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The relationship between zinc intake and cadmium burden is influenced by smoking status

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ABSTRACT

A preliminary study by our group suggested that the absorption and accumulation of cadmium may be affected by zinc intake. Tobacco smoke is one major source of cadmium exposure that highly influences cadmium burden among smokers, but it is unclear whether this zinc-cadmium relationship differs by smoking status. The objective of this study was to examine whether the association between zinc intake and cadmium burden differs by smoking status using data from 3900 US adults in the National Health and Nutrition Examination Survey 2007–2012. In an adjusted regression model, dietary cadmium was positively associated with blood and urinary cadmium. There was a significant interaction between zinc intake and smoking status, so we analyzed associations within smoking status subgroups. In an adjusted regression model, zinc intake was inversely associated with urinary cadmium only among non-smokers. Failure to meet the Recommended Dietary Allowance (RDA) for zinc was more common among current smokers than non-smokers, and among those in the highest quintile of blood and urinary cadmium than those in lower quintiles. Zinc intake was inversely associated with urinary cadmium only among subjects meeting the zinc RDA, suggesting that the relationship between zinc intake and cadmium burden differs by smoking status.

1. Introduction

Cd is a toxic heavy metal emitted as a byproduct of industrial processes into soil and water where it can subsequently be absorbed by and accumulated in plants, including agricultural products destined for the food supply (Agency for Toxic Substances and Disease Registry, 2012). Diet is the main source of Cd for most of the US population (Kim et al., 2018; Agency for Toxic Substances and Disease Registry, 2012), but tobacco smoke is another important source of Cd exposure among smokers (Pappas et al., 2006). Due to its long half-life in the human body, Cd can accumulate in multiple tissues. Cd toxicity has been linked to cancer (Hartwig, 2013), kidney dysfunction (Mortensen et al., 2011), cardiovascular disease (Peters et al., 2010), diabetes (Bernhoft, 2013), reproductive dysfunction (Godt et al., 2006), osteoporosis (Gallagher et al., 2008), and increased mortality (McCarty, 2012).

Following its entry via the intestine and lung, Cd is transported to the liver where it stimulates the synthesis of metallothionein. Cd circulates in the blood bound to metallothionein, a form in which it is essentially innocuous. However, in the kidney, Cd-metallothionein is readily filtered at the glomerulus and reabsorbed in the proximal tubule, where it tends to remain and accumulate (Godt et al., 2006). Within the tubular cells, metallothionein is degraded, thereby releasing free Cd, which can cause tubular damage (Friberg, 1984). Cd-induced damage to the kidney and other tissues may occur through several mechanisms: free Cd ions may inactivate metal-dependent enzymes (Brzóska and Moniuszko-Jakoniuk, 2001), activate calmodulin (Agency for Toxic Substances and Disease Registry, 2012), and damage cell membranes through the formation of reactive oxygen species (Kukongviriyapan et al., 2016). Cd may also increase cancer risk through the inhibition of DNA repair mechanisms (McCarty, 2012).

A major pathologic mechanism of Cd is the competitive interference with the actions of metals including zinc (Zn). Cd and Zn ions compete

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Abbreviations

Ca	Calcium
Cadmium	Cadmium
CI	Confidence interval
FNDDS	Food and Nutrient Database for Dietary Studies
ICP-MS	inductively coupled plasma-mass spectrometry
NHANES	National Health and Nutrition Examination Survey
PIR	poverty income ratio
RDA	Recommended Dietary Allowance
TDS	Total Diet Study
Zinc	Zinc

for uptake into cells and for binding to various proteins and intracellular sites, and Cd may displace Zn in these biological processes. Both metals bind metallothionein and can induce its synthesis. Because of its slightly higher affinity for metallothionein, Cd can displace Zn from this protein, resulting in the synthesis of more metallothionein, thus enabling further absorption of Cd from the gastrointestinal tract (Brzóska and Moniuszko-Jakoniuk, 2001). Therefore, Zn intake may have important consequences on the absorption, accumulation, and availability of Cd in the body due to its effects on intestinal absorption of Cd and its interactions with Cd at cellular transporters, metallothionein, and other proteins.

In various animal studies, Zn-deficient diets have been shown to drastically increase Cd absorption (McCarty, 2012), while Zn supplementation has been shown to protect against bone fractures and toxicity to the kidney, liver, and spleen (Brzóska et al., 2011; Bulat et al., 2008; Rogalska et al., 2011). A preliminary study by our group showed that in US adults, Zn intake is associated with lower Cd exposure, presumably by influencing the absorption and accumulation of Cd (Vance and Chun, 2015). Other human studies have revealed that urinary Cd was positively associated with total prostate-specific antigen level only among men with low Zn intake level (van Wijngaarden et al., 2008), and that Cd exposure is an independent risk factor for cancer mortality, and that this risk appears to be exaggerated among those with inadequate Zn intake (Lin et al., 2013). These human studies suggest that dietary Zn may protect against Cd toxicity in humans, but this hypothesis has not been well explored among different segments of the population with differing levels and sources of Cd exposure. To our knowledge, no study has examined whether this Zn-Cd relationship is affected by smoking status, an important predictor and determinant of total body Cd burden. Therefore, the objective of this study was to examine whether the relationship between dietary Zn intake and urinary Cd levels differs depending on smoking status in US adults.

2. Methods

2.1. Study population

This cross sectional study included 3900 US adults aged 20 years and older from the National Health and Nutrition Examination Survey (NHANES) 2007–2012. Exclusion criteria included those with dietary recalls coded as unreliable or incomplete (n = 3684) and those with missing data on sociodemographic characteristics, dietary variables, and biomarkers used in statistical modeling such as age, gender, BMI, ethnicity, poverty income ratio (PIR), education level, smoking status, alcohol consumption, supplement use, calcium intake, iron intake, energy intake, blood Cd, and urinary Cd (n = 10,129). The study protocols for NHANES received National Center for Health Statistics research ethics review board approval.

2.2. Estimation of dietary Cd and nutrient intake

Dietary data were gathered from participants through two 24-hr dietary recalls. These structured interviews, which are intended to capture detailed information about all the foods and drinks consumed by the respondent on the preceding day, were conducted by trained interviewers using the USDA Automated Multiple Pass Method (Raper et al., 2004). To estimate dietary Cd intake, the database of the Total Diet Study (TDS) in the 2006 through 2013 market baskets, which contains Cd concentrations of 260 individual foods (US Food and Drug Administration, 2017), was used. Cd intakes were estimated from two days of 24-hr dietary recalls by matching intake data with the Cd database of the TDS. This study used the USDA Food and Nutrient Database for Dietary Studies (FNDDS) version 4.1 (USDA Food and Nutrient Database for Dietary Studies, 4.1, 2010), the FNDDS version 5.0 (USDA Food and Nutrient Database for Dietary Studies, 5.0, 2012), and the FNDDS version 2011–2012 (USDA Food and Nutrient Database for Dietary Studies, 2011-2012, 2014) to link the Cd database of the TDS with the NHANES 2007–2012 food consumption data. Total Ca and Zn intake were estimated from both diet and dietary supplements. Participants were also classified as having met or having failed to meet the RDA for Zn based on the average Zn intake from the two days of dietary recalls.

2.3. Biomarker data

Participants' blood and urine were collected in the mobile examination center. Blood Cd and urine Cd were measured as described in the NHANES Laboratory Procedures Manual. Blood Cd and urinary Cd concentrations were determined using inductively coupled plasma-mass spectrometry.

2.4. Statistical analysis

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC), using SAS survey procedures and the appropriate weight, strata, and cluster variables to account for the complex survey design. Participants were grouped into quintiles based on Ca and Zn intake from both diet and supplements. Mean and confidence interval (CI) of blood Cd and urinary Cd were calculated across sociodemographic factors and quintiles of Ca and Zn consumption. P-values for differences in blood Cd and urinary Cd between subgroups were obtained by *t*-test and ANOVA.

Participants were grouped by PIR as follows: < 1.0, $1.0 \leq$ to < 1.3, $1.3 \leq$ to < 1.85 and ≥ 1.85. Based on the number of drinks of any type of alcoholic beverage per day, alcohol consumption was defined as no consumption (0 drinks), moderate consumption (no more than 2 drinks/d for men and no more than 1 drink/d for women), and heavy consumption (more than 2 drinks/d for men and more than 1 drink/d for women) (Krauss et al., 2001). Current smokers were defined as those who have had at least 100 cigarettes per year and smoke some days or every day. Non-smokers were defined as those having smoked fewer than 100 cigarettes in their lifetime and serum cotinine level ≤ 0.05 ng/mL or having quit smoking over 3 years ago with serum cotinine level ≤ 0.05 ng/mL. Passive smokers were defined as having smoked fewer than 100 cigarettes in their lifetime and serum cotinine level > 0.05 ng/mL, or having quit smoking over 3 years ago with serum cotinine level > 0.05 ng/mL, or inhaling the smoke from others' cigarettes at work or at home and serum cotinine level > 0.05 ng/mL. To examine the relationship between Cd intake from foods and blood and urinary Cd by smoking status, multivariate regression model was used and adjusted for age, gender, ethnicity, BMI, PIR, alcohol consumption, education level, dietary supplement use, Ca intake and Zn intake. In regression models, blood Cd and urinary Cd were log-transformed. The interaction between Zn intake and smoking status was

tested for significance in the regression model. Meeting or failing to meet the RDA for Zn was based on the average Zn intake from two days of dietary data from both diet and supplements. Geometric means of blood and urinary Cd were calculated across quintiles of Zn intake by smoking status and by subjects meeting or failing to meet the RDA for Zn intake, both with and without dietary supplements considered. Beta coefficients and p-trends were calculated in a model adjusted for relevant covariates. All P-values reported are two sided ($\alpha = 0.05$).

3. Results

The arithmetic means of blood and urinary Cd concentrations of participants were 0.50 μg/L and 0.33 μg/g creatinine, respectively (Table 1). The subjects with higher blood and urinary Cd were more likely to be older, female, current smokers, and to be classified as underweight based on BMI and had low levels of education. Additionally, the subjects with higher blood Cd were more likely to be heavy alcohol consumers, supplement non-users, and to have a lower income. Those in the highest quintiles of Ca and Zn intake tended to have lower blood and urinary Cd concentrations than those who consumed less Ca or Zn (Table 2).

In a regression model fully adjusted for age, gender, ethnicity, BMI, income, education level, alcohol consumption, dietary supplement use, and total Ca and Zn intake, total Cd intake from foods was positively associated with blood and urinary Cd concentrations only among non-smokers ($\beta = 0.0113$, P-trend < 0.05; $\beta = 0.0167$, P-trend < 0.05,

Table 1
Average blood and urinary Cd concentrations of US adults aged ≥ 20 y by sociodemographic and lifestyle factors in NHANES 2007–2012 (n = 3900).

All	n	Blood Cd (μg/L)			n	Urinary Cd (μg/g creatinine)		
		Mean	95% CI	P for mean difference		Mean	95% CI	P for mean difference
	3900	0.5	(0.47, 0.52)		3900	0.3	(0.31, 0.35)	
Age (y)				< 0.05				< 0.0001
20–30 y	702	0.4	(0.39, 0.49)		702	0.1	(0.13, 0.16)	
31–50 y	1336	0.5	(0.45, 0.55)		1336	0.3	(0.26, 0.35)	
51–70 y	1231	0.5	(0.47, 0.56)		1231	0.4	(0.40, 0.47)	
70 + y	631	0.5	(0.50, 0.57)		631	0.5	(0.48, 0.55)	
Gender				< 0.001				< 0.0001
Male	1892	0.5	(0.42, 0.48)		1892	0.3	(0.24, 0.27)	
Female	2008	0.5	(0.50, 0.57)		2008	0.4	(0.37, 0.44)	
BMI[a]				< 0.0001				< 0.0001
BMI < 18.5	61	0.9	(0.40, 1.33)		61	0.7	(0.17, 1.15)	
18.5 ≤ BMI < 25	1061	0.6	(0.52, 0.62)		1061	0.4	(0.32, 0.40)	
25 ≤ BMI < 30	1304	0.5	(0.42, 0.52)		1304	0.4	(0.30, 0.40)	
30 ≤ BMI	1474	0.5	(0.41, 0.48)		1474	0.3	(0.27, 0.30)	
Ethnicity (%)				0.115				0.664
White	1836	0.5	(0.47, 0.53)		1836	0.34	(0.31, 0.37)	
Black	810	0.6	(0.52, 0.63)		810	0.31	(0.28, 0.35)	
Hispanic	569	0.4	(0.34, 0.40)		569	0.28	(0.24, 0.32)	
Others	685	0.5	(0.44, 0.53)		685	0.35	(0.32, 0.39)	
Poverty income ratio[b]				< 0.0001				0.296
< 1.3	1211	0.6	(0.56, 0.70)		1211	0.34	(0.31, 0.38)	
1.3–1.85	523	0.6	(0.53, 0.71)		523	0.38	(0.31, 0.44)	
1.85–3.5	971	0.5	(0.45, 0.53)		971	0.33	(0.30, 0.36)	
≥ 3.5	1195	0.4	(0.37, 0.44)		1195	0.32	(0.28, 0.36)	
Alcohol consumption[c]				< 0.001				0.079
None	1420	0.5	(0.44, 0.51)		1420	0.36	(0.34, 0.39)	
Moderate	1213	0.4	(0.39, 0.45)		1213	0.33	(0.30, 0.35)	
Heavy	1267	0.6	(0.53, 0.62)		1267	0.32	(0.28, 0.36)	
Education level				< 0.0001				< 0.01
Less than high school	999	0.6	(0.56, 0.72)		999	0.43	(0.38, 0.48)	
High school equivalent	882	0.6	(0.51, 0.66)		882	0.33	(0.30, 0.35)	
College	1107	0.5	(0.44, 0.52)		1107	0.31	(0.28, 0.34)	
Graduate	912	0.4	(0.33, 0.40)		912	0.3	(0.24, 0.36)	
Dietary supplement use				< 0.05				0.077
Yes	1943	0.5	(0.41, 0.50)		1943	0.35	(0.32, 0.38)	
No	1957	0.5	(0.49, 0.59)		1957	0.31	(0.28, 0.34)	
Smoking status[d]				< 0.0001				< 0.0001
Current smokers	799	1.2	(1.11, 1.24)		799	0.47	(0.41, 0.52)	
Non-smokers	2118	0.3	(0.30, 0.33)		2118	0.31	(0.28, 0.34)	
Passive smokers	983	0.3	(0.30, 0.36)		983	0.26	(0.24, 0.29)	
Tap water source				0.305				0.359
Community supply	2652	0.5	(0.47, 0.53)		2652	0.3	(0.31, 0.37)	
Well or spring	419	0.5	(0.47, 0.59)		419	0.3	(0.29, 0.36)	
Don't drink tap water	738	0.5	(0.42, 0.50)		738	0.3	(0.29, 0.35)	

[a] Body Mass Index (kg/m[b]).
[b] Poverty income ratio.
[c] Alcohol consumption: defined based on the number of drinks of any type of alcoholic beverage per day, with no consumption as 0 drinks, moderate consumption as no more than 2 drinks/d for men and no more than 1 drink/d for women, and heavy as more than 2 drinks/d for men and more than 1 drink/d for women.
[d] Current smokers were defined as those who have had at least 100 cigarettes per year and smoke some days or every day. Non-smokers were defined as those having smoked fewer than 100 cigarettes in their lifetime and serum cotinine level ≤ 0.05 ng/mL or having quit smoking over 3 years ago with serum cotinine level ≤ 0.05 ng/mL. Passive smokers were defined as having smoked fewer than 100 cigarettes in their lifetime and serum cotinine level > 0.05 ng/mL or having quit smoking over 3 years ago with serum cotinine level > 0.05 ng/mL or inhaling the smoke from others' cigarettes at work or at home and serum cotinine level > 0.05 ng/mL.

Table 2
Geometric means of blood and urinary Cd by quintiles of Ca and Zn intake in NHANES 2007–2012 (n = 3900).

	n	Blood Cd (μg/L)			n	Urinary Cd (μg/g creatinine)		
		Mean	95% CI	P for trend[b]		Mean	95% CI	P for trend[b]
Ca intake (mg/d)[a]				< 0.01				< 0.01
Q1	780	0.4	(0.40, 0.48)		780	0.28	(0.25, 0.31)	
Q2	780	0.4	(0.34, 0.39)		780	0.2	(0.21, 0.26)	
Q3	780	0.4	(0.35, 0.43)		780	0.2	(0.22, 0.26)	
Q4	780	0.3	(0.28, 0.32)		780	0.2	(0.19, 0.23)	
Q5	780	0.3	(0.28, 0.32)		780	0.2	(0.19, 0.23)	
Zn intake (mg/d)[a]				0.068				< 0.01
Q1	780	0.4	(0.38, 0.47)		780	0.3	(0.26, 0.31)	
Q2	780	0.4	(0.36, 0.44)		780	0.2	(0.22, 0.27)	
Q3	779	0.3	(0.31, 0.36)		779	0.2	(0.20, 0.23)	
Q4	781	0.3	(0.30, 0.36)		781	0.2	(0.19, 0.23)	
Q5	779	0.3	(0.26, 0.31)		779	0.2	(0.19, 0.23)	

[a] Intake from diet and supplements.
[b] Adjusted for age, gender, ethnicity, BMI, poverty income ratio, alcohol consumption, education level, dietary supplement use and smoking status.

respectively) (Table 3).

We found that there was interaction between Zn intake and smoking status in a fully adjusted regression model (P-trend < 0.05). Thus, we further analyzed the associations by dividing the study participants into three subgroups by smoking status. In an unadjusted model, Zn intake was inversely associated with blood Cd concentrations among non-smokers and passive smokers. However, these associations were attenuated and no longer significant after adjusting for relevant covariates. In an unadjusted model, Zn intake was inversely associated with urinary Cd concentrations among non-smokers and current smokers, whereas in a fully adjusted regression model, the inverse association was significant only among non-smokers (β = −0.034, P-trend < 0.05) (Table 4).

Failure to meet the RDA for Zn intake from diet and from diet and supplements was less common among non-smokers (34.6% and 22.4%, respectively) compared to current smokers (46.2% and 38.8%, respectively) (Fig. 1). Failure to meet the RDA for Zn intake from diet and supplements was more common among those in the highest quintile of blood Cd and urinary Cd compared to those with lower blood and urine Cd concentrations (Fig. 2).

In an unadjusted model, Zn intake was inversely associated with blood and urinary Cd concentrations among all participants, regardless of whether dietary Zn intake met the RDA. After adjustment for relevant variables, Zn intake was no longer significantly associated with blood Cd concentrations. In a fully adjusted regression model, dietary Zn intake was inversely associated with urinary Cd concentrations only among participants meeting the RDA for Zn (Table 5).

4. Discussion

In this nationally representative study, US adults with the highest blood and urinary Cd concentrations tended to be older, current smokers, and to be underweight. This finding is consistent with previous work reporting the highest Cd burden in older adults and current smokers in a sample of Canadian adults (Garner and Levallois, 2016). Also, our results are in agreement with a Flemish study showing that BMI was inversely associated with urinary Cd (Dhooge et al., 2010). The present study also found that females had higher blood Cd and urinary Cd than males, which is consistent with a previous report showing that blood and urinary Cd concentrations were 1.8 and 1.4 times greater, respectively, in women than men (Olsson et al., 2002).

The current study showed that dietary Zn intake is inversely associated with urinary Cd in the US adult population. This finding is consistent with previous research from our group reporting that Zn intake is associated with lower Cd burden in US adults (Vance and Chun, 2015). Because Zn and Cd share transporters and can be transported via transmembrane proteins ZIP8 and ZIP14 (Jenkitkasemwong et al., 2012), it is plausible that this finding may be explained by the competitive interactions between Cd and Zn at the levels of various transporters and metallothionein. The Omega study, involving 558 women from Seattle and Tacoma, Washington, showed that dietary Zn intake was positively associated with urinary Cd (Osorio-Yáñez et al., 2018), which is not consistent with our findings in this study. One possible reason for this inconsistency may be related to the different methods of estimating dietary Zn intake. While Osorio-Yanez et al. estimated Zn intake from diet only, we estimated Zn intake from both diet and supplements. In our analysis, Zn intake from supplements accounted for 29% of total Zn intake on average from both diet and supplements, indicating that previous work not accounting for supplemental Zn may substantially underestimate Zn intake.

Of importance is our finding that the relationship between dietary Zn and urinary Cd concentrations differed by smoking status. In a fully adjusted multivariate regression model, there was an interaction between Zn intake and smoking status, indicating that the relationship between Zn intake and urinary Cd is significantly different by smoking status. We therefore investigated the associations of Zn intake with urinary Cd by smoking status. In a fully adjusted multivariate regression model, Zn intake was inversely associated with urinary Cd among non-smokers, but not among current or passive smokers. Diet is known to be the most significant source of Cd exposure among non-smokers (Garner and Levallois, 2016), but tobacco smoke has been reported to be the greatest contributor to Cd burden among smokers (Jenkitkasemwong et al., 2012). Diet is estimated to provide approximately 30 μg Cd per day, of which roughly 1–10% is absorbed into the body (Agency for Toxic Substances and Disease Registry, 2012). It is also estimated that a single cigarette contains between 1 and 3 μg Cd

Table 3
Association between Cd intake from foods and blood and urinary Cd by smoking status in NHANES 2007–2012 (n = 3900).

Cd from foods (μg/d)	Blood Cd (μg/L)		Urine Cd (μg/g creatinine)	
	β	P trend[b]	β	P trend[b]
All[a]	0.0065	0.085	0.0121	< 0.05
Non-smokers	0.0113	< 0.05	0.0167	< 0.05
Passive smokers	0.0079	0.210	0.0101	0.173
Current smokers	−0.0073	0.431	−0.0058	0.450

[a] Additionally adjusted for smoking status; Blood Cd and urinary Cd were used as outcome variables and were log-transformed.
[b] Multivariate regression model was adjusted for age, gender, ethnicity, BMI, poverty income ratio, alcohol consumption, education level, dietary supplement use, Ca intake and Zn intake.

Table 4
Geometric means of blood and urinary Cd (μg/g creatinine) by quintiles of Zn intake in NHANES 2007–2012 (n = 3900).

Quintile of Zn intake (mg/d)	Blood Cd (μg/L)								
	Smoking status								
	Nonsmokers[a]			Passive smokers[b]			Current smokers[c]		
	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
Q1	423	0.31	(0.29, 0.34)	196	0.32	(0.28, 0.37)	159	0.94	(0.78, 1.13)
Q2	425	0.27	(0.25, 0.30)	197	0.26	(0.23, 0.30)	161	1.01	(0.87, 1.18)
Q3	423	0.25	(0.23, 0.27)	197	0.29	(0.26, 0.32)	159	0.98	(0.83, 1.17)
Q4	423	0.28	(0.25, 0.30)	197	0.24	(0.21, 0.27)	160	0.83	(0.71, 0.96)
Q5	424	0.25	(0.23, 0.27)	196	0.25	(0.23, 0.29)	160	0.9	(0.78, 1.03)
P-trend[d]		< 0.01			< 0.01			0.281	
P-trend[e]		0.137			0.992			0.745	
Quintile of Zn intake (mg/d)	Urinary Cd (μg/g creatinine)								
	Smoking status								
	Nonsmokers[a]			Passive smokers[b]			Current smokers[c]		
	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
Q1	423	0.26	(0.23, 0.30)	196	0.22	(0.17, 0.28)	159	0.37	(0.28, 0.49)
Q2	425	0.23	(0.20, 0.26)	197	0.18	(0.15, 0.21)	161	0.38	(0.32, 0.46)
Q3	423	0.21	(0.18, 0.24)	197	0.19	(0.16, 0.23)	159	0.3	(0.25, 0.37)
Q4	423	0.21	(0.19, 0.24)	197	0.15	(0.13, 0.18)	160	0.28	(0.23, 0.34)
Q5	424	0.22	(0.19, 0.24)	196	0.19	(0.16, 0.22)	160	0.27	(0.22, 0.33)
P-trend[d]		< 0.05			0.170				
P-trend[e]		< 0.05	(β = −0.034)		0.295			0.338	

[a] Non-smokers were defined as those having smoked fewer than 100 cigarettes in their lifetime and serum cotinine level ≤ 0.05 ng/mL or having quit smoking over 3 years ago with serum cotinine level ≤ 0.05 ng/mL.
[b] Passive smokers were defined as having smoked fewer than 100 cigarettes in their lifetime and serum cotinine level > 0.05 ng/mL or having quit smoking over 3 years ago with serum cotinine level > 0.05 ng/mL or inhaling the smoke from others' cigarettes at work or at home and serum cotinine level > 0.05 ng/mL.
[c] Current smokers defined as those who have had at least 100 cigarettes per year and smoke some days or every day.
[d] Unadjusted.
[e] Adjusted for: age, gender, BMI, ethnicity, poverty income ratio, education level, alcohol intake, dietary supplement intake, Ca intake and Cd intake.

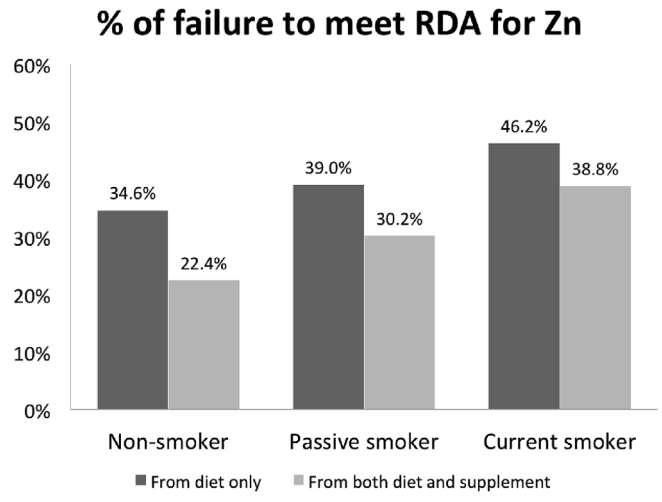

Fig. 1. Percentages of participants failing to meet the RDA for Zn intake by smoking status in NHANES 2007–2012.

(Bernhard et al., 2005; Elinder et al., 1983; Pappas et al., 2006). About 10% of the cigarette's Cd is inhaled when it is smoked (McCarty, 2012) and 50% or more of the Cd deposited in the alveoli will ultimately be absorbed (Agency for Toxic Substances and Disease Registry, 2012). Consequently, smokers may have two or more times the Cd burden of non-smokers (Agency for Toxic Substances and Disease Registry, 2012). Increased Zn intake may help moderate Cd absorption from the intestinal tract by increasing competition for binding to metallothionein, thereby reducing metallothionein synthesis. However, it is plausible that among smokers, whose main Cd exposure may be through smoke inhalation rather than through diet, the Zn-Cd relationship is relatively less important for determining total Cd burden compared to non-smokers. However, further research is needed to confirm whether the protective effects of Zn on Cd burden observed in this study are causal in nature, and to examine the mechanisms by which Zn may reduce Cd burden.

This study showed that in the US adult population, the levels of blood and urinary Cd were higher among current smokers than non-smokers. It was also found that failure to meet the RDA for Zn from diet and supplements was more common among those in the highest quintile of blood Cd and urinary Cd, and more common among current smokers compared to non-smokers. In a fully adjusted regression model, Zn intake was inversely associated with urinary Cd concentrations only among subjects meeting the RDA for Zn. These findings suggest that the protective effect of dietary Zn intake on Cd burden differs by smoking status and that there is likely a threshold intake level of Zn below which no protective effect is observable.

A major strength of the present study is the use of a large, nationally representative sample of the US population. Use of this large survey additionally allows for detailed analysis of the Zn-Cd relationship across participants with a wide range of Zn intakes, both below and above the RDA, and among those with varied smoking behaviors and Cd exposure profiles from diet and tobacco smoke. However, this study has several limitations. First, no causal inference can be drawn from these findings because of this study's cross-sectional design. Second, estimation of Zn and Cd intakes were based on two days of 24-hr dietary recall data, which may not accurately reflect usual intake. Third, we did not consider metabolism and bioavailability of Cd and Zn. Fourth, Cd intake

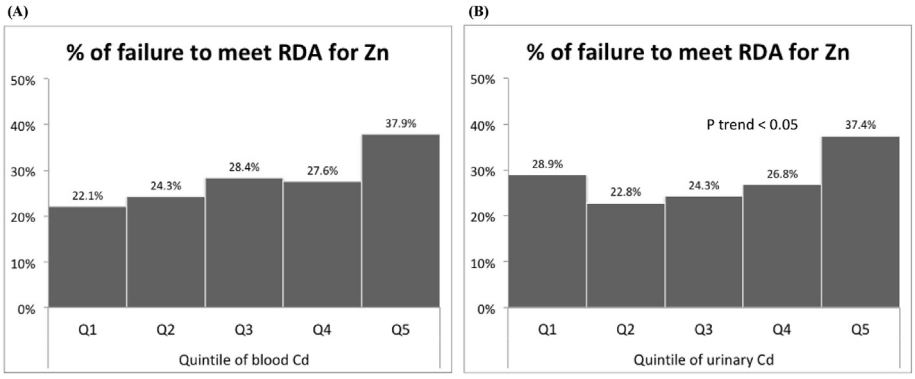

Fig. 2. Percentages of participants failing to meet the RDA for Zn intake by quintiles of (A) blood Cd (μg/L) and (B) urinary Cd (μg/g creatinine) in NHANES 2007–2012.

Table 5
Geometric means of blood Cd (μg/L) and urinary Cd (μg/g creatinine) of subjects by quintile of Zn intake among those meeting and failing to meet dietary Zn adequacy in NHANES 2007–2012 (n = 3900).

Zn intake (mg/d)	Blood Cd (μg/L)						Urinary Cd (μg/g creatinine)					
	Subjects under RDA of Zn			Subjects above RDA of Zn			Subjects under RDA of Zn			Subjects above RDA of Zn		
	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
Q1	251	0.47	(0.40, 0.55)	527	0.41	(0.37, 0.46)	251	0.31	(0.25, 0.38)	527	0.28	(0.25, 0.32)
Q2	253	0.42	(0.35, 0.50)	528	0.32	(0.29, 0.35)	253	0.29	(0.25, 0.34)	528	0.2	(0.18, 0.23)
Q3	253	0.37	(0.31, 0.44)	528	0.32	(0.30, 0.35)	253	0.25	(0.20, 0.31)	528	0.2	(0.18, 0.23)
Q4	253	0.4	(0.34, 0.47)	528	0.33	(0.30, 0.36)	253	0.24	(0.19, 0.32)	528	0.21	(0.19, 0.24)
Q5	252	0.34	(0.29, 0.41)	528	0.28	(0.25, 0.31)	252	0.18	(0.16, 0.21)	528	0.21	(0.19, 0.24)
P-trend[a]		< 0.01			< 0.0001			< 0.001			< 0.01	
P-trend[b]		0.929	(β = −0.002)		0.057	(β = −0.034)		0.384	(β = −0.026)		< 0.05	(β = −0.031)

[a] Unadjusted.
[b] Adjusted for: age, gender, BMI, ethnicity, poverty income ratio, education level, alcohol intake, dietary supplement intake, Ca intake and Cd intake.

may have been underestimated because Cd database in TDS may contain values for only a fraction of food consumed by US population. Finally, residual confounding may remain in this analysis, although we attempted to adjust all relevant covariates available in the NHANES dataset. Future research is needed to clarify the population groups in which dietary Zn may be most protective and the optimal intake level of Zn to maximize its potential benefit.

In conclusion, our results demonstrate that the Zn-Cd relationship differs by smoking status. Greater Zn intake was associated with lower urinary Cd concentration only among non-smokers, but not in smokers, supporting the hypothesis that dietary Zn may protect against Cd burden.

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Transparency document

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