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Interrelationships of Cadmium, Smoking, and Angina in the National Health and Nutrition Examination Survey, a Cross-Sectional Study

Eric M. Hecht[a] Kristopher L. Arheart[a] David J. Lee[a] Charles H. Hennekens[b–d] WayWay M. Hlaing[a]

[a]Department of Public Health Sciences, University of Miami Miller School of Medicine, Miami, FL, USA; [b]Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA; [c]Department of Preventive Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA; [d]Department of Family Medicine and Community Health, University of Miami Miller School of Medicine, Miami, FL, USA

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Abstract
The interrelationships between cadmium biomarker levels, smoking, and myocardial infarction and stroke have been established. In this cross-sectional analysis, we explored the interrelationships of blood cadmium levels, smoking, and angina. We analyzed the National Health and Nutrition Examination Survey (NHANES, 2003–2014) accounting for the multi-staged complex sampling design. Participants 40–79 years of age with blood cadmium levels but without a history of myocardial infarction and/or stroke were included (n = 14,832). We examined blood cadmium levels (3 tertile groups) in relation to 3 (diagnosed, undiagnosed, and composite diagnosed and/or undiagnosed) angina outcomes. Multivariable logistic regression models adjusted for age, diabetes, smoking status, and household income were used to estimate odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). Of 14,832 participants, 741 (4.2%) had positive composite angina. The crude and adjusted ORs comparing those in the lowest tertile (referent group) of blood cadmium to those in the highest tertile for the composite outcome were 1.82 (95% CI 1.42–2.34) and 1.45 (95% CI 1.12–1.88), respectively. These cross-sectional data from a nationally representative sample contribute to the hypothesis that there are interrelationships between smoking, cadmium, and angina.

Introduction

In previous cross-sectional analyses, we demonstrated a linear dose-response relationship between smoking dose (cigarettes per day) and cadmium biomarker levels. Additional interrelationships were also observed between cadmium biomarker levels and myocardial infarction and stroke [1, 2]. Our findings are compatible with earlier investigations [3–6]. The plausibility of these findings is enhanced by observations that cadmium is a metal found in abundance in cigarette smoke and has been hypothesized to have cardiovascular toxicity [7]. After absorption into the circulation, cadmium infiltrates the medial layers of the arterial vasculature, where it is estimated to have a biological half-life of many decades [8]. Cad-

E-Mail karger@karger.com
www.karger.com/crd

Eric M. Hecht, MD, MSPH, PhD
Department of Public Health Sciences
University of Miami Miller School of Medicine
Miami, FL 33031 (USA)
E-Mail hechte@mac.com

mium can then initiate deleterious changes in the vascular endothelium, including inflammation, impaired nitric oxide production, decreased endothelial cell migration, endothelial cell death, and atherosclerosis [9]. While cigarette smoking is associated with coronary artery disease [10, 11], to the best of our knowledge, there are no epidemiological data exploring the interrelationships of cadmium, smoking, and angina. The National Health and Nutrition Examination Survey (NHANES) provided a unique opportunity to explore these interrelationships cross-sectionally.

Methods

The NHANES is an on-going cross-sectional survey of the civilian, noninstitutionalized US population. The surveys are conducted biannually using stratified, multistage-cluster probability sampling resulting in a representative US sample. NHANES consists of 3 parts: a health interview survey, a health examination survey, and a nutrition survey [12].

In the current analyses, we pooled 6 cycles of cross-sectional data from the years 2003–2014 to arrive at a sample of 61,087 individuals. There were 14,832 subjects who met the study criteria which included individuals 40–79 years old with blood cadmium and angina measures but without a prior history of myocardial infarction and/or stroke. We restricted the age group to 40–79 years based on a published study of NHANES participants that explored the relationship between angina and other sociodemographic covariates [13]. This specific age group in the NHANES also completed the Rose Questionnaire which included questions pertaining to chest pain symptoms [14].

Health interview data included self-reported information on age, gender, household income, race, medical history, education, hypertension, diabetes, hypercholesterolemia, and smoking history. Weight and height were measured during the physical examination, and body mass index was calculated as weight in kilograms divided by height in meters squared.

Smoking status was based on the response to the following question: "Have you smoked at least 100 cigarettes in your life?" Respondents were then classified as never smokers (<100 cigarettes smoked in a lifetime) or ever smokers (≥100 cigarettes smoked in a lifetime).

We created 3 distinct outcome measures using self-report data to define angina using a methodology similar to that used by other investigators [15]. Participants who responded "yes" to the question "Has a doctor ever told you that you had angina?" were classified as having "diagnosed angina." If the participant described a history of chest pain or discomfort that (1) was brought on by exertion, (2) was situated in the central or left anterior chest, (3) forced the subject to slow down or stop, and (4) was relieved by rest within 10 min, they were then classified as having "undiagnosed angina." These questions were a part of the validated Rose Questionnaire [14] previously described. We then created a dichotomous composite outcome variable where those individuals who were classified as having had diagnosed, undiagnosed, or both classifications of angina were labeled "positive" and those individuals who did not have angina by any of the 3 classifications diagnosed, undiagnosed, or both were labeled as "negative."

Specimen collection and processing instructions as well as NHANES quality assurance and quality control (QA/QC) protocols for blood cadmium are discussed in detail in the NHANES Laboratory/Medical Technologists Procedures Manual [16]. In brief, the NHANES QA/QC protocols met the 1988 Clinical Laboratory Improvement Act mandates, and the protocol was consistent in all study cycles (2003–2014) [16]. Blood cadmium levels were measured in 89% of randomly selected participants. Blood cadmium was measured using whole blood from vacutainer tubes containing ethylenediaminetetraacetic acid. Blood cadmium specimens were processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, and Centers for Disease Control and Prevention for analysis. Levels were determined using inductively coupled plasma mass spectrometry. This multi-element analytical technique is based on quadrupole inductively coupled plasma mass spectrometry technology [17]. Laboratory tests with results below the lower detection limit were replaced in the NHANES dataset with a value equal to the detection limit divided by the square root of 2 [17, 18].

Statistical analyses were performed using SAS software (v9.4; SAS Institute, Inc.; Cary, NC, USA). Survey sample weights were used accounting for a complex sampling design in all analyses to produce unbiased point estimates representative of the US population. Blood cadmium levels were divided into equal tertiles for the analysis of the entire sample, and equal tertile groups were used for smoking- and gender-specific analyses. Prespecified cutoff points for education [19] and household income [20] were chosen from previous studies that utilized the NHANES database.

We examined the prevalence of 3 angina measures (diagnosed, undiagnosed, and the composite outcome, i.e., diagnosed, undiagnosed, or both). We used logistic regression models to compute crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) between the lowest tertile (referent group) and the middle and highest tertile groups of blood cadmium for diagnosed, undiagnosed, and the composite measure of angina. With respect to multivariate control of confounding, we included individual variables that had true confounding potential, such that each variable was associated with both the exposure and with the outcome, independent of the exposure. In addition, we required that included variables when tested individually had a >10% change in the beta coefficient of the main exposure variable. If a variable did not fulfill these criteria, it was not included in the final model. In adjusted models, we initially included relevant demographic and health-related variables, including age, smoking status, gender, income, education, body mass index, race, self-reported hypercholesterolemia, hypertension, and diabetes. Based upon biological, statistical criteria and stratified analyses results, we retained age, income, diabetes, and smoking status in the final models. Multivariable logistic models for the odds of angina were built for all participants as well as smoking and gender groups separately.

Results

Of the 14,832 participants, 741 had a positive composite outcome (diagnosed or undiagnosed angina, or both) measure. These participants were slightly older, more

Table 1. Characteristics of the study sample by presence or absence of the compositea outcome measure (n = 14,832)

	Angina				p value
	positive (n = 741)	95% CI	negative (n = 14,091)	95% CI	
Age, years	57.1	(55.7, 58.5)	54.8	(54.5, 55.1)	0.0013
Body mass index, kg/m^2	30.7	(30.0, 31.4)	29.1	(28.9, 29.2)	<0.0001
Blood cadmium, μg/L	0.67	(0.60, 0.73)	0.54	(0.53, 0.56)	<0.0001
Male	39.6%	(34.2, 45.0)	47.5%	(46.6, 48.4)	0.0056
Less than HS education	27.5%	(23.4, 31.5)	16.3%	(14.9, 17.6)	<0.0001
Income <20,000 USD/year	27.5%	(23.2, 31.8)	12.5%	(11.5, 13.5)	<0.0001
Race					0.0743
Mexican	5.1%	(3.2, 7.0)	6.2%	(4.9, 7.4)	
Other Hispanic	4.9%	(3.3, 6.5)	4.0%	(3.1, 5.0)	
Non-Hispanic White	70.4%	(65.7, 75.9)	74.1%	(71.3, 76.8)	
Non-Hispanic Black	14.3%	(11.5, 17.1)	9.9%	(8.5, 11.4)	
Other	5.3%	(3.5, 7.1)	5.8%	(4.9, 6.7)	
Hypertension[b]	61.4%	(56.3, 66.5)	37.4%	(36.3, 38.6)	<0.0001
Hypercholesterolemia[b]	64.4%	(59.7, 69.2)	45.2%	(43.9, 46.5)	<0.0001
Diabetic[b]	19.4%	(15.7, 23.1)	10.3%	(9.6, 11.0)	<0.0001
Smoking status					0.0069
Never	40.3%	(34.9, 45.7)	51.4%	(50.2, 52.6)	
Ever	29.9%	(25.0, 34.8)	19.1%	(18.1, 20.2)	
Blood cadmium					<0.0001
Tertile 1 (0.07–0.28 μg/L)	26.8%	(22.7, 30.8)	37.4%	(36.0, 38.8)	
Tertile 2 (0.29–0.51 μg/L)	33.4%	(29.0, 37.9)	32.1%	(30.8, 33.5)	
Tertile 3 (0.52–10.8 μg/L)	39.7%	(34.6, 44.9)	30.5%	(29.2, 31.7)	

Values are means or weighted percentages. HS, high school. [a] Composite outcome positive: diagnosed angina or undiagnosed angina or both; composite outcome negative: neither diagnosed nor undiagnosed angina. [b] Defined by self-report.

likely to be female and to have a history of ever smoking, hypercholesterolemia, hypertension, diabetes, an annual household income less than USD 20,000, and less than a high school education than those participants without angina (Table 1).

The weighted prevalence of our composite outcome measure was 4.2% (n = 741), 1.5% (n = 258) of whom had diagnosed angina, and 2.7% (n = 483) of whom had undiagnosed angina. Among individuals with a prior history of smoking, the weighted prevalence of our composite outcome measure was 5.1%, versus 3.3% for never smokers. The weighted prevalence of our composite outcome measure was higher for women than men (4.8 vs. 3.5%) (Table 2).

The range of blood cadmium for the entire study sample extended from 0.07 to 10.8 μg/L. Higher ranges of blood cadmium were observed for the "ever" than the "never" smoking group, (0.07–10.8 vs. 0.07–2.66 μg/L, respectively) and for women than men (0.07–10.8 vs. 0.07–9.30 μg/L, respectively).

Those with the highest (3rd tertile) blood cadmium level were significantly more likely to have the composite angina than those with the lowest (1st tertile or referent group) blood cadmium level (crude OR = 1.82, 95% CI 1.42–2.34; adjusted OR = 1.45, 95% CI 1.12–1.88). A dose-response relationship was evident in both crude and adjusted measures of association (i.e., higher odds of composite angina with higher blood cadmium levels). Similar statistically significant results and dose-response relationships were found for the undiagnosed angina group (third vs. first tertile group) (crude OR = 2.11, 95% CI 1.44–3.09; adjusted OR = 1.69, 95% CI 1.16–2.48) but not for the diagnosed angina group (third vs. first tertile group) (crude OR = 1.33, 95% CI 0.89–1.99; adjusted OR = 1.05, 95% CI 0.68–1.62). Subgroup analysis by smoking status showed statistically significant results

Table 2. Prevalence of outcome measures according to smoking status, gender, and tertiles of blood cadmium biomarker levels

	All, prevalence % (95% CI) (*n* = 14,832)	Never smokers, prevalence % (95% CI) (*n* = 7,554)	Ever smokers, prevalence % (95% CI) (*n* = 7,270)	Men, prevalence % (95% CI) (*n* = 7,151)	Women, prevalence % (95% CI) (*n* = 7,681)
Composite[a]					
All	4.18 (3.76–4.60)	3.31 (2.84–3.77)	5.08 (4.35–5.81)	3.51 (2.82–4.19)	4.78 (4.27–5.29)
Tertile 1	3.03 (2.52–3.54)	2.91 (2.17–3.66)	3.89 (2.99–4.80)	2.37 (1.63–3.10)	4.13 (3.17–5.10)
Tertile 2	4.34 (3.55–5.13)	3.53 (2.68–4.37)	5.46 (4.20–6.72)	3.24 (2.27–4.22)	4.69 (3.73–5.64)
Tertile 3	5.38 (4.56–6.21)	3.56 (2.76–4.36)	6.04 (4.82–7.26)	5.26 (3.77–6.76)	5.62 (4.66–6.57)
Diagnosed angina					
All	1.45 (1.17–1.73)	1.20 (0.92–1.48)	1.71 (1.27–2.15)	1.45 (1.07–1.83)	1.45 (1.06–1.83)
Tertile 1	1.18 (0.84–1.52)	1.16 (0.69–1.64)	1.54 (0.96–2.12)	0.92 (0.44–1.41)	1.52 (0.94–2.1)
Tertile 2	1.65 (1.14–2.15)	1.32 (0.83–1.81)	1.81 (1.09–2.53)	1.55 (0.95–2.16)	1.46 (0.86–2.05)
Tertile 3	1.56 (1.07–2.06)	1.11 (0.54–1.67)	1.79 (1.09–2.50)	2.01 (1.05–2.97)	1.36 (0.75–1.97)
Undiagnosed angina					
All	2.73 (2.41–3.04)	2.10 (1.67–2.53)	3.37 (2.76–3.99)	2.05 (1.56–2.55)	3.33 (2.89–3.76)
Tertile 1	1.85 (1.39–2.30)	1.75 (1.11–2.39)	2.35 (1.58–3.12)	1.44 (0.86–2.03)	2.61 (1.79–3.43)
Tertile 2	2.69 (2.12–3.26)	2.20 (1.45–2.96)	3.64 (2.62–4.66)	1.69 (0.84–2.53)	3.23 (2.47–3.99)
Tertile 3	3.82 (3.06–4.57)	2.45 (1.81–3.09)	4.24 (3.09–5.39)	3.24 (2.16–4.33)	4.25 (3.34–5.16)

CI, confidence interval. [a] Composite outcome positive: diagnosed or undiagnosed angina or both; composite outcome negative: neither diagnosed nor undiagnosed angina.

Table 3. Crude and adjusted ORs regarding the association between blood cadmium levels and angina by smoking status and gender

	All[a], OR (95% CI) (*n* = 14,832)	Never smoked[b], OR (95% CI) (*n* = 7,554)	Ever smoked[b], OR (95% CI) (*n* = 7,270)	Men[a], OR (95% CI) (*n* = 7,151)	Women[a], OR (95% CI) (*n* = 7,681)
Composite[c]					
Crude T2 vs. T1	1.45 (1.14–1.85)	1.22 (0.85–1.74)	1.43 (1.04–1.95)	1.38 (0.91–2.10)	1.14 (0.81–1.61)
Crude T3 vs. T1	1.82 (1.42–2.34)	1.23 (0.87–1.75)	1.59 (1.13–2.23)	2.29 (1.53–3.45)	1.38 (1.01–1.89)
Adjusted T2 vs. T1	1.31 (1.03–1.67)	1.14 (0.79–1.65)	1.37 (0.97–1.93)	1.16 (0.75–1.79)	1.06 (0.75–1.50)
Adjusted T3 vs. T1	1.45 (1.12–1.88)	1.04 (0.71–1.51)	1.53 (1.07–2.18)	1.60 (0.96–2.65)	1.13 (0.84–1.54)
Diagnosed angina					
Crude T2 vs. T1	1.40 (0.94–2.08)	1.13 (0.65–1.97)	1.18 (0.76–1.83)	1.70 (0.90–3.19)	0.96 (0.60–1.54)
Crude T3 vs. T1	1.33 (0.89–1.99)	0.95 (0.45–1.99)	1.17 (0.66–2.06)	2.21 (1.02–4.76)	0.89 (0.51–1.55)
Adjusted T2 vs. T1	1.10 (0.73–1.66)	0.97 (0.54–1.72)	1.05 (0.66–1.66)	1.36 (0.71–2.58)	0.82 (0.47–1.41)
Adjusted T3 vs. T1	1.05 (0.68–1.62)	0.72 (0.34–1.54)	1.34 (0.76–2.34)	1.89 (0.76–4.67)	0.71 (0.37–1.34)
Undiagnosed angina					
Crude T2 vs. T1	1.47 (1.08–1.99)	1.27 (0.79–2.03)	1.57 (1.04–2.38)	1.17 (0.63–2.19)	1.25 (0.81–1.91)
Crude T3 vs. T1	2.11 (1.44–3.09)	1.41 (0.90–2.21)	1.84 (1.15–2.93)	2.29 (1.32–3.97)	1.66 (1.08–2.54)
Adjusted T2 vs. T1	1.42 (1.05–1.93)	1.25 (0.77–2.03)	1.55 (0.99–2.43)	0.99 (0.52–1.86)	1.17 (0.78–1.76)
Adjusted T3 vs. T1	1.69 (1.16–2.46)	1.27 (0.79–2.02)	1.63 (1.00–2.66)	1.31 (0.72–2.36)	1.35 (0.93–1.97)

T1 refers to the first tertile of blood cadmium (reference), T2 refers to the second tertile of blood cadmium, T3 refers to the third tertile of blood cadmium. OR, odds ratio; CI, confidence interval. [a] Covariates for adjusted models include age, diabetes, smoking status, and household income. [b] Covariates for adjusted models include age, diabetes, and household income. [c] Composite outcome positive: diagnosed angina or undiagnosed angina or both; composite outcome negative: neither diagnosed nor undiagnosed angina.

with a positive dose-response relationship among "ever" smokers only (third vs. first tertile group) (crude OR = 1.59, 95% CI 1.13–2.23; adjusted OR = 1.53, 95% CI 1.07–2.18) (Table 3).

Discussion

In this cross-sectional study, individuals with higher cadmium biomarker concentrations were 45% likely to have angina after adjustments for smoking status and other confounding variables. There was also evidence of a positive dose-response relationship. The prevalence of angina stratified by blood cadmium tertile levels was significantly higher in the entire sample as well as for each of the smoking and gender subgroups. The magnitude and direction of these estimates are consistent with other NHANES investigations that have reported associations between cadmium biomarker levels and cardiovascular disease other than angina [1, 3–6].

There were statistically significant dose-response findings for blood cadmium and angina when using the Rose Questionnaire (undiagnosed angina) but not by a subject's self-report (diagnosed angina) of a physician having told them they had angina. Why this inconsistency appears in our data is unclear as both outcome measures have useful applications in research. Self-report for cardiovascular outcomes has previously been studied and has demonstrated substantial agreement when compared to medical record diagnoses [21], and the detection of angina symptoms using the Rose Questionnaire has also been shown to possess reasonable sensitivity and specificity for angina when compared to clinical judgment (sensitivity of 81% and specificity of 97%) [22] and coronary angiography (sensitivity of 50% and specificity of 75%) [23]. Nevertheless, in our sample, we found poor agreement between these 2 methods of classification (kappa = 0.15, data not shown) and that our "diagnosed angina" subjects were more likely to be older, male, and more likely to report cardiovascular risk factors, such as a positive smoking history, self-reported hypertension, self-reported hypercholesterolemia, and self-reported diabetes, as compared to our "undiagnosed angina" subjects. The stronger association between blood cadmium levels and undiagnosed angina versus diagnosed angina could therefore be due to true clinical differences between the 2 definitions of angina, or to biases relating to how the information was obtained, or a lower statistical power to identify the true association between blood cadmium and either definition of angina.

The chief limitation of these cross-sectional data is the lack of time sequence between exposure (cadmium) and outcome (angina). Other limitations include the possible misclassification of exposure, outcome, and other covariates due to the self-reporting of smoking characteristics, angina, and other cardiovascular conditions, such as high cholesterol, blood pressure, and diabetes. The use of a single measure as well as missing and undetectable values of blood cadmium from participants might also have led to an inaccurate assessment of a true blood cadmium level. This limitation would have an unpredictable effect on our results, but nondifferential misclassification generally biases results towards the null. We were also unable to ascertain from our sample occupational and oral ingestion sources of exposure to cadmium. Our study was also not designed or sufficiently powered to detect a cadmium threshold level regarding the risk of angina outcomes.

The strengths of the study rely upon high-quality data collection and subject sampling. NHANES data are collected using extensive quality control measures and by technicians trained and certified in all aspects of data collection. Sampling for NHANES data relies upon a probability cluster sampling method and a sampling frame that is representative of the US noninstitutionalized civilian population.

Our findings are compatible with the hypothesis of positive interrelationships between smoking, blood cadmium levels, and angina. This observation is biologically plausible, as cadmium biomarker levels are elevated in current and former smokers, and high cadmium level has been found in animal models and human autopsy data to be associated with atherosclerosis [8, 24]. Our study suggests the need for analytic studies designed a priori to test this hypothesis longitudinally.

Statement of Ethics

According to the University of Miami Institutional Review Board (IRB), this study does not qualify as human subject research and therefore does not require IRB oversight.

Disclosure Statement

Drs. Hecht, Arheart, Lee, and Hlaing report no conflicts of interest. Professor Hennekens reports that he is funded by the Charles E. Schmidt College of Medicine at Florida Atlantic University; serves as an independent scientist in an advisory role to investigators and sponsors as Chair or Member of Data and Safety Monitoring Boards for Amgen, AstraZeneca, Bayer, British Heart

Foundation, Cadila, Canadian Institutes of Health Research, DalCor, Lilly, Regeneron, and the Wellcome Foundation; to the United States (US) Food and Drug Administration, UpToDate, and to Pfizer and its legal counsel; receives royalties for authorship or editorship of 3 textbooks and as coinventor on patents for inflammatory markers and cardiovascular disease that are held by Brigham and Women's Hospital; has an investment management relationship with the West-Bacon Group within SunTrust Investment Services, which has discretionary investment authority and does not own any common or preferred stock in any pharmaceutical or medical device company.

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