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Cadmium Exposure in Young Adulthood Is Associated with Risk of Nonalcoholic Fatty Liver Disease in Midlife

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Abstract

Background—Studies have suggested that cadmium (Cd) may be involved in the etiology of nonalcoholic fatty liver disease (NAFLD), but available data in human is sparse.

Aims—We aimed to examine Cd exposure in young adulthood in relation to prevalent NAFLD in midlife among American adults.

Methods—This study included 2446 participants from the Coronary Artery Risk Development in Young Adults study with toenail Cd measurement at exam year 2 (baseline) and computed tomography quantification of liver fat at exam year 25. Toenail Cd concentrations were considered as a reliable marker of long-term exposure. NAFLD was defined if liver attenuation < 51 Hounsfield units after excluding other possible causes of liver fat. Multivariable-adjusted logistic regression models were used to estimate the odds ratio of NAFLD by Cd exposure.

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Conflict of interest No potential conflicts of interest relevant to this article were reported.

Results—Median toenail Cd concentration was 8.2 ppb (inter-quartile range 4.3–18.6 ppb). After 23 years from baseline, 580 participants with prevalent NAFLD (24% prevalence) in midlife were identified. Compared with individuals in the lowest quartile, those in the highest quartile of toenail Cd had a significantly higher odds of NAFLD (OR: 1.43, 95% CI: 1.02, 1.99, *P* for trend: 0.04) after adjustment for demographics, socioeconomics, major lifestyle factors, and baseline levels of body mass index, lipids, and fasting insulin. The association was not significantly modified by race, sex, BMI, or smoking status at baseline.

Conclusions—Toenail Cd concentration was associated with a higher odds of prevalent NAFLD23 years later in life in this cohort of US general population.

Keywords

Nonalcoholic fatty liver disease; Toenail cadmium; CARDIA study; American young adults

Introduction

Nonalcoholic fatty liver disease (NAFLD) reflects excessive fat accumulation in the liver without a history of alcohol abuse or other causes of secondary hepatic steatosis presents [1]. NAFLD is a serious public health problem world-wide with an overall global prevalence of around 25% [2]. NAFLD is highly correlated to obesity and insulin resistance, but its pathophysiology has not been fully elucidated [3–5]. Recent studies indicate that exposure to environmental pollutants such as heavy metals may play an important role in NAFLD etiology [6–8].

Cadmium (Cd) is a toxic heavy metal found widely in the environment. For the general population, the two main sources of Cd exposure are cigarette smoking and consumption of contaminated foods and water [9]. Once Cd is absorbed, it accumulates in most organs, with the liver being one of the main reservoirs. Since the biological half-life of Cd in tissues exceeds 10 years, human exposure to Cd has raised serious health concerns [10]. Besides its possible contribution to a variety of cancers, including liver cancer [11, 12], and toxic effects on bones [13] and the cardiovascular system [14], Cd exerts toxic effects on the endocrine system [15]. A meta-analysis of seven studies with 20,555 individuals found that Cd exposure, even at low-to-moderate exposure levels, was associated with a higher risk of diabetes [16]. Since insulin resistance is considered in the pathogenesis of NAFLD, it is reasonably hypothesized that Cd exposure may increase the risk of NAFLD.

Theoretically, Cd can hamper liver function by inducing inflammation and oxidative stress, interfering with iron metabolism, and hindering lipid metabolism and fatty acid biosynthesis [17–19]. In animal models, a higher plasma level of liver enzymes, including aspartate transaminase (AST) and alanine transaminase (ALT), and a trend that fat accumulated in the liver were observed in mice treated with low-dose Cd [20]. However, human studies of Cd exposure, especially at low-to-moderate exposure level, and NAFLD are limited. The Third National Health and Nutrition Examination Survey in 1988–1994 (NHANES III) found that urinary Cd concentrations were associated with risk of NAFLD and nonalcoholic steatohepatitis (NASH) in the US general population in a cross-sectional analysis [21]. However, the association between long-term Cd exposure in young adulthood and NAFLD

risk later in midlife has not been investigated. Therefore, using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, we investigated baseline toenail Cd concentration in adults age 20–32 years old in relation to NAFLD risk 23 years later in a large cohort of black and white American adults.

Methods

Study Population

The study design and protocol of CARDIA has been previously reported [22]. CARDIA is a longitudinal cohort study that enlisted 5115 black and white men and women from four filed sites located in Chicago, IL; Birmingham, AL; Oakland, CA; and Minneapolis, MN. Participants were initially aged 18–30 years at exam year 0 (1985–1986) and were subsequently followed up in eight examination cycles (exam years 2, 5, 7, 10, 15, 20, and 25) over three decades. The response rates in follow-up exams are 91%, 86%, 81%, 79%, 74%, 72%, and 72% of the surviving cohort, respectively. Detailed information on the study design and protocol has been published.

Of the 5115 participants enrolled in CARDIA, 4623 returned at exam year 2 (Y2) when toenail Cd was measured (baseline). We excluded those who did not complete abdominal computed tomography (CT) at exam year 25 (Y25, $n = 1606$), who did not have toenail Cd measurements ($n = 151$), who were pregnant at Y25 ($n = 2$), who self-reported liver problems, cirrhosis, or hepatitis at Y25 ($n = 80$), who had high alcohol intake during follow-up (cumulative average consumption from baseline to Y25: ≥ 14 drinks/week for men or ≥ 7 drinks/week for women; $n = 290$), who had medications known to cause hepatic steatosis at Y25 ($n = 28$), and who had human immune deficiency virus at Y25($n = 20$). Thus, the analytic sample in this study included 2446 participants. We compared the major characteristics of CARDIA participants recruited at Y0 ($n = 5114$), returned at Y2 ($n = 4623$), and those included in this analysis ($n = 2446$). The results are showed in Supplemental Table 1. All participants gave written informed consent and the study's protocol was approved by the institutional review board of each participating institution.

Assessment of Toenail Cadmium and Other Trace Minerals

Toenail clippings collected at Y2 were stored in a central laboratory at ambient room temperature and humidity until analysis. The concentrations of Cd and arsenic were assessed at the University of Missouri-Columbia Research Reactor Center using collision-cell inductively coupled-plasma mass-spectrometry (CC-ICP-MS). Toenail selenium, mercury, zinc, and lead were quantified by instrumental neutron-activation analysis (INAA) [23].

Ascertainment of NAFLD

The detailed methods of adiposity assessments in the CARDIA study have been described previously [24]. In brief, abdominal CT was performed at Y25 using GE LightSpeed VCT 64 and GE 750HD 64 (GE Healthcare, Waukesha, WI) or Sensation 64 (Siemens Medical Solutions, Erlangen, Germany) multi-detector CT scanners [24]. Quality control and image analysis were conducted at Wake Forest University Health Sciences, Winston-Salem, NC. After we excluded other possible causes of liver fat (listed earlier), participants with CT liver

attenuation (LA) < 51 Hounsfield units were defined to have NAFLD that was equivalent to at-least-mild NAFLD [25]. LA assessment was conducted in the right lobe of the liver using CT slices through the upper abdomen. It was reported as the average of nine measurements on three slices using circular regions of interest of 2.6 cm^2. In a validation study of randomly selected 156 participants, the intra-class correlation coefficient between different readers was 0.975, suggesting a high reproducibility of CT measured LA in this study [26].

Assessment of Covariates

Demographic, socioeconomic, lifestyle, and clinical measurement variables were collected at baseline and each follow-up examination, unless specified otherwise. Participants were asked about their age, sex, race, and education level in a self-administered questionnaire and these information were verified during clinic examinations [22]. Daily intake of alcohol was assessed using CARDIA Alcohol Use Questionnaire and classified into four groups: 0 (never), 0.1–11.9, 12.0–23.9 or ≥ 24.0 mL/day. Smoking status was self-reported and classified into three groups: never, former, and current smokers. Using the CARDIA Physical Activity History Questionnaire, a physical activity score (exercise units, EU) was computed to assess moderate to vigorous physical activity [27]. Cumulative average alcohol consumption and physical activity through Y25 were calculated and used in the analyses to represent long-term lifestyle choices. During the clinical examinations, body mass index (BMI) was calculated using weight and height, and systolic and diastolic blood pressure (SBP and DBP) were measured by sphygmomanometer. Lipid profile including fasting plasma total cholesterol, triglycerides, and high-density lipoprotein (HDL)-cholesterol were analyzed by using an enzymatic procedure after dextran sulfate–magnesium precipitation, and low-density lipoprotein (LDL)-cholesterol was quantified by the Friedewald equation [22]. At Y0, 5, 7, 10, 15, 20, and 25, fasting plasma insulin and glucose concentrations were measured by the radioimmunoassay and hexokinase ultraviolet method, respectively [22].

Statistical Analysis

Participants were grouped in quartiles by the distribution of toenail Cd concentration. The characteristics of the study population were described in means ± standard deviations or percentages. Comparisons of the characteristics among groups were performed using ANOVA, Kruskal–Wallis test, or chi-squared test, as appropriate. Multivariable-adjusted logistic regression models were used to examine the association of toenail Cd concentration with risk of NAFLD by estimating odds ratios (ORs) and 95% confidence intervals (CIs). We adjusted for potential confounders with sequential modeling. First, we adjusted for age, sex, race, and field center. Additionally, we adjusted for educational attainment, baseline smoking status, cumulative average alcohol consumption through Y25, cumulative average physical activity through Y25, and baseline BMI. Further, we adjusted for a few clinical measurements. To avoid overfitting of the model, potential confounders were chosen based on their univariate associations with toenail Cd concentration and stepwise selection. Thus, baseline levels of HDL-cholesterol and insulin (Y0) were selected and adjusted for in model 3. A continuous variable was created using the median values of each Cd quartile for testing the trend.

To test the robustness of the results, a few sensitivity analyses were conducted. First, pregnant women at any examination were excluded. Second, some other trace minerals or heavy metals have been suggested to induce liver toxicity. To reduce the possible confounding by these elements, we further adjusted model 3 for toenail concentrations of arsenic, mercury, selenium, zinc, and lead. Third, NAFLD defined as CT LA < 40 Hounsfield units (equivalent to moderate-severe fat NAFLD) [26] was assessed in a sensitivity analysis. In stratified analyses, the association between toenail Cd concentration and NAFLD risk was examined in subgroups of race (White vs. Black individuals), sex (female *vs.* male), baseline smoking status (ever- vs. never-smokers), and baseline BMI (≥ 25 kg/m^2 vs. < 25 kg/m^2). The same quartile classification was used in the subgroup analyses. SAS (version 9.4; SAS Institute, Cary, NC, USA) was used for all data management and analyses. Statistically significance was defined as a *P* value ≤ 0.05.

Results

Characteristics of the study population are presented in Table 1. The median concentrations (inter-quartile ranges) of toenail Cd across quartiles were 2.9 (2.3–3.6), 6.0 (5.1–7.1), 11.7 (9.9–14.4), and 41.0 (25.9–87.2) ppb. Participants in higher quartiles of toenail Cd concentration were younger and more likely to be female and black. They also had a lower level of education. In addition, participants in higher quartiles of Cd concentrations were more likely to be current smokers, though the difference across quartiles was not statistically significant.

After 23 years from baseline, 580 participants had prevalent NAFLD identified by CT (23.7% NAFLD prevalence). Participants in the highest quartile of toenail Cd had a significantly higher odds of NAFLD, compared with those in the lowest quartile (multivariable-adjusted OR: 1.43, 95% CI: 1.02, 1.99, model 3, Table 2). A linear trend of toenail Cd concentration associated with odds of NAFLD was also observed (*P* for trend: 0.04, model 3, Table 2). In sensitivity analyses, the association was slightly attenuated when excluding pregnant women at any examination [quartile 2–4 vs. quartile 1; multivariable-adjusted OR (95% CI): 1.20 (0.86, 1.67), 1.05(0.75, 1.47), 1.40 (0.998, 1.98), *P* for trend: 0.06] or when further adjusting for toenail concentrations of arsenic, mercury, selenium, zinc, and lead [quartile 2–4 vs. quartile 1; multivariable-adjusted OR (95% CI): 1.21 (0.87, 1.67), 1.03 (0.74, 1.43), 1.40 (0.99, 1.98), *P* for trend: 0.07]. The association with moderate-to-severe NAFLD was not statically significant, presumably due to a much smaller number of cases (*n* = 241 vs. 580 at-least-mild NAFLD as the main outcome) and reduced power [quartile 2–4 vs. quartile 1; multivariable-adjusted OR (95% CI): 1.33 (0.86, 2.04), 1.24 (0.80, 1.93), 1.43 (0.91, 2.26), *P* for trend: 0.25]. In addition (Table 3), the observed association of Cd with NAFLD was not significantly modified by sex, race, BMI or smoking status. All *P* values for interaction were greater than 0.1.

Discussion

By prospectively following up a large cohort Americans for 23 years, we found that toenail Cd concentration in young adulthood was associated with higher prevalence of NAFLD

in midlife. This association was not significantly modified by sex, race, BMI, or smoking status.

The US general population is considered for low-to-moderate level of Cd exposure [28]. However, it has been suggested that Cd exposure, even at low levels, may be associated with metabolic diseases such as obesity, diabetes, and metabolic syndrome [29]. The potential mechanisms underlying Cd toxicity on metabolic systems include Cd-induced abnormal adipocyte differentiation, expansion, and function, which may lead to the development of insulin resistance [30], and link to NAFLD pathophysiology. In addition, evidence from animal studies found that low-level oral Cd administration caused metabolic dysregulation in mice liver, such as impaired fatty acid biosynthesis and lipid metabolism, as well as stimulating hepatocyte cell death and mitochondrial oxidative phosphorylation, which would potentially lead to the development of NAFLD [20]. In our sensitivity analysis that was adjusted for BMI, lipids, glucose, or insulin levels at Y25, the inverse association between Cd and NAFLD was attenuated to be nonsignificant, which supports the hypothesis that Cd may affect NAFLD pathophysiology through weight gain or insulin resistance.

Although the hepatotoxicity of Cd is biologically plausible, human data of Cd exposure and NAFLD are limited. Evidence from cross-sectional studies generally support the potential toxicity of Cd on liver function. In a study of 3914 Korean adults, blood Cd concentration was significantly correlated with liver enzyme levels including AST, ALT, and alkaline phosphatase (ALP) [31]. Since high levels of liver enzymes are commonly used to determine individuals at higher risk of NAFLD at screening after excluding other liver diseases, findings from that study suggest that Cd exposure may be associated with hampered liver function and higher risk of NAFLD. In NHANES III that included 5988 men and 6744 women in the USA, a significant cross-sectional association between urinary Cd concentration and risk NAFLD was found in men, but not in women [21]. However, we did not find a similar effect modification by sex in the present study.

To the best of our knowledge, this is the first prospective cohort study that examined the association between Cd exposure and risk of NAFLD. This study included a large cohort of black and white men and women in the USA and followed them for 23 years from young adulthood into midlife. Available studies of cadmium exposure have included too few black participants, limiting the ability to compare across studies [21]. Because randomized clinical trials are not feasible for toxic substances (e.g., Cd), longitudinal studies such as the present one provide important information. In addition, the use of toenails for measuring long-term Cd exposure is a great advantage in the present study. Toenail specimens generally reflect a relatively long-term exposure compared to other bio-specimens, such as urinary and blood biomarkers [32, 33].

We acknowledge some limitations of this study. First, we defined our NAFLD outcome based on LA measured by non-contrast CT after excluding secondary causes of liver fat. The LA cutoff was chosen based on previous studies that correlated LA with histology [25]. Compared to magnetic resonance imaging, this approach had high specificity but lower sensitivity for NAFLD detection [20]. However, the prevalence of NAFLD in this study (23.7%) is consistent with published population estimates [34]. High specificity largely

reduces the influence of measurement bias, but may attenuate the potential association between Cd and NAFLD. Second, LA was not assessed in CARDIA at baseline (Y2 exam in this study) or at any point prior to the Y25 examination. Thus, causality cannot be inferred. However, we excluded those who self-reported cirrhosis, hepatitis, or other liver problems at baseline. Compared to a previous study including lean adults in the USA, our study population had a similar average BMI (25 kg/m^2 vs. 22 kg/m^2 in the prior study) and were on average 8 years younger (32 years vs. 40 years in the prior study). Thus, the NAFLD prevalence at baseline in this study should be lower than 7.4% that was observed in lean individuals in the prior study [35]. The possibility that a large portion of participants had undiagnosed NAFLD at baseline is relatively low. In addition, the exact time when a person developed NAFLD is unknown. However, the detection of NAFLD in midlife is clinically common since NAFLD is asymptomatic and is usually incidentally diagnosed when examining for other illness using imaging [27]. Third, the data of liver enzymes or data to differentiate simple steatosis from NASH were not available in this study. Further studies with such information will provide more solid evidence regarding the hepatotoxicity of Cd. Forth, while toenail Cd reflects relatively long-term exposure [36], it was measured only a single time at baseline. This limitation may have attenuated the observed association. Fifth, although the models have adjusted for a list of available potential confounders, the findings are still subject to residual confounding and confounding from unknown or unmeasured factors, similar to other observational studies. Furthermore, because of the nature of observational studies, causal relationship cannot be established based on the findings only from this study.

In conclusion, we found that toenail Cd concentration measured in young adulthood was related to higher prevalence of NAFLD in midlife. Considering the relatively low level of Cd exposure in the US general population, Cd-induced hepatotoxicity may be even more pronounced in other populations at higher exposure levels. Future longitudinal studies in other populations are warranted to confirm our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the study population by quartiles of toenail Cd concentrations: the CARDIA study

Characteristics	Quartiles of toenail Cd concentrations				Total	*P* value
	Q1 (lowest)	Q2	Q3	Q4 (highest)		
n	613	613	609	611	2446	–
Median Cd level (ppb)	2.9 (2.3–3.6)	6.0 (5.1–7.1)	11.7 (9.9–14.4)	41.0 (25.9–87.2)	8.2 (4.3–18.6)	–
Age at Y25 (year)	50.5 ± 3.5	50.3 ± 3.6	49.9 ± 3.7	49.7 ± 3.7	50.1 ± 3.6	< 0.01
Female (%)	51.1	61.3	59.1	58.9	57.6	< 0.01
Black (%)	40.5	45.0	52.6	51.6	47.4	< 0.01
Education levels at Y25 (year)	15.5 ± 2.6	15.4 ± 2.7	14.9 ± 2.6	14.8 ± 2.7	15.1 ± 2.7	< 0.01
Smoking status at Y2 (%)						0.36
Never smoker	62.3	62.8	63.2	59.7	62.0	
Former smoker	15.7	13.5	12.2	13.5	13.7	
Current smoker	22.0	23.7	24.6	26.8	24.3	
Alcohol consumption (mL/day)	7.2 ± 9.6	8.2 ± 12.0	8.4 ± 11.3	8.0 ± 11.0	7.9 ± 11.0	0.59
Physical activity (exercise unit)	361 ± 218	347 ± 217	344 ± 229	347 ± 214	350 ± 220	0.29
BMI at Y2 (kg/m^2)	25.0 ± 5.3	25.4 ± 5.3	25.4 ± 5.5	25.4 ± 5.2	25.3 ± 5.3	0.49
Systolic blood pressure at Y2 (mmHg)	107.17 ± 10.27	107.01 ± 10.77	107.47 ± 10.38	107.42 ± 9.97	107.27 ± 10.35	0.85
Diastolic blood pressure at Y2 (mmHg)	67.8 ± 9.1	67.4 ± 9.7	67.1 ± 9.1	66.7 ± 9.5	67.3 ± 9.3	0.25
Total cholesterol at Y2 (mg/dL)	183.5 ± 33.1	185.0 ± 36.8	184.1 ± 34.7	184.6 ± 36.1	184.3 ± 35.2	0.89
HDL-cholesterol at Y2 (mg/dL)	53.6 ± 13.3	55.1 ± 14.1	55.2 ± 13.9	55.5 ± 15.0	54.9 ± 14.1	0.10
LDL-cholesterol at Y2 (mg/dL)	114.3 ± 31.7	114.2 ± 34.1	113.8 ± 32.8	114.2 ± 33.7	114.1 ± 33.1	0.993
Triglycerides at Y2 (mg/dL)	78.4 ± 50.6	79.2 ± 56.2	78.0 ± 65.1	75.6 ± 44.9	77.8 ± 54.7	0.82
Glucose at Y0 (mg/dL)	82.3 ± 13.8	82.1 ± 9.7	82.1 ± 13.0	81.2 ± 7.8	81.9 ± 11.3	0.34
Insulin at Y0 (uU/mL)	7.83 ± 3.47	8.15 ± 3.78	7.96 ± 3.54	8.12 ± 3.72	8.02 ± 3.63	0.49

The results are presented by means ± standard deviations, medians (inter-quarter ranges), or proportions

P values are for any difference across quartiles of toenail Cd levels by using analysis of variance, Kruskal–Wallis test, or chi-squared test, as appropriate

BMI Body mass index, *CARDIA* coronary artery risk development in young adults, *Cd* cadmium *HDL* high-density lipoproteins, *LDL* low-density lipoproteins *Q*, quartile, *Y* CARDIA exam year

Table 2

Multivariable-adjusted ORs and 95% CIs of nonalcoholic fatty liver disease (NAFLD) by quartiles of toenail Cd concentrations: the CARDIA study

	Quartiles of toenail Cd concentrations				*P* for trend
	Q1 (lowest)	**Q2**	**Q3**	**Q4 (highest)**	
Range (ppb)	< 4.40	4.40–8.30	8.30–18.70	≥ 18.7	–
No. of cases/participants	130/613	141/613	138/609	171/611	–
Model 1	1 (Ref.)	1.19 (0.90, 1.58)	1.07 (0.80, 1.42)	1.25 (0.94, 1.66)	0.23
Model 2	1 (Ref.)	1.18 (0.88, 1.58)	1.03 (0.77, 1.39)	1.26 (0.93, 1.71)	0.19
Model 3	1 (Ref.)	1.21 (0.87, 1.67)	1.05 (0.76, 1.47)	1.43 (1.02, 1.99)	0.04

All models were constructed by using logistic regression models. *P* for trend was examined by using the medians of toenail Cd quartiles

Model 1 was adjusted for age (continuous), sex (female or male), race (black or white), and study center

Model 2 was additionally adjusted for education through Y25 (< 12.0, 12.0–15.9, or ≥ 16.0, year), baseline smoking status (never, former, or current), cumulative average alcohol consumption through Y25 (0, 0.1–11.9, 12.0–23.9, or ≥ 24.0, mL/day), cumulative average physical activity through Y25 (quartiles), and baseline BMI (< 25.0, 25.0–29.9, or ≥ 30.0, kg/m^2)

Model 3 was additionally adjusted for baseline levels of HDL-cholesterol and insulin (continuous) based on stepwise model selection

BMI Body mass index, *CARDIA* coronary artery risk development in young adults, *CI* confidence interva, *OR* odds ratio, *Q* quartile, *Ref.* reference, *Y* CARDIA exam year

Table 3

Associations [ORs (95% CI)] between toenail Cd concentrations and nonalcoholic fatty liver disease (NAFLD) stratified by pre-specified factors: the CARDIA study

	No. of cases/participants	Cd [mean (SD)]	Quartiles of toenail Cd concentrations				*P* for trend
			Q1 (lowest)	Q2	Q3	Q4 (highest)	
Sex							
Female	259/1,409	27.13 (96.66)	1 (Ref.)	1.06 (0.66, 1.70)	0.78 (0.47, 1.28)	1.19 (0.73, 1.94)	0.29
Male	321/1,037	26.15 (138.19)	1 (Ref.)	1.32 (0.83, 2.08)	1.37 (0.87, 2.16)	1.68 (1.05, 2.68)	0.07
P for interaction	–	–	0.98				
Race							
Black	261/1,159	29.30 (105.48)	1 (Ref.)	1.46 (0.86, 2.48)	1.20 (0.71, 2.01)	1.88 (1.11, 3.17)	0.03
White	319/1,287	24.38 (124.84)	1 (Ref.)	1.11 (0.72, 1.70)	1.10 (0.70, 1.72)	1.17 (0.74, 1.83)	0.60
P for interaction	–	–	0.11				
BMI at Y2							
< 25 kg/m^2	200/1,413	29.20 (147.07)	1 (Ref.)	1.38 (0.84, 2.27)	1.05 (0.63, 1.76)	1.46 (0.88, 2.42)	0.23
≥ 25 kg/m^2	380/1,033	23.31 (48.02)	1 (Ref.)	1.19 (0.77, 1.83)	1.12 (0.73, 1.74)	1.42 (0.90, 2.23)	0.15
P for interaction	–	–	0.73				
Smoking status							
Never-smoker	334/1,517	26.04 (94.69)	1 (Ref.)	1.22 (0.79, 1.87)	1.34 (0.88, 2.07)	1.72 (1.10, 2.69)	0.02
Ever-smoker	246/929	27.82 (144.39)	1 (Ref.)	1.24 (0.74, 2.09)	0.74 (0.43, 1.26)	1.12 (0.67, 1.88)	0.64
P for interaction	–	–	0.34				

All models were constructed using logistic regression models with the adjustment for covariates in model 3, Table 2. *P* for trend was examined by using the median of each toenail Cd quartile

BMI Body mass index, *CARDIA* coronary artery risk development in young adults, *Cd* cadmium, *CI* confidence interval, *Q* quartile, *Ref.* reference, *SD* standard deviation, *Y* CARDIA exam year