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Cigarette smoking, cadmium exposure, and zinc intake on obstructive lung disorder

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Abstract

Background and objective: This study examined whether zinc intake was associated with lower risk of smoking-induced obstructive lung disorder through interplay with cadmium, one of major toxicants in cigarette smoke.

Methods: Data were obtained from a sample of 6,726 subjects aged 40+ from the Third National Health and Nutrition Examination Survey. The forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were measured using spirometry. Gender-, ethnicity-, and age-specific equations were used to calculate the lower limit of normal (LLN) to define obstructive lung disorder as: observed FEV1/FVC ratio and FEV1 below respective LLN. Zinc intake was assessed by questionnaire. Logistic regression analysis was applied to investigate the associations of interest.

Results: The analyses showed that an increased prevalence of obstructive lung disorder was observed among individuals with low zinc intake regardless of smoking status. The adjusted odds of lung disorder are approximately 1.9 times greater for subjects in the lowest zinc-intake tertile than those in the highest tertile (odds ratio = 1.89, 95% confidence interval = 1.22-2.93). The effect of smoking on lung function decreased considerably after adjusting for urinary cadmium. Protective association between the zinc-to-cadmium ratio (log-transformed) and respiratory risk suggests that zinc may play a role in smoking-associated lung disorder by modifying the influence of cadmium.

Conclusions: While zinc intake is associated with lower risk of obstructive lung disorder, the role of smoking cessation and/or prevention are likely to be more important given their far greater effect on respiratory risk. Future research is warranted to explore the mechanisms by which zinc could modify smoking-associated lung disease.

Background

Obstructive lung disorders including chronic obstructive pulmonary disease (COPD) are characterized by chronic airway inflammation and ensuing airflow limitation. Although cigarette smoking is the most important risk factor for obstructive lung disease, the underlying mechanisms are still not completely understood. For instance, it has been suggested that COPD results from smoking-associated inflammation and oxidative damage to key enzymes (e.g., alpha 1-antitrypsin deficiency) [1], but not all smokers develop COPD [2], and some former smokers have persistent inflammation and remain at risk [3]. Both animal and human epidemiologic data indicate that exposure to cadmium (Cd), a constituent of cigarette smoke, is associated with oxidative stress and chronic inflammation [4-7]. Increasing evidence indicates that Cd

may play a role in smoking-induced disorders including impaired lung function [8,9], diabetes and hypertension [10-12]. Of note, once entering the body, Cd is transported in the blood and bound to plasma proteins, mainly metallothionein [13], a cysteine rich protein and scavenger of OH radical [14]. Thus the binding of metallothionein with Cd is an essential adaptation to Cd poisoning because it can prevent free Cd ions from exerting their toxicity [15]. The resulting metallothionein mediated reduction in Cd toxicity however, potentially comes at the expense of lowering the reserve capacity for buffering OH radicals; thus exposing tissues to oxyradical damage from other sources [16].

Given zinc (Zn) is a trace element and an effective inducer of metallothionein, we proposed the hypothesis that the risk of developing smoking-associated obstructive lung disease could be modified by Zn intake through modification of Cd toxicity. To test this hypothesis, we evaluated whether the association between obstructive lung disorders and cigarette smoking varies with dietary

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Zn intake, accounting for other risk factors. The analysis was conducted using a population-based, nationally representative sample from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-94).

Materials and methods

Data source and study population

The NHANES is a series of national health examination surveys, conducted by the National Center for Health Statistics (NCHS) of the Center for Disease Control and Prevention, to collect data on the health and nutritional status of a representative sample of the non-institutionalized civilian US population by using a multistage, stratified sampling design [17]. The protocol was approved by the NCHS Research Ethics Review Board (ERB) and all subjects provided written informed consent. The analysis of this study was restricted to 8,745 non-Hispanic Whites, non-Hispanic Blacks, and Mexican Americans aged 40 yrs or older with valid spirometry measurements in the NHANES III survey (1988-94). A total of 868 subjects with missing information for covariates of interest (e.g., urinary Cd) were excluded from the analyses. Pregnant subjects (n = 65) and those with unreliable or incomplete information on Zn intake, such as type, frequency, and amount of vitamin and mineral supplement use (n = 1,086) were excluded. This resulted in a final sample of 6,726 subjects in the current analysis.

Lung function measurement and Definition of obstructive lung disorders

Lung function was assessed with standard determinations of the forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) with dry rolling-seal spirometer (Ohio 827 rolling seal spirometer; Ohio Medical Instrument Company, Cincinnati, Ohio) following the procedures described by the American Thoracic Society (ATS) in 1987 [18]. The largest FVC and FEV1 obtained from acceptable maneuvers were used for the analysis. As suggested by ATS and European Respiratory Society (ERS) [19], the predicted values for the lower limit of normal (LLN) of the FEV1/FVC ratio and FEV1 were calculated for each subject using gender-, ethnicity-, and age-specific equations reported by Hankinson et al. (1999) [20]. In the current analysis, the subject was categorized as having obstructive lung disorder if his/her observed FEV1/FVC ratio and FEV1 were less than respective LLN [20,21].

Collection of demographic, dietary, and laboratory data

Self-reported demographic characteristics including age, gender, body mass index (BMI), race/ethnicity, and cigarette smoking status were obtained during the survey interview. BMI was calculated from measured height and weight, and categorized as underweight (<18.5 kg/m²),

normal (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), and obese (≥ 30 kg/m²) [22]. Smoking status was classified as: never-smokers (<100 life time cigarettes), former smoker (≥ 100 but not currently smoking), and current smoker (≥ 100 and current smoking) [23]. The average time of smoking cessation for former smokers was 18.2 years (range: <1 - 87 years)(data not shown). Pack-years of smoking was also determined as the reported average number of packs smoked per day by the number of years smoked (1 pack-year = 20 cigarettes/day for 1 year). The concentrations of serum cotinine (the metabolite of nicotine) were also measured from all subjects using high performance liquid chromatography (HPLC)-atmospheric pressure chemical ionization tandem mass spectrometry [24] to control for environmental smoking.

Dietary intake data were collected by trained interviewers using an automated NHANES III Dietary Data Collection System described previously [25]. In brief, total intake of daily Zn was estimated by summing dietary Zn intake from food, beverage and supplements (vitamins and mineral products used during the past month) assessed by 24-hr dietary recall and food-frequency interviews. Urinary Cd concentration, commonly used to characterize cadmium exposure [26,27], was measured using Zeeman graphite furnace atomic absorption spectrometry (Perkin-Elmer Corp., Norwalk, CT) [24] with a detection limit of 0.01 µg/L and was adjusted for urinary creatinine [28,29].

Statistical analyses

To investigate the role of Zn intake in smoking-related lung disorder, the differences in prevalence of obstructive lung disorder across demographic characteristics were first assessed with Cochran-Mantel-Haenszel chi-square tests. The odds ratios (OR) with 95% confidence interval (95% CI) generated from logistic regression models were then used to examine the association of interests. The interactions of zinc intake with smoking and cadmium exposure were also examined, and the chi-squared trend test was used to evaluate whether there were trends in the odds ratios across categories of zinc intake and cigarette smoking/cadmium exposure. Logarithmic transformations were performed to normalize the data distribution where necessary. We applied mobile examination center (MEC)/home-examined statistical sampling weight to account for the complex stratified multistage sampling in NHANES III and used SUDAAN 9.03 (Research Triangle Institute, 2004) with the Taylor series linearization method [30] to obtain unbiased standard errors for all statistical analyses. Thus, the percentages and regression estimates reported here represent estimates for the U.S. population. Tertile cutoffs of dietary Zn and urinary Cd were determined according to the weighted distribution

in the study samples. The level of statistical significance was set at 0.05.

Results

The crude prevalence of obstructive lung function by demographic characteristics of the participants aged 40 years or older is shown in table 1. As expected, the prevalence of obstructive lung disorder increased in the order: never-smokers (2.99%) < former smokers (9.55%) < active smokers (17.7%). A similar pattern of results was evident for pack-years of cigarettes as: zero pack-years (3.08%) < greater than zero-19 pack years (6.50%) < greater than 20

pack-years (19.6%). Individuals with low Zn intake (in the low tertile of Zn intake < 8.35 mg/day) had higher prevalence of obstructive lung disorder than did those with middle (8.35-14.4 mg/day) and high (> 14.4 mg/day) Zn intake ($p = 0.01$). The geometric mean and 5th-to-95th percentile range for daily Zn intake were 11.0 and 4.09-34.4 mg/day, respectively (data not shown). Also, obstructive lung disorder was generally more prevalent among elderly and non-Hispanic whites. For instance, the prevalence of individuals with obstructive lung function among those aged 55 years or older was approximately twice that of subjects aged 40-54. BMI was inversely asso-

Table 1: Prevalence of obstructive lung disorder by demographic characteristics

Characteristics	N	Prevalence of obstructive lung function (95%CI) ^a	P-value ^b
Smoking status			< 0.001
Never-smokers	2948	2.99 (2.14-4.16)	
Former smokers	2306	9.55 (7.77-11.7)	
Active smokers	1472	17.7 (15.2-20.6)	
Pack years of cigarettes			< 0.001
0	3171	3.08 (2.24-4.23)	
>0-19	1874	6.50 (5.05-8.33)	
? 20	1681	19.6 (16.7-22.9)	
Zinc intake, mg/d			0.01
Tertile 1 (< 8.35)	2464	11.4 (8.78-14.7)	
Tertile 2 (8.30-14.4)	2135	8.66 (6.99-10.7)	
Tertile 3 (>14.4)	2127	6.60 (5.39-8.07)	
Age, yrs			< 0.001
40-54	2484	5.97 (4.38-8.10)	
55 or older	4242	11.5 (10.2-12.9)	
Gender			0.16
Male	3288	9.55 (8.06-11.3)	
Female	3438	8.13 (6.62-9.94)	
Race/Ethnicity			< 0.001
Mexican American	1522	4.86 (3.70-6.37)	
Non-Hispanic black	1500	5.58 (4.09-7.57)	
Non-Hispanic white	3704	9.26 (7.93-10.8)	
Body mass index, kg/m ²			0.001
<18.5	106	33.9 (20.0-51.3)	
18.5-24.9	2120	9.80 (7.66-12.5)	
25-29	2634	7.96 (6.59-9.60)	
? 30	1866	7.10 (5.87-8.57)	

^a Obstructive lung disorder was defined as: observed FEV1/FVC ratio < [FEV1/FVC]_{LLN} and observed FEV1 < [FEV1]_{LLN} [20,21]. The estimated prevalence of obstructive lung disorder was calculated using the NHANES III sample weights.

^b Cochran-Mantel-Haenszel chi-square test.

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced volume vital capacity; LLN, lower limit of normal.

ciated with obstructive lung function that was significantly increased among underweight subjects (BMI less than 18.5) as compared to subjects with higher BMI. The relationship of obstructive lung disorder with low body weight may represent existing poor health in this subgroup. Overall, the age-adjusted (2000 U.S. population) prevalence of obstructive lung disease among U.S. adults aged 40+ was 8.63% (95% CI = 7.39-10.1%, data not shown).

When all of the covariates were considered jointly in a multiple logistic regression model on obstructive lung disease, the protective effect of Zn intake remained significant (table 2). For instance, as shown in model 1, those who currently had lowest Zn intake were twice as likely to have obstructive lung disorder compared to those with the highest tertile of Zn intake after adjustment for covariates (OR = 1.97, 95% CI = 1.28-3.03). Of other risk factors examined in the study, cigarette smoking is the leading cause of obstructive lung disorder, followed by BMI, age, and race-ethnicity. Comparable results were obtained by replacing smoking status with pack years of cigarettes (Additional file 1).

Interestingly, the effect (estimated OR) of smoking on the obstructive lung disorder decreased approximately 20-40% in model 2 as compared to model 1. Whereas the influence of Zn on respiratory risk remained the same, the odds ratios for both smoking status and urinary Cd were reduced by another 15-50% with further adjustment of pack years of cigarettes (data not shown). Indeed, pack years of cigarettes, urinary Cd, and smoking status were significantly correlated with each other. For instance, urinary Cd was associated with both pack years of cigarettes (Spearman correlation = 0.34, $p < 0.001$, data not shown) and cigarette smoking status that the geometric means (standard error) for urinary Cd were 0.87 (0.04), 0.53 (0.02), and 0.36 (0.02) $\mu\text{g/g}$ creatinine in active smokers, former smokers, and never-smokers, respectively ($p < 0.001$, data not shown). On the other hand, the cadmium effect on obstructive lung disorder is also significant and is independent of smoking (model 2). Despite the lack of statistical significance for either Zn-smoking ($p = 0.68$) or Zn-Cd interactions ($p = 0.06$) (data not shown), there are positive trends in the odds ratios among individuals who had low Zn intake across all smoking status categories (figure 1a), or urinary cadmium concentrations (figure 1b) ($P_{trend} < 0.05$ for both). In addition, there was an inverse relationship between Zn intake and urinary Cd following adjustment for other covariates (the estimated regression coefficient \pm standard error = -0.097 ± 0.023 , $p < 0.001$, data not shown). The plot of an adjusted log-odds of obstructive lung disorder versus the ratio of Zn to Cd suggested that higher ratios were in fact protective (figure 2). These results indicate that Zn may moderate the toxic role of Cd in cigarette smoking.

Discussion

While the current findings are consistent with earlier studies suggesting that smoking is the leading cause of obstructive lung disease in the U.S. population aged 40+ [31,32], we also found that Zn intake is associated with lower risk of obstructive lung disorder across cigarette smoking status. The effect persisted even after adjustment for other respiratory risk factors such as age. Of note, the negative effect of cigarette smoking on obstructive lung disorder decreased after adjusting for urinary Cd in the multivariable analyses. Indeed, cigarette smoking is one of the major sources of environmental exposure to Cd [33,34]. It has been suggested that Cd plays an important role in promoting oxidative stress and inflammation [5,6]. The current findings support the prior evidence suggesting that cadmium exposure, as a risk factor independent of cigarette smoking, is associated with impaired lung functions and presumably other cadmium-associated diseases such as cardiovascular disease [8,35]. Considering its 10-30 year half-life in the body compared to other shorter lived constituents of cigarette smoke [13,36], Cd might reasonably explain some of the sustained obstructive lung disorder observed among former smokers who had not smoked in years [3].

The current analyses reveal a protective association between the zinc-to-cadmium ratio (log-transformed) and reduced respiratory risk suggesting that Zn may moderate the risk of smoking-associated lung disorders through interplay with Cd. Zn is essential to the production of metallothionein, a key component in the detoxification kinetics of Cd in the human body [13,14]. Metallothionein alone can passively extract the interfering Cd and reduce its toxic load directly. The inverse association between Zn and Cd adds support to the hypothesis that when sufficient Zn is available, metallothionein not only extracts the offending Cd, but actively restores structure and function by donating the missing Zn [37]. Alternatively, the positive influence of Zn may also result from the anti-inflammatory and anti-oxidant activities of a spectrum of Zn-dependent enzymes and transcription factors [38,39]. It was found, for instance, reported that zinc can decrease the production of inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) via inhibition of NF-kappaB activation [38].

The current findings were generally compatible with the U.S. Recommended Dietary Allowances (RDAs) for Zn intake at 11 and 8 mg/day for men and women aged 19+, respectively [40]. Adequate intake of Zn is associated with lower risk of obstructive lung disease, presumably through mitigation of inflammatory and oxidative stresses associated Cd exposure. A potential benefit of higher Zn intake may exist for former smokers, who demonstrate a consistent trend toward lower risk at higher Zn

Table 2: Multivariate-adjusted logistic regression of obstructive lung disorder using smoking status as the measure of tobacco exposure

	Model 1b		Model 2b	
	OR (95% CI)	p	OR (95% CI)	p
Smoking status		< 0.001		< 0.001
Never-smokers	1.00 (1.00-1.00)		1.00 (1.00-1.00)	
Former smokers	3.37 (2.21-5.14)		2.60 (1.67-4.06)	
Active smokers	7.66 (4.97-11.79)		4.38 (2.71-7.08)	
Zinc intake, mg/d		0.01		0.01
Tertile 1 (< 8.35)	1.97 (1.28-3.03)		1.89 (1.22-2.93)	
Tertile 2 (8.30-14.4)	1.36 (0.95-1.96)		1.29 (0.91-1.82)	
Tertile 3 (>14.4)	1.00 (1.00-1.00)		1.00 (1.00-1.00)	
Age, yrs (55 or older)	2.39 (1.75-3.25)	< 0.001	1.82 (1.33-2.49)	< 0.001
Gender (male)	1.13 (0.84-1.53)	0.38	1.37 (0.99-1.89)	0.05
Race/Ethnicity		< 0.001		0.001
Mexican American	0.61 (0.42-0.88)		0.61 (0.41-0.89)	
Non-Hispanic black	0.45 (0.30-0.69)		0.47 (0.31-0.73)	
Non-Hispanic white	1.00 (1.00-1.00)		1.00 (1.00-1.00)	
Body mass index, kg/m ²		0.001		0.001
<18.5	3.99 (1.81-8.79)		3.63 (1.72-7.63)	
18.5-24.9	1.00 (1.00-1.00)		1.00 (1.00-1.00)	
25-29	0.83 (0.62-1.11)		0.81 (0.60-1.11)	
? 30	0.78 (0.56-1.08)		0.79 (0.56-1.11)	
Urinary cadmium, ?g/g creatinine				0.001
Tertile 1 (< 0.39)	-		1.00 (1.00-1.00)	
Tertile 2 (0.39-0.79)	-		1.54 (0.98-2.43)	
Tertile 3 (>0.79)	-		3.48 (2.54-4.76)	

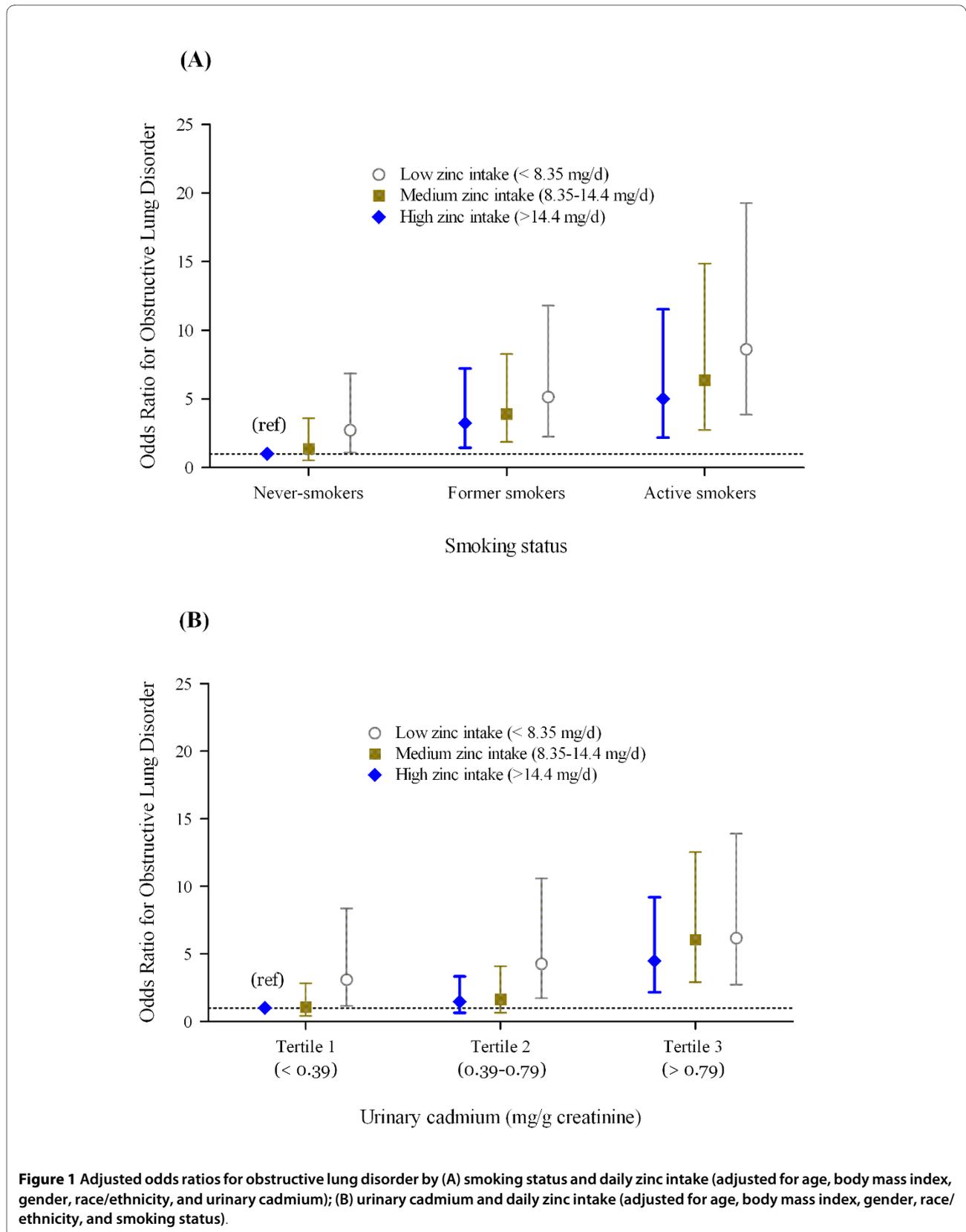
^a Obstructive lung disorder was defined as: observed FEV1/FVC ratio < [FEV1/FVC]_{LLN} and observed FEV1 < [FEV1]_{LLN} [20,21]. The estimated prevalence of obstructive lung disorder was calculated using the NHANES III sample weights.

^b Both model 1 and 2 accommodated smoking status, zinc intake, and other covariates including age, gender, race/ethnicity, and body mass index, whereas model 2 was further adjusted for urinary cadmium.

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced volume vital capacity; LLN, lower limit of normal.

intakes suggesting again that the Zn-Cd exchange may be an important clearance mechanism. Although the most appropriate Zn intake related to a lower risk of obstructive lung disorder is unclear, the increased respiratory risk of low Zn intake is apparent even in never smokers. There were several limitations of the current study that need to be addressed. First, the cross-sectional design of NHANES data only permits the investigation of associations rather than causation among Cd, Zn, smoking, and obstructive lung disease. The results, nevertheless, were biologically plausible and supported by epidemiologic and animal data [15,38]. Future work with a longitudinal follow-up design would help verify these findings. Second, despite its demonstrated validity as a reliable mea-

surement of food intake [41,42], the 24-hour recall and self-reported dietary supplement data may not provide a precise estimation of Zn intake. When available, serum or urinary Zn levels, which were not measured in NHANES III, could help clarify the role of Zn in smoking-associated lung disease. Finally, although we adjusted for a number of confounding factors, such as age, the confounding influences of unmeasured factors (e.g. genetic background) cannot be excluded. For instance, tumor necrosis factor-alpha (TNF-?) and interleukin-10 (IL-10) represent pro- and anti-inflammatory cytokines, respectively, and polymorphisms in TNF-? and IL-10 have been associated with obstructive lung disease [43,44], a complex disease characterized by airway obstruction and



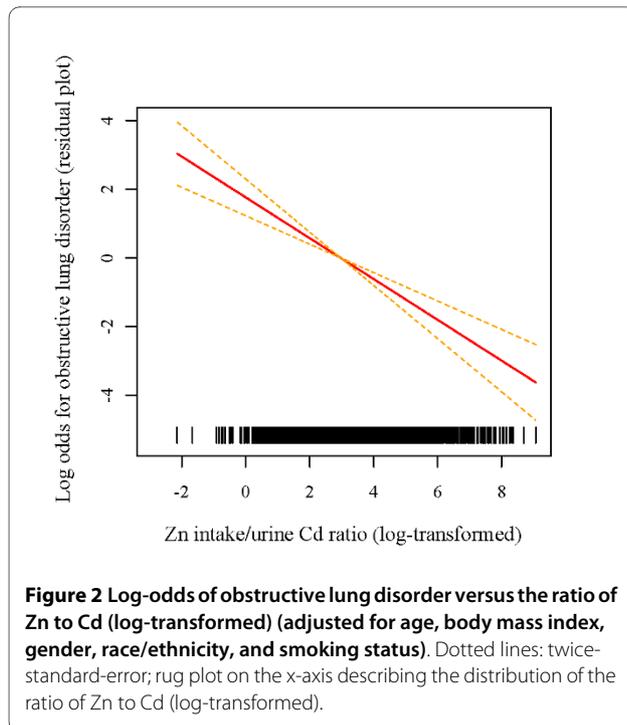


Figure 2 Log-odds of obstructive lung disorder versus the ratio of Zn to Cd (log-transformed) (adjusted for age, body mass index, gender, race/ethnicity, and smoking status). Dotted lines: twice-standard-error; rug plot on the x-axis describing the distribution of the ratio of Zn to Cd (log-transformed).

inflammation. Thus, a delicate balance between pro- and anti-inflammatory responses could well determine protection from or susceptibility to the pathogenesis of obstructive lung disease such as COPD [45]. In conclusion, the current study demonstrated that Zn intake is associated with lower risk of developing smoking-associated obstructive lung disorder for smokers and non-smokers alike. The interplay between Zn and Cd presumably plays a role in mediating the toxic effect of smoking. Although Zn intake is associated with lower risk of obstructive lung disease, the risk reduction associated with smoking cessation or never smoking is much greater. Thus, smoking prevention and cessation programs should remain a cornerstone of public health policy to reduce the subsequent risk of obstructive lung disease.

Selected Abbreviations

Cd: Cadmium; COPD: Chronic obstructive pulmonary disease; LLN: Lower limit of normal; NHANES III: The Third National Health and Nutrition Examination Survey; OR: Odds ratio; Zn: zinc; 95% CI: 95% confidence interval.

Disclaimers

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention. The corresponding author has full access to all of the data in the study and takes responsibility for the integrity of the

data and the accuracy of the data analysis. The authors do not have any affiliation with NHANES.

Additional material

Additional file 1 Multivariate-adjusted logistic regression of obstructive lung disorder using pack-years of cigarettes as the measure of tobacco exposure.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JWL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YSL carried out the study. JWL and MHC participated in the design of the study and performed the statistical analysis. JLC and ND participated in the data interpretation and drafted the manuscript. All authors read and approved the final manuscript.

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