium in former and current smokers is likely the result of past smoking along with contribution from other chronic cadmium sources. A study of cadmium workers after the cessation of exposure reported estimates of blood cadmium half-life: 2.5-4 months for the fast component, relevant for recent exposure; and from 7.4-16.0 years for the slow component, relevant for past exposure.(Jarup et al., 1983) Overall blood cadmium half-life for the underlying present-day population of the current study may be thought to fall between these two estimates as it should reflect both slow and fast components (yet we caution that the very concept of blood cadmium half-life is rather poorly defined for a group of individuals with heterogeneous past and concurrent cadmium exposure such as our underlying population). Of note, anybody may be exposed to cadmium through second-hand (Oberg et al., 2011) and third-hand (Northrup et al., 2016) smoking at home or workplace, which could be more frequent and/or intense for current smokers than former smokers (as well as former smokers than never smokers) due to correlated smoking behaviors. Given similar current and historical non-smoking exposure to cadmium, never smokers are expected to have lower blood cadmium than former smokers, who in turn are expected to have lower blood cadmium than current smokers.

Occupational exposure is another source of human cadmium exposure other than smoking and diet (ATSDR, 2012). The International Agency for Research on Cancer identified 30 occupations with potential exposure to cadmium including various production involving metal, plastic, or battery, as well as smelting (IARC, 1993). It is difficult to examine whether those occupations are over-represented by Asians since the official U.S. labor force statistics uses an occupation grouping scheme different from the one used by IARC. Nonetheless, based on the official 2015 labor statistics for the U.S.: Asians do not appear to be over-represented in production occupations, which included 6.2% Asians (5.8% of the entire workforce aged 16 and over are were Asians); Occupation subgroups with descriptors “metal” and/or “plastic” under production occupations, for which “percent of employed” is reported for Asians, do not appear to be overrepresented by Asians (Bureau of Labor Statistics, 2016). We cannot exclude the possibility that some metal- or plastic-related occupation subgroups, for which “percent of employed” is not reported for Asians in the official 2015 labor statistics, in aggregate may have been overrepresented by Asians. It is unlikely, though, that occupational exposure is a major determinant of blood cadmium among adults overall, given that production occupations account for a minor portion, just about one-tenth, of the entire workforce (Bureau of Labor Statistics, 2016).

In addition to occupational exposure, cadmium exposure can occur through environmental media such as air, soil and dust from waste facilities such as waste incinerators and landfills for municipal and industrial waste (ATSDR, 2012), potentially resulting in higher cadmium exposure for the individuals living near such facilities. A substantial body of literature documents that polluting facilities are more likely to be located in areas with a higher proportion of minority residents (Mohai et al., 2009). A recent analysis on siting of commercial hazardous waste facilities in 1991-1995 found that higher percentages of Asian residents, not those of black and Hispanic residents, in the surrounding area were strongly associated with higher likelihood of siting of such facilities, with or without adjustment for socioeconomic characteristics of the surrounding area (Mohai and Saha, 2015). This finding indicates that the observed tendency for non-Hispanic Asians to have the highest blood cadmium among never and former smokers of three racial minority groups could be potentially explained in part by the unequal burden of living near polluting facilities borne by Asians. It is notable, however, that living near a polluting facility may not necessarily result in an appreciable increase in exposure to cadmium. For instance, residential vicinity to an urban solid waste incinerator was not associated with blood and urinary cadmium in a Belgian study (Schroijen et al., 2008), and similar lack of association has been reported from Korea (Lee et al., 2012), Portugal (Reis et al., 2007), and Spain (Zubero et al., 2010). It has been documented that cadmium in outdoor air (Ciarrocca et al., 2015) and house dust (Hogervorst et al., 2007), some but not all of which would originate from waste facilities, are potentially important determinants of cadmium exposure. More studies are needed to elucidate how those sources contribute to the difference by race/Hispanic origin we reported.

We provided evidence for previous findings that women had higher blood cadmium than men (Adams and Newcomb, 2014; CDC, 2015; Mortensen et al., 2011). We observed this sex difference within most smoking status-race/Hispanic origin groups, despite the tendency that women had lower or similar smoking intensities. Other authors have suggested that iron deficiency, which is more prevalent in women, may lead to greater cadmium absorption (Vahter et al., 2007).

A limitation of this exploratory study is that smoking status determination was based solely on self-report and did not incorporate serum cotinine data (in part due to the unavailability of serum cotinine data for 2013-2014). We relied on self-reported smoking status because only self-reported former and current smokers were asked about smoking intensity. We found that self-reported never and former smokers included adults who could be considered as active smokers based on their serum cotinine levels. Due to this misclassification of smoking status, our mean estimates of blood cadmium in never and former smokers would have overestimated the true levels. The extent of such overestimation may also depend on race/Hispanic origin thereby affecting the observed difference by race/Hispanic origin. Our analysis has limited power due to relatively small sample sizes, despite the oversampling of Asians and Hispanics in the NHANES.

A strength of our study is adjustment for age, which is positively associated with blood cadmium (Adams and Newcomb, 2014; CDC, 2015; Mortensen et al., 2011) and varies by race/Hispanic origin (Day, 1996). Without age adjustment, we would have underestimated the difference between non-Hispanic Asian adults and non-Hispanic white adults, because the former overall was younger than the latter (Day, 1996). Another strength was the use of interval regression (an extension of Tobit regression), which allowed mean estimation for a censored variable without employing a strong distributional assumption. This is a potentially useful alternative to the widely used approach of substituting the censored values with a discrete value, e.g., substituting values below LOD with LOD/($\sqrt{2}$) under the assumption that values below LOD follow a triangular distribution (Hornung and Reed, 1990). The alternative approach using LOD/($\sqrt{2}$) would introduce bias, specifically, overestimation of geometric means and underestimation of their standard error, and the magnitude of such biases would increase with the < LOD proportion (Hornung and Reed, 1990). The mean overestimation in the alternative approach would result in underestimation of a difference in any two means because the smaller of the two, which tends to involve a higher proportion of < LOD observations, would be more overestimated than the other, bringing the two mean estimates falsely closer. Results from our sensitivity analyses were consistent with these anticipated directions of the biases. Of note, detection of statistically significant pairwise difference was similar in the alternative approach. This similarity arises because the mean overestimation and standard error underestimation affect statistical inference on pairwise comparisons in the opposite directions, i.e., the former attenuates but the latter exaggerates the true statistical significance.

Given the increasing concerns over health effects of low level exposure to cadmium, especially those on bone and kidney (Akesson et al., 2014; Jarup and Akesson, 2009), it is important to determine population subgroups with even slightly elevated cadmium exposures and possible sources. To our knowledge, this is the first report on blood cadmium of non-Hispanic Asian adults compared with adults of other race/Hispanic origin in the U.S. Our results confirm that smoking is a major source of blood cadmium, but factors other than smoking also appear to contribute to higher blood cadmium among non-Hispanic Asians. Our findings overall inform further research on how different sources of cadmium exposure may have contributed to the observed differences in blood cadmium by race/Hispanic origin. Such research in turn may lead to identification of avoidable cadmium exposure sources other than smoking, contributing to the efforts to prevent cadmium-induced adverse health effects in the U.S. population.

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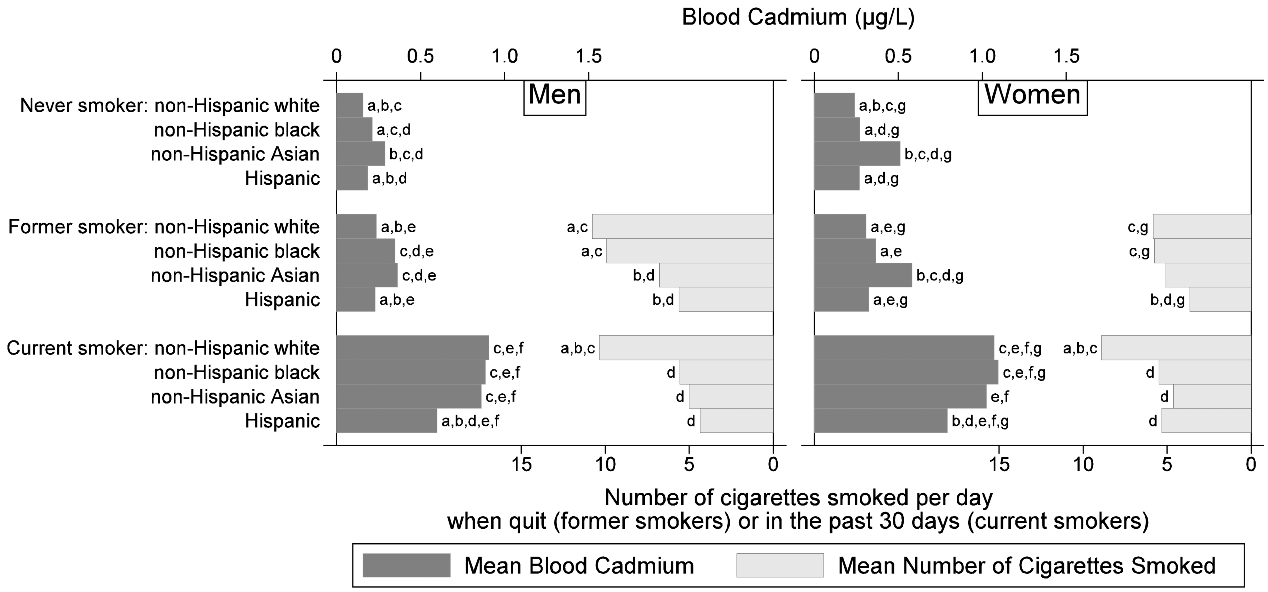

Figure 1.

Age-adjusted mean blood cadmium levels and number of cigarettes smoked among adults by sex, smoking status, and race/Hispanic origin, NHANES 2011-2014. Alphabet at the tip of each bar indicates statistically significant pairwise difference (p <0.05): within same sex and smoking status, different from [a] non-Hispanic Asian, [b] non-Hispanic black, [c] Hispanic, or [d] non-Hispanic white; within same sex and race/Hispanic origin, different from [e] never smokers, or [f] former smokers; within same smoking status and race/Hispanic origin, different from [g] men.

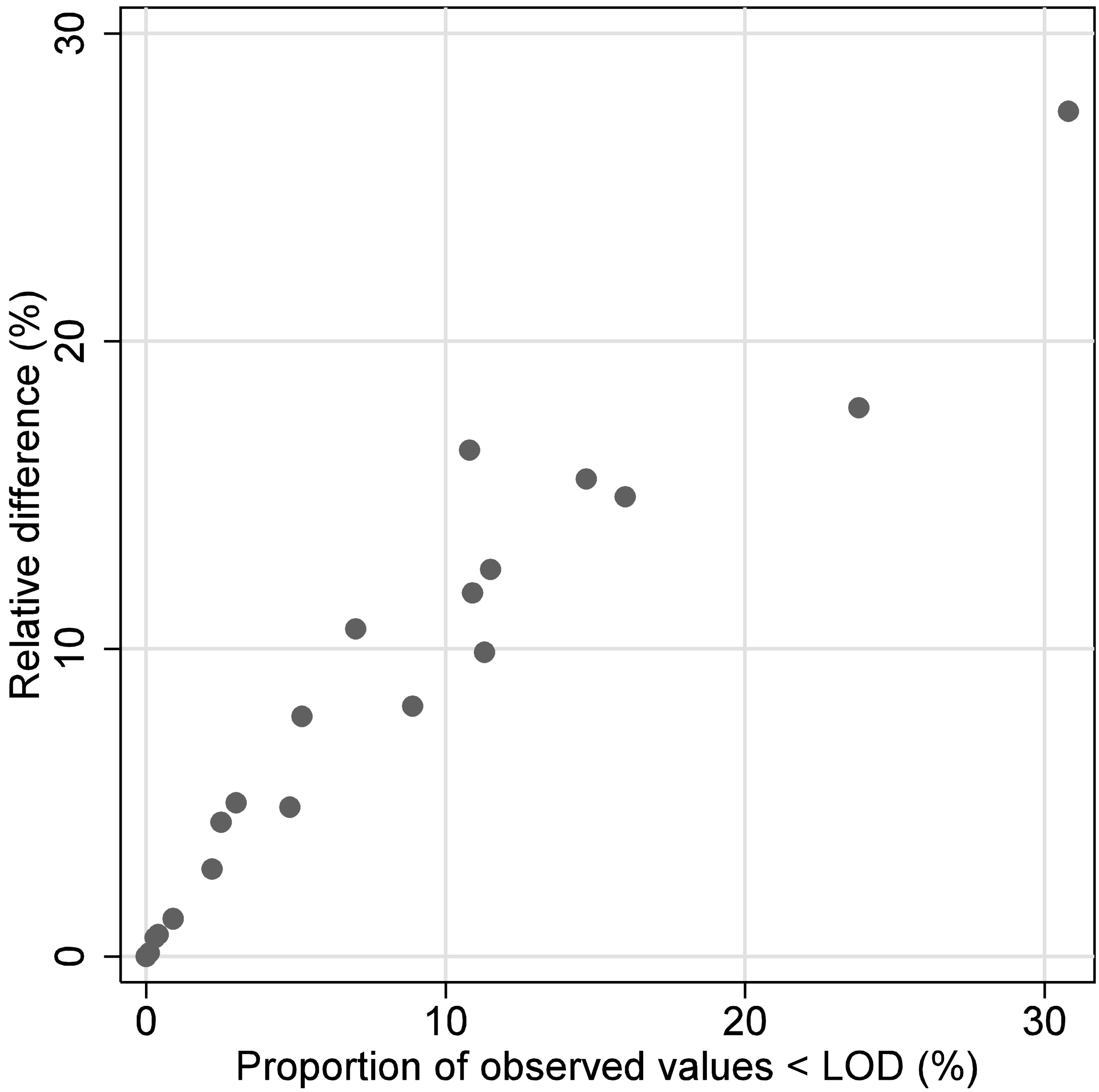

Figure 2.

Relationship between relative difference in age-adjusted geometric means by sex, race/Hispanic origin, and smoking status by estimation method, estimates based on conventional method with LOD/sqrt(2)-substitution vs. estimates based on interval regression.

Table 1

Age-adjusted mean[a] blood cadmium levels and number of cigarettes smoked among adults by sex, smoking status, and race/Hispanic origin, NHANES 2011-2014

				Blood Cadmium		Number of Cigarettes Smoked Per Day[b]
Sex	**Smoking Status**	**Race/Hispanic Origin**	**Sample Size**	**Mean [c] (95% CI) (μg/L)**	**Below LOD (%)**	**Mean [c] (95% CI)**
Men	Never Smoker	Non-Hispanic white	642	0.16 (0.15, 0.17)	30.8	-
		Non-Hispanic black	417	0.21 (0.19, 0.24)	16.0	-
		Non-Hispanic Asian	282	0.29 (0.26, 0.32)	8.9	-
		Hispanic	375	0.19 (0.18, 0.20)	23.8	-
	Former Smoker	Non-Hispanic white	458	0.24 (0.22, 0.26)	10.8	10.8 (8.7, 13.4)
		Non-Hispanic black	191	0.35 (0.31, 0.39)	7.0	9.9 (8.3, 11.8)
		Non-Hispanic Asian	122	0.36 (0.31, 0.42)	3.0	6.8 (5.6, 8.3)
		Hispanic	219	0.23 (0.21, 0.26)	14.7	5.6 (4.5, 7.0)
	Current Smoker	Non-Hispanic white	360	0.91 (0.83, 0.99)	0.1	10.4 (9.0, 11.9)
		Non-Hispanic black	247	0.89 (0.81, 0.97)	0.4	5.5 (4.8, 6.4)
		Non-Hispanic Asian	77	0.86 (0.73, 1.02)	0.9	5.0 (3.9, 6.5)
		Hispanic	172	0.60 (0.56, 0.65)	2.2	4.4 (3.5, 5.4)
Women	Never Smoker	Non-Hispanic white	834	0.24 (0.23, 0.25)	11.5	-
		Non-Hispanic black	650	0.27 (0.25, 0.29)	10.8	-
		Non-Hispanic Asian	457	0.51 (0.48, 0.55)	0.9	-
		Hispanic	636	0.27 (0.26, 0.28)	11.3	-
	Former Smoker	Non-Hispanic white	369	0.31 (0.28, 0.34)	5.2	5.8 (5.0, 6.9)
		Non-Hispanic black	106	0.37 (0.32, 0.41)	2.5	5.7 (4.4, 7.6)
		Non-Hispanic Asian	39	0.58 (0.50, 0.68)	0	5.1 (3.5, 7.5)
		Hispanic	121	0.32 (0.27, 0.38)	4.8	3.6 (2.8, 4.7)
	Current Smoker	Non-Hispanic white	334	1.07 (1.00, 1.14)	0.3	8.9 (7.8, 10.2)
		Non-Hispanic black	168	1.10 (0.98, 1.23)	0	5.5 (4.8, 6.3)
		Non-Hispanic Asian[d]	18	1.02 (0.73, 1.45)	0	4.6 (2.8, 7.6)

Sex	Smoking Status	Race/Hispanic Origin	Sample Size	Blood Cadmium		Number of Cigarettes Smoked Per Day[b]
				Mean [c] (95% CI) (μg/L)	Below LOD (%)	Mean [c] (95% CI)
		Hispanic	74	0.79 (0.68, 0.92)	0	5.3 (4.0, 7.0)

[a]Direct age adjustment was performed with three age groups (20-39, 40-59, 60 and over) on log-transformed variables followed by back transformation to present results as geometric means.

[b]Self-reported average number of cigarettes smoked per day before quitting for former smokers or in the last 30 days for current smokers.

[c]Means were calculated as geometric means.

[d]Relative standard errors (RSEs), i.e., (standard error of mean)/mean, for this subgroup of smallest sample size were 16.9% and 24.1% for blood cadmium and number of cigarettes smoked per day, which were the highest among all subgroups.