Association of blood cadmium and metabolic syndrome: A cross-sectional analysis of National Health and Nutrition Examination Survey 2017-2020

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Research Article

Keywords: Heavy metal, Blood cadmium, NHANES, Metabolic syndrome

Posted Date: August 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1863364/v1

Abstract

Previous findings have reported the role of different types of heavy metals in cardiometabolic diseases. In the present research, we aim to evaluate the association between blood cadmium levels and MetS base on the large-sample NHANES data. Public availably data from NHANES 2017–2020 cycle was obtained. Participants were divided into MetS and non-MetS groups according to waist circumference (WC), triglyceride (TG), high-density lipoprotein (HDL), blood pressure (BP) and fasting plasma glucose (FPG) levels based on the National Cholesterol Education Program (NCEP) criteria. Student's t test, Mann-Whitney U test, and Chi-square test were performed for univariate analysis. Multivariate logistic analysis was performed to explore the relationship between blood cadmium and MetS and research findings were presented in forest plot. We also investigated the association of blood cadmium and MetS in subgroups stratified by age, gender and race. Population with MetS had significantly higher levels of blood cadmium compared with those without MetS [0.30 (0.18–0.54) vs. 0.24 (0.15–0.46) ug/L, $p < 0.001$]. Higher blood cadmium concentrations were also observed in participants with elevated WC, TG, BP and FPG compared with those with normal metabolic parameters. Multivariate logistic regression showed that one unit increasement of blood cadmium was associated with 1.25 times higher prevalence ratios for MetS after adjusting potential confounders (95% CI: 1.06–1.48, $p = 0.0083$). Stratified multiple logistic regression analysis indicated that the positive association between blood cadmium and MetS remained significant in subjects less than 60 years old and female subgroup. In conclusion, the cross-sectional survey suggested the positive association between blood cadmium levels and risk for MetS, prospective research need to be conducted for further evaluation of the causal relationship between blood cadmium and MetS.

Introduction

Metabolic syndrome (MetS) comprises of a cluster of metabolic conditions, including central obesity, hypertension, distorted glucose metabolism and atherogenic dyslipidemia [Rizvi et al. 2021]. MetS has emerged as a public health issue due to its rapidly increasing prevalence and association with diabetes, cardiovascular diseases and all-cause mortality [Sundström et al. 2006]. The prevalence rate of MetS is estimated to affect nearly one quarter of population worldwide [Saklayen 2018]. A nationally representative survey conducted in China from 2015–2017 reported the standard prevalence rate of MetS had reached 31.3% (men 30.0%, women 32.3%) in residents aged over 20 [Yao et al. 2021]. Therefore, further understanding of risk of MetS is of great clinical significance.

It has been widely acknowledged environmental contaminants could contribute to the development of MetS [Lind et al. 2017]. Recently, interest has grown toward the association of environmental heavy metal exposure and MetS with uncontrolled industrialization and increased awareness of environmental health. Recent studies have provided evidence that exposure to heavy metals could contribute to metabolic disorders [Zhou et al. 2022]. For instance, higher prevalence of MetS was associated with higher blood lead levels [Rhee et al. 2013]. Park et al. reported a positive association between serum HDL-c level and blood mercury concentration in Korean men with MetS [Park et al. 2016]. Adjusted multivariable regression model showed only plasma titanium level was related to the risk for Mets through increasing waist circumference (WC) and triglyceride (TG) in 2019 participants who underwent occupational exposure to heavy metals [Huang et al. 2021].

Among these heavy metals, cadmium plays no physiological role [Tian et al. 2021]. Cadmium has been designated as class Ⅰ carcinogen [Wang et al. 2021] and identified as top ten chemicals of major public health concern due to its high toxicity [Planchart et al. 2018]. Additionally, its biological half-life is up to 10–35 years [Kubier et al. 2019]. Nowadays, cadmium contamination has become a ubiquitous environmental issue posing threat to human health [Satarug 2018] due to large amount anthropogenic release from industrial process including mining, smelting, wastewater irrigation, industrial and vehicles emissions, et al [Khan et al. 2017].

Several cross-sectional studies have evaluated the association between blood cadmium and MetS components. It was reported blood cadmium levels were positively associated with Type 2 Diabetes Mellitus and fasting glucose levels in the general population from Norway [Hansen et al. 2017] and China [Nie et al. 2016], respectively. Epidemiological research provided conflicting results on the association between cadmium exposure and the risk for MetS. For example, a meta-analysis revealed cadmium exposure was significantly associated with MetS in Asian studies [Lu et al. 2022], while Nour et al. found a negative association between serum cadmium and the prevalence of diabetes and obesity in Lebanon population[Ayoub et al. 2021]. Another two researches from KNHANES data suggested a positive association between blood cadmium and MetS in males but not females [Lee et al. 2013, Lee et al. 2016]. Considering the inconsistent findings on the association of cadmium exposure and MetS, in the present study, we aim to investigate the association of blood cadmium with MetS and its components based on the large-sample research data from NHANES 2017–2020.

Methods

Data source and study population

NHANES program refers to a cross-sectional survey conducted among noninstitutionalised participants to collect a detailed data on health and nutritional status in the U.S. In the current study, 15560 data were initially included from NHANES 2017-2020 cycle. 11467 subjects were excluded for missing data of WC, BP, HDL, TG and FPG. Another 9 subjects were excluded due to lack of blood lead data. Thus, a total of 4084 participants were eventually included in the analysis (Figure 1). All of the participants provided written informed consent, and the program was approved by the National Center for Health Statistics Ethics Review Board.

Measurement of blood and urinary metals

Blood samples were collected and stored under appropriate frozen (−30°C) conditions until they are shipped to National Center for Environmental Health for testing. Whole blood concentrations of cadmium, lead, manganese, mercury, and selenium were measured using triple quadrupole inductively coupled

plasma mass spectrometer (ICP-QQQ-MS). Detailed measurement methods and quality control process could be found on NHANES 2017–2020 Data Documentation of Lead, Cadmium, Total Mercury, Selenium, and Manganese.

Urine samples were processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA for analysis. arsenic, chromium, barium, cadmium, cesium, cobalt, manganese, molybdenum, lead, antimony, thallium, tin, tungsten, and other elemental content of urine specimens were measured using inductively coupled plasma universal cell technology mass spectrometry (ICP-UCT-MS) after a simple dilution sample preparation step. Detailed measurement methods and quality control process could be found on NHANES 2017–2020 Data Documentation of Metals-Urine.

Definition of MetS

Metabolic syndrome was diagnosed according to the (National Cholesterol Education Program-Adult treatment Panel) NCEP ATP criteria [NCEP 2002]. Population with three or more of the following conditions were diagnosed as MetS: 1. Central obesity: waist circumference>102 cm in man or >88 cm in women; 2. Raised triglyceride level: ≥1.7 mmol/L (150mg/dl); 3. Reduced HDL cholesterol: <1.03 mmol/L (40mg/dL) in man or 1.29 mmol/L (50mg/dL) in woman; 4. Raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; 5. Impaired fasting glucose (fasting plasma glucose ≥6.1 mmol/L).

Covariates

Standard questionnaires by trained interviewers using Computer-Assisted Personal Interview (CAPI) system were asked to obtain demographic characteristics, life style and clinical factors from participants. Demographic and anthropometric variables including age, gender, race, BMI, questionnaire data consisting of smoking, drinking, physical activity and cancer, and blood parameters comprising ALT, AST, Scr, CRP and blood metals levels were selected covariates in the current study based on previous reports on the risk factors of MetS. Race was classified as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black and other race. Current smoker was defined from the dataset with question “Have you smoked at least 100 cigarettes in your entire life?” and “Do you now smoke cigarettes?”). Self-reported drinking behavior during the past 30 days was used for alcohol consumption assessment. Physical activity was categorized as mild, moderate and vigorous work.

Statistical analysis

R software 4.2.0 and SPSS 22.0 (SPSS Inc. Chicago, USA) were used for all statistical analyses. Mean ± standard deviation or median (25%-75%) were used to describe normally and non-normally distributed continuous variables, respectively. Categorical data was presented as frequencies and percentages. Student’s t test or Mann-Whitney U test, and Chi-square test were performed to compare continuous and categorical data in different groups. Blood cadmium levels were treated as continuous and categorical variables (classified as quartiles, Q1-Q4). Logistic regression analysis was utilized for investigation of the independent risk factors of MetS, and the results were presented in forest plot. Both crude and adjusted model including the confounders of age, sex, BMI, race, physical activity, smoking, drinking, cancer, ALT, AST, Scr, CRP, blood lead, blood mercury and blood selemium were developed to explore the relationship between blood cadmium and risk for MetS. Then, the association between blood cadmium and risk of MetS was evaluated in population stratified by age, gender and race. A two-side p value 0.05 was recognized as statistically significant.

Results

Baseline characteristic of study population

Among 4084 participants, 2038 (49.9%) were male and 2046 (50.1%) were female, with the average age of 45.26 ± 20.31. MetS was present in 1040 study participants, while 3044 subjects didn’t meet the diagnostic criteria for MetS. Baseline characteristics were compared between MetS and non-MetS group. Subjects with MetS were older, and they had higher anthropometric parameters including: SBP, DBP, HR, BMI, WC and hip circumference. Additionally, they had higher smoking and drinking rate, higher prevalence in hypertension, diabetes, hyperlipidemia, CHD, heart failure, stroke and cancer. ALT, AST, ALP and Scr were all significantly higher in individuals with MetS. Participants with MetS were more prevalent in elevated blood metabolic and inflammatory indicators, such as TG, TC, LDL, FPG, insulin and CRP. However, lower HDL were observed in participants with MetS compared with those without MetS. Of note, MetS patients presented significantly higher blood lead [0.89 (0.55–1.45) vs. 0.77 (0.46–1.13) ug/dL, $p < 0.001$], cadmium [0.30 (0.18–0.54) vs. 0.24 (0.15–0.46) ug/L, $p < 0.001$], mercury [0.63 (0.32–1.27) vs. 0.56 (0.20–1.24) ug/L, $p = 0.019$] and selemium levels (187.68 ± 27.42 vs. 183.37 ± 25.72 ug/L, $p < 0.001$), whereas no significance was found in blood manganese concentration between MetS and non-MetS group (9.89 ± 3.61 vs. 9.88 ± 3.58 ug/L, $p = 0.548$). Furthermore, the distribution of blood heavy metals in population with and without MetS were presented in Fig. 2. In addition, higher urinary lead, cadmium, arsenic and tin levels were also observed in population with MetS. The details of other characteristics were showed in Table 1.

Table 1
Baseline characteristics of participants with MetS and without MetS.

Variables	MetS (n = 1040)	Non-MetS (n = 3044)	P value
Age	55.33 ± 16.05	41.82 ± 20.47	< 0.001
Male	502 (48.27%)	1536 (50.46%)	0.223
SBP	132.32 ± 19.79	118.38 ± 17.47	< 0.001
DBP	79.37 ± 11.95	71.47 ± 11.14	< 0.001
HR	70.52 ± 11.85	67.86 ± 11.53	< 0.001
BMI	34.02 ± 7.26	27.42 ± 6.70	< 0.001
WC	112.41 ± 15.06	93.41 ± 16.54	< 0.001
Hip circumference	114.58 ± 15.15	103.06 ± 13.56	< 0.001
Elevated WC	953 (91.63%)	1239 (40.70%)	< 0.001
Elevated TG	508 (48.85%)	177 (5.81%)	< 0.001
Low HDL	691 (66.44%)	475 (15.60%)	< 0.001
Elevated BP	675 (64.90%)	684 (22.47%)	< 0.001
Elevated FPG	751 (72.21%)	448 (14.72%)	< 0.001
Race			0.016
Mexican American	154 (14.81%)	380 (12.48%)	
Other Hispanic	108 (10.38%)	293 (9.63%)	
Non-Hispanic White	379 (36.44%)	1022 (33.57%)	
Non-Hispanic Black	240 (23.08%)	794 (26.08%)	
Other Race: Including Multi-Racial	159 (15.29%)	555 (18.23%)	
Physical activity			0.060
Mild work	367 (35.29%)	1176 (38.63%)	
Moderate work	438 (42.12%)	1160 (38.11%)	
Vigorous work	235 (22.60%)	708 (23.26%)	
Smoking	489 (47.02%)	1014 (33.31%)	< 0.001
Drinking	152 (14.62%)	327 (10.74%)	< 0.001
Hypertension	585 (56.25%)	763 (25.07%)	< 0.001
Diabetes	350 (33.65%)	204 (6.70%)	< 0.001
Hyperlipidemia	504 (48.46%)	775 (25.46%)	< 0.001
Coronary heart disease	69 (6.63%)	79 (2.60%)	< 0.001
Heart failure	60 (5.77%)	61 (2.00%)	< 0.001
Stroke	68 (6.54%)	97 (3.19%)	< 0.001
Cancer	146 (14.04%)	213 (7.00%)	< 0.001
ALT	16 (12–23)	21 (14–31)	< 0.001
AST	19 (16–23)	19 (16–25)	< 0.001
ALP	75 (61–93)	81 (66–98)	< 0.001
Scr	72.49 (60.11–84.86)	73.37 (61.22–89.28)	< 0.001
TG	1.64 (1.09–2.23)	0.81 (0.58–1.16)	< 0.001
TC	4.77 ± 1.18	4.60 ± 1.03	< 0.001
HDL	1.13 ± 0.28	1.47 ± 0.40	< 0.001
LDL	2.80 ± 1.02	2.70 ± 0.88	0.023

Variables	MetS (n = 1040)	Non-MetS (n = 3044)	P value
FPG	7.59 ± 3.08	5.68 ± 1.14	< 0.001
Insulin	97.62 (63.97-151.91)	51.78 (33.93–80.61)	< 0.001
CRP	3.31 (1.63–6.28)	1.31 (0.58–3.26)	< 0.001
Blood heavy metals			
Lead	0.89 (0.55–1.45)	0.77 (0.46–1.13)	< 0.001
Cadmium	0.30 (0.18–0.54)	0.24 (0.15–0.46)	< 0.001
Mercury	0.63 (0.32–1.27)	0.56 (0.20–1.24)	0.019
Selemium	187.68 ± 27.42	183.37 ± 25.72	< 0.001
Manganese	9.89 ± 3.61	9.88 ± 3.58	0.548
Urinary heavy metals			
Lead	0.34 (0.21–0.58)	0.30 (0.16–0.53)	0.005
Cadmium	0.29 (0.17–0.52)	0.20 (0.09–0.42)	< 0.001
Arsenic	7.21 (3.81–13.25)	6.23 (3.32–13.32)	0.007
Chromium	0.13 (0.13–0.29)	0.13 (0.13–0.26)	0.144
Barium	0.99 (0.49–0.98)	1.01 (0.48–0.96)	0.860
Cobalt	0.32 (0.17–0.54)	0.33 (0.17–0.60)	0.356
Cesium	4.86 (3.09–7.14)	4.60 (2.81–6.67)	0.075
Molybdenun	41.27 (21.94–62.93)	39.41 (22.12–65.21)	0.822
Manganese	0.09 (0.09–0.15)	0.09 (0.09–0.14)	0.098
Antimony	0.05 (0.03–0.07)	0.05 (0.03–0.08)	0.521
Tin	0.54 (0.30–1.18)	0.49 (0.22-1.00)	0.007
Thallium	0.18 (0.11–0.26)	0.19 (0.11–0.27)	0.624
Tungsten	0.07 (0.03–0.11)	0.06 (0.03–0.12)	0.830

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; HR; heart rate; BMI: body mass index; WC: waist circumference; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; Scr: serum creatinine; TG: triglyceride; HDL: high-density lipoprotein; FPG: fasting plasma glucose; TC: total cholesterol; LDL: low-density lipoprotein; CRP: C reactive protein.

Blood cadmium concentration in MetS and its components group

As mentioned before, higher blood cadmium levels were found in individuals with MetS. Then, we compared blood cadmium concentrations in subjects with different WC, TG, HDL, BP and FPG levels. As shown in Fig. 3, the concentrations of blood cadmium were significantly higher in participants with elevated WC [0.28 (0.17–0.49) vs. 023 (0.14–0.47) ug/L, $p < 0.001$], TG [0.28 (0.16–0.52) vs. 0.26 (0.15–0.47) ug/L, $p = 0.029$], BP [0.33 (0.19–0.60) vs. 0.23 (0.14–0.42) ug/L, $p < 0.001$] and FPG [0.29 (0.18–0.51) vs. 0.24 (0.15–0.47) ug/L, $p < 0.001$] compared with those with normal metabolic parameters. However, participants in low HDL group and normal HDL group had comparable blood cadmium levels, and no statistical significance was found [0.25 (0.15–0.47) vs. 0.26 (0.16–0.49) ug/L, $p = 0.332$].

Univariate analysis for MetS

The relationship between different variables and MetS were evaluated using univariate analysis. As shown in Table 2, age, BMI, smoking, drinking, ALT, AST, Scr, CRP were all risk factors for the MetS, whereas participants of Non-Hispanic Black and other race had lower risk developing MetS compared with those Mexican American. In terms of blood metals, higher blood lead (OR = 1.08, 95% CI: 1.02–1.14, $p = 0.0053$), cadmium (OR = 1.29, 95% CI: 1.14–1.47, $p < 0.0001$) and selemium levels (OR = 1.01, 95% CI: 1.00-1.01, $p < 0.0001$) were all associated with increased risk for MetS. Furthermore, population with increased urinary cadmium and arsenic levels were more likely to have MetS.

Table 2
Univariate analysis for MetS.

Variables	OR (95% CI)	P value
Age	1.04 (1.03, 1.04)	< 0.0001
Gender		
Male	Reference	
Female	1.09 (0.95, 1.26)	0.2226
BMI	1.13 (1.12, 1.15)	< 0.0001
Race		
Mexican American	Reference	
Other Hispanic	0.91 (0.68, 1.21)	0.5207
Non-Hispanic White	0.92 (0.73, 1.14)	0.4317
Non-Hispanic Black	0.75 (0.59, 0.94)	0.0151
Other Race: Including Multi-Racial	0.71 (0.55, 0.91)	0.0082
Mild work	Reference	
Moderate work	1.18 (1.02, 1.36)	0.0223
Vigorous work	0.96 (0.81, 1.14)	0.6615
Smoking	1.78 (1.54, 2.05)	< 0.0001
Drinking	1.42 (1.16, 1.75)	0.0008
Cancer	2.17 (1.74, 2.71)	< 0.0001
ALT	1.02 (1.02, 1.03)	< 0.0001
AST	1.01 (1.00, 1.01)	0.0008
ALP	1.00 (1.00, 1.00)	0.0907
Scr	1.00 (1.00, 1.01)	0.0009
CRP	1.04 (1.03, 1.05)	< 0.0001
Blood heavy metals		
Lead	1.08 (1.02, 1.14)	0.0053
Cadmium	1.29 (1.14, 1.47)	< 0.0001
Mercury	1.02 (0.99, 1.04)	0.2176
Selemium	1.01 (1.00, 1.01)	< 0.0001
Manganese	1.00 (0.98, 1.02)	0.9263
Urinary heavy metals		
Lead	1.23 (0.98, 1.56)	0.0797
Cadmium	1.72 (1.30, 2.27)	0.0001
Arsenic	1.00 (1.00, 1.01)	0.0327
Chromium	1.12 (0.91, 1.38)	0.2875
Barium	1.01 (0.96, 1.06)	0.6076
Cobalt	0.95 (0.78, 1.15)	0.5880
Cesium	1.03 (0.99, 1.07)	0.1045
Molybdenum	1.00 (1.00, 1.00)	0.9860
Manganese	1.04 (0.85, 1.27)	0.7060
Antimony	0.72 (0.30, 1.73)	0.4594
Tin	1.02 (0.98, 1.06)	0.3000

Variables	OR (95% CI)	P value
Thallium	0.91 (0.36, 2.28)	0.8326
Tungsten	0.63 (0.25, 1.60)	0.3292
Abbreviations: BMI: body mass index; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; Scr: serum creatinine; CRP: C reactive protein;		

Multivariate logistic regression analysis of MetS

Multivariate logistic regression analysis was further performed to identify the independent risk factors for MetS and presented in Fig. 4. After adjusting confounding factors, blood cadmium remained independently associated with the presence of MetS (OR = 1.253, 95% CI: 1.059–1.478, p = 0.00829). In addition, age (OR = 1.044, 95% CI: 1.038–1.050, p < 0.00001), BMI (OR = 1.139, 95% CI: 1.124–1.155, p < 0.00001) and ALT (OR = 1.036, 95% CI: 1.026–1.046, p < 0.00001) were independent risk factors of MetS, while Non-Hispanic White (OR = 0.685, 95% CI: 0.523–0.896, p = 0.00579), Non-Hispanic Black (OR = 0.559, 95% CI: 0.417–0.749, p = 0.00010), and AST (OR = 0.970, 95% CI: 0.958–0.983, p < 0.00001) were independently negatively associated with the presence of MetS.

The association of blood cadmium and risk for MetS and its components

Both crude and adjusted models were constructed to assess the association between blood cadmium and the risk for MetS. In crude model, no covariates were adjusted, and blood cadmium was treated as continuous and categorical variables, respectively. As shown in Table 3, blood cadmium level was significantly positively related to the prevalence of MetS. Specifically, an increasement of one unit in blood cadmium was associated with 1.29 times higher risk for MetS (95% CI: 1.14–1.47, p < 0.0001). The relationship between blood cadmium and risk for MetS components were also evaluated. Higher blood cadmium was found correlated to higher risk for elevated TG, low HDL and elevated BP, while no statistical significances were found between blood cadmium and elevated WC or elevated FPG. Then, participants were equally divided into 4 groups according to the blood cadmium concentration: Q1 (blood cadmium ≤ 0.155), Q2 (0.155 < blood cadmium ≤ 0.260), Q3 (0.260 < blood cadmium ≤ 0.481), and Q4 (blood cadmium > 0.481). When treating blood cadmium as a categorical variable, highest blood cadmium concentration (Q4) had remarkably increased risk for MetS compared with those with Q1 of blood cadmium levels (OR = 1.63, 95% CI: 1.33-2.00, p < 0.0001). In the model adjusted for age, sex, BMI, race, physical activity, smoking, drinking, cancer, ALT, AST, Scr, CRP, blood lead, mercury and selemium, per 1ug/L blood cadmium increasement was associated with 1.25 times higher risk for MetS (95% CI: 1.06–1.48, p = 0.0083). When recognized as a continuous variable, the association between blood cadmium and MetS components in the adjusted model remained significant. However, compared with Q1, blood cadmium at Q4 was only associated with increased elevated risk for BP but not MetS and other MetS components.

Table 3
Association of blood cadmium and risk of MetS and its components in crude and adjusted models.

Exposure	MetS		Elevated WC		Elevated TG		Low HDL		Elevated BP		Elevated FPG	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Blood cadmium	1.29(1.14, 1.47)	< 0.0001	1.10(0.98, 1.24)	0.1168	1.20(1.04, 1.39)	0.0105	1.13(1.00, 1.29)	0.0484	1.53(1.35, 1.73)	< 0.0001	1.12(0.99, 1.27)	0.0710
Blood cadmium quartile												
Q1	Reference		Reference		Reference		Reference		Reference		Reference	
Q2	1.28(1.03, 1.58)	0.0240	1.42(1.20, 1.70)	< 0.0001	1.15(0.91, 1.47)	0.2381	0.90(0.74, 1.09)	0.2749	1.64(1.34, 2.01)	< 0.0001	1.39(1.14, 1.70)	0.0013
Q3	1.75(1.43, 2.14)	< 0.0001	1.84(1.54, 2.19)	< 0.0001	1.20(0.95, 1.52)	0.1232	0.88(0.73, 1.07)	0.2051	2.44(2.01, 2.97)	< 0.0001	1.87(1.54, 2.27)	< 0.0001
Q4	1.63(1.33, 2.00)	< 0.0001	1.43(1.20, 1.71)	< 0.0001	1.24(0.98, 1.57)	0.0686	0.89(0.74, 1.08)	0.2450	2.87(2.36, 3.49)	< 0.0001	1.58(1.30, 1.93)	< 0.0001
P for trend	< 0.0001		< 0.0001		0.068		0.244		< 0.0001		< 0.0001	
Adjusted model												
Blood cadmium	1.25(1.06, 1.48)	0.0083	1.30(0.97, 1.74)	0.0809	1.21(1.02, 1.44)	0.0317	1.29(1.10, 1.51)	0.0014	1.25(1.07, 1.45)	0.0042	0.98(0.83, 1.15)	0.8057
Blood cadmium quartile												
Q1	Reference		Reference		Reference		Reference		Reference		Reference	
Q2	0.90(0.69, 1.16)	0.4119	0.87(0.59, 1.28)	0.4730	0.97(0.74, 1.26)	0.7931	0.88(0.71, 1.09)	0.2478	1.12(0.89, 1.42)	0.3214	0.91(0.71, 1.16)	0.4359
Q3	0.91(0.70, 1.18)	0.4834	0.90(0.60, 1.36)	0.6297	0.89(0.67, 1.17)	0.4021	0.92(0.74, 1.16)	0.4950	1.13(0.89, 1.44)	0.2998	0.82(0.64, 1.06)	0.1287
Q4	1.05(0.79, 1.40)	0.7481	1.12(0.72, 1.75)	0.6031	1.00(0.74, 1.36)	0.9901	1.04(0.81, 1.34)	0.7553	1.51(1.17, 1.95)	0.0018	0.82(0.63, 1.08)	0.1671
P for trend	0.673		0.560		0.888		0.726		0.0003		0.136	

Adjusted model: adjusted for age, sex, BMI, race, physical activity, smoking, drinking, cancer, ALT, AST, Scr, CRP, blood lead, mercury and selemium.

Abbreviations: MetS: metabolic syndrome; WC waist circumference; TG: triglyceride; HDL: high-density lipoprotein; BP: blood pressure; FPG: fasting plasma glucose;

OR: odds ratio.

Association of blood cadmium and risk for MetS in different subgroups

Stratified multiple logistic regression analysis were performed in different age, gender and race groups to explore potential heterogeneities. Table 4 showed the associations between blood cadmium levels and the risk for MetS in different age, gender and race groups. The associations between MetS and blood levels of cadmium remained significant in subjects less than 60 years old (OR = 1.33, 95% CI: 1.08–1.64; p = 0.0078) and females (OR = 1.35, 95% CI: 1.08–1.70, p = 0.0089). While no significant associations were present between blood cadmium and the risk for MetS in population elder than 60, males and any race.

Table 4
Association between blood cadmium and MetS, stratified by age, gender and race.

Blood cadmium	OR (95% CI)	P value	P for interaction
Age			0.0002
≤ 60	1.33 (1.08, 1.64)	0.0078	
> 60	1.15 (0.87, 1.51)	0.3201	
Gender			
Male	1.24 (0.96, 1,61)	0.1021	0.1313
Female	1.35 (1.08, 1.70)	0.0089	
Race			0.7204
Mexican American	1.10 (0.50, 2.42)	0.8055	
Other Hispanic	1.63 (0.71, 3.78)	0.2506	
Non-Hispanic White	1.25 (0.96, 1.62)	0.0945	
Non-Hispanic Black	1.21 (0.89, 1.63)	0.2200	
Other Race: Including Multi-Racial	1.51 (0.94, 2.43)	0.0867	
Abbreviations: OR: odds ratio.			

Discussion

The current representative research established an association between blood cadmium and MetS. Participants with MetS had remarkably increased blood lead, cadmium, mercury and selemium levels compared with those without MetS. Multiple logistic regression analysis revealed blood cadmium was independently associated with the prevalence of MetS and its components, including elevated TG, low HDL and elevated BP after adjusting confounding factors. The positive association between blood cadmium and MetS remained significant in subgroup aged less than 60 and females.

Increasing reports have revealed MetS is closely related to higher cardiovascular risk and mortality, and MetS has become a global public health concern due to its life-threatening property and high prevalence nowadays [Nilsson et al. 2019]. It has been reported that MetS is a multiple factor-related metabolic disorder and the risk for MetS can be enhanced by environmental pollutant exposure to a large extent [Hou et al. 2020]. Recently, the effect of heavy metals exposure on cardiometabolic health has received extensive attention from researchers, and compelling evidence have confirmed its association and MetS [Xu et al. 2020]. Among these heavy metals, cadmium is a kind of widespread environmental contaminant with a release of 2.2×10^4 t globally due to steadily increasing industrial activities, and cadmium has been recognized as a metabolic disruptor [Barn et al. 2019]. Occupational exposure to cadmium is very common in mining, welding and battery recycling workers, which posed adverse impact on health [Baloch et al. 2020]. Cadmium has no biological role in human, additionally, cadmium has an extreme long biological life-time of approximately nearly 20–30 years and rather low excretion rate, leading to huge cardiometabolic threat to residents [Branca et al. 2018]. Recently, higher levels of cadmium levels were reported in subjects with MetS. Liu et al. reported urinary cadmium was significantly higher in diabetic coke oven workers compared with normoglycemia workers [Liu et al. 2016].

Previous reports have investigated the effect of cadmium exposure on MetS risk in different population. However, the existing results of these researches remained contradictory. For instance, rats exposed to cadmium for 3 months displayed significant MetS phenotype characterized by dyslipidemia, hyperglycemia, and visceral adiposity [Sarmiento-Ortega et al. 2021]. Chronic exposure to cadmium indicated by higher urinary cadmium increased the odds for MetS among current smokers [Noor et al. 2018]. On the contrary, blood concentration of cadmium showed a negative association with MetS in Korean population [Moon 2014]. Another research suggested cadmium contributed negatively to the environmental risk for the development of MetS among 15 heavy metals in a prospective cohort [Wang et al. 2022]. The present research indicated an independent positive correlation between blood cadmium and the prevalence of MetS.

The research findings on the relationship between cadmium exposure and MetS individual components also remained inconsistent. For example, Korea National Health and Nutrition Examination Survey showed blood cadmium levels was associated with waist circumference [Park et al. 2021]. In aggrement with these studies showing significant positive association between blood cadmium, blood pressure levels, and the prevalence of hypertension [Garner et al. 2017, Wang et al. 2018], the current research indicated blood cadmium was remarkedly correlated to the prevalence of elevated BP when treated as a continous (OR = 1.25, 95% CI: 1.07–1.45, p = 0.0042) and categorical variable (Q4 vs. Q1: OR = 1.51, 95% CI: 1.17–1.95, p = 0.0018). Nevertheless, some previous research investigating the relationship between blood cadmium and blood pressure were conflicting [Tellez-Plaza et al. 2008]. The differences in research population, research design, methodology, and confounding factors might give an explanation on the conflicting results.

Compelling evidence has indicated cadmium exposure increased the risk for hyperlipidemia. Elevated serum cadmium level was found significantly associated with 3 times higher risk for dyslipidemia in academic institution staff in Beirut [Ayoub et al. 2021]. A Korean study also revealed higher blood cadmium concentration increased high TG/HDL-c ratio risk [Kim 2012]. A dose-dependent relationship between blood cadmium and the prevalence of

elevated TG and low HDL-c was identified in Chinese worker occupationally exposure to cadmium [Zhou et al. 2016]. Consistently with previous reports, the present research suggested blood cadmium was significantly positively associated with 1.21 and 1.29 times higher risk for elevated TG and low HDL, respectively. The underlying molecular mechanism of increased cadmium exposure to dyslipidemia remained largely unexplored. Experimental research revealed alteration in macroautophagy regulating lipid storage and reduced expression of LDL receptor might be involved in cadmium induced dyslipidemia [Liu et al. 2020, Rosales-Cruz et al. 2018]. Moreover, considering cadmium could exhaust protein and glutathione-bound sulfhydryl groups, upregulation of lipid peroxidation might also participate in the underlying mechanism [Dong et al. 2021].

With respect to the findings of hyperglycemia, in a longitudinal prospective cohort including 3521 Chinese adults, chronic cadmium exposure indicated by urinary cadmium levels was found associated with increased FPG, which elucidated the diabetogenic effect of cadmium [Xiao et al. 2021]. Cadmium has been categorized as hyperglycemia metal through upregulation of gluconeogenesis and pancreatic islet dysfunction [Hong et al. 2021]. In detail, the exposure of cadmium affected the expression of essential enzymes and proteins in insulin signaling transduction. Cadmium may also disturb the production of insulin through inflammation, oxidative stress damage, and mitochondrial dysfunction [Buha et al. 2020]. While no statistical significance was found in the present research between blood cadmium and FPG after adjustment of confounding factors, which could be due to the differences in research population, different definition criteria used for elevated FPG, etc. Consistent with our research, Yan et al. reported a negative association between blood cadmium concentration, blood glucose level, insulin level and incidence of diabetes [Borné et al. 2014].

In the stratified logistic regression analysis, we further explored the association between blood cadmium and risk for MetS in population stratified by age, gender and race. The findings showed that the positive association between blood cadmium and MetS remain significant in participants aged no more than 60 and females, which might help identify the susceptible individuals to cadmium exposure. Previous research showed conflicting results that subjects with higher cadmium had lower risk for MetS in all age groups and both genders [Zhou et al. 2022]. In a cross-sectional research conducted in Korea, blood cadmium levels were found associated with MetS only in men but not women [Lee et al. 2013]. We speculated that the different research findings between the current and previous studies might arise from population with different countries and races. The exact mechanism of gender- and age- specificity remained unclear, more large-scale, multi-center prospective research are needed for further elucidating the association of cadmium exposure and MetS in population with different age and gender.

The current research has some advantages. First of all, it is a large-scale survey conducted in a representative general population with detailed data in America. Additionally, stratified multivariate logistic regression analysis was performed, females and subjects under 60 were identified susceptible to MetS under exposure to cadmium. However, there exist several limitations in the present study. Firstly, we could not give the causal interference between cadmium exposure and MetS temporarily on the basis of the cross-sectional study. Secondly, blood cadmium levels rather than urinary cadmium levels were investigated in the current research due to relatively large missing data of urinary metals. Blood cadmium was recognized as the most reliable biomarker for recent rather than long-term cadmium exposure [Akerstrom et al. 2013]. Large-scale, prospective and longitudinal studies are warranted to elucidate the impact of cadmium exposure on MetS in the future.

Conclusion

In conclusion, our findings highlighted an association between blood cadmium and MetS in a large-sample representative population. Blood cadmium levels were significantly higher in individuals with MetS, and blood cadmium was identified as an independent risk factor for MetS after adjusting confounding factors. The findings also suggested population aged ≤ 60 and females were vulnerable to the deleterious effect of cadmium exposure on MetS.

Declarations

Acknowledgement

The authors appreciate the time and effort given by participants and research staff during the data collection phase of the NHANES project, we also thank CDC for publicizing the NHANES database.

Author contribution

Study conception and design: Weilong Xing, Lei Wang; data collection: Weilong Xing, Lei Wang, Wen Gu; data analysis and interpretation: Weilong Xing, Lei Wang, Wen Gu, Mengyuan Liang, Zhen Wang, Deling Fan, Bing Zhang; manuscript writing and reviewing: Weilong Xing; study supervision: Weilong Xing. All authors read and approved the final manuscript.

Funding

The study was supported by the grants from Central Scientific Research Projects for Public Welfare Research Institutes (ZX2022QT020) and the Doctoral Program of Entrepreneurship and Innovation in Jiangsu Province (JSSCBS20211323).

Data availability

Publicly available datasets were analyzed in this study. This data can be found at: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethical approval and consent to participate

The program was approved by the National Center for Health Statistics Ethics Review Board. All of the participants provided written informed consent.

Consent for publication

Not applicable

Competing interests

The authors declared no competing interests.

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Figures

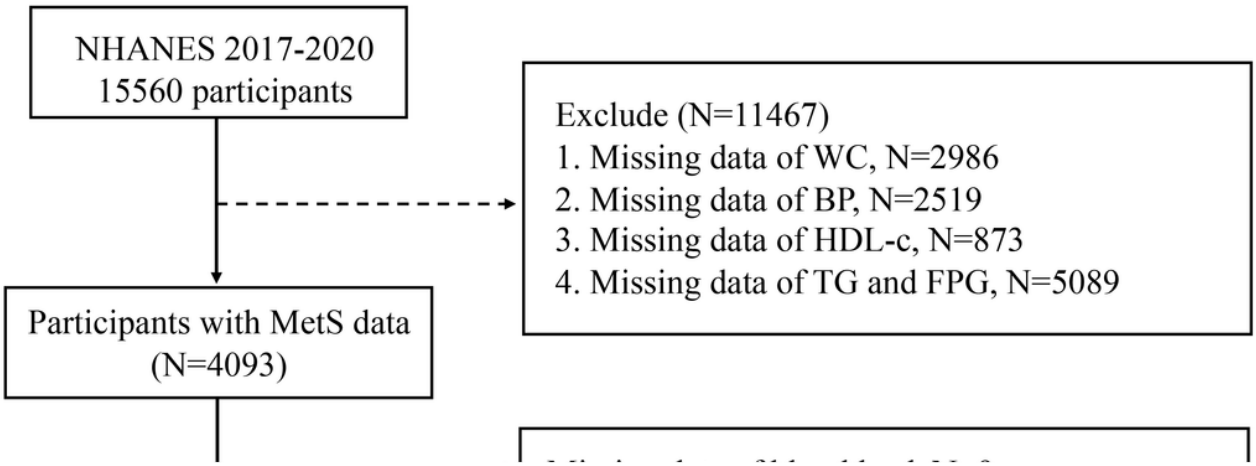

Figure 1

The flow diagram of subject inclusion and exclusion.

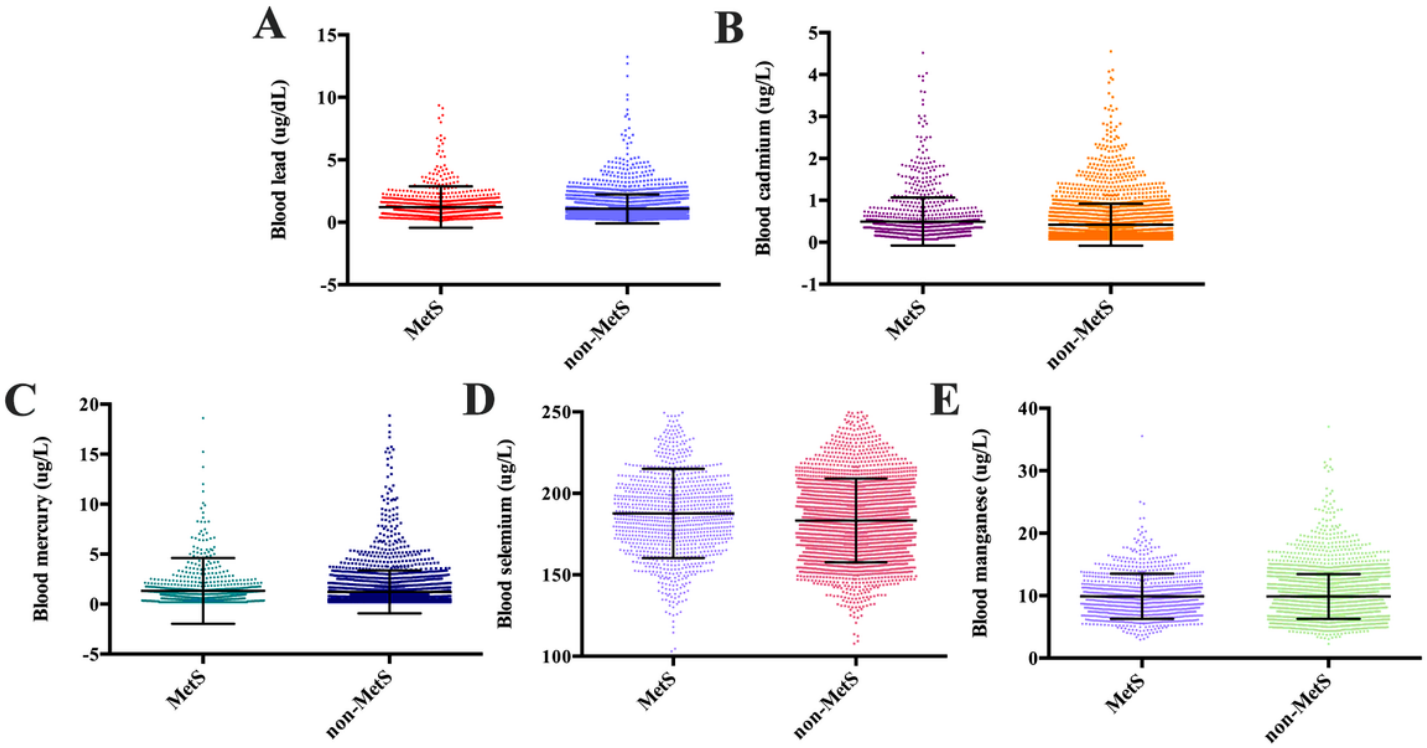

Figure 2

The distribution of different blood heavy metals in MetS and non-MetS group.

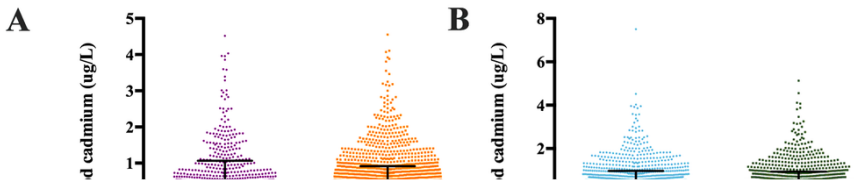

Figure 3

The distribution of blood cadmium in MetS and its components.

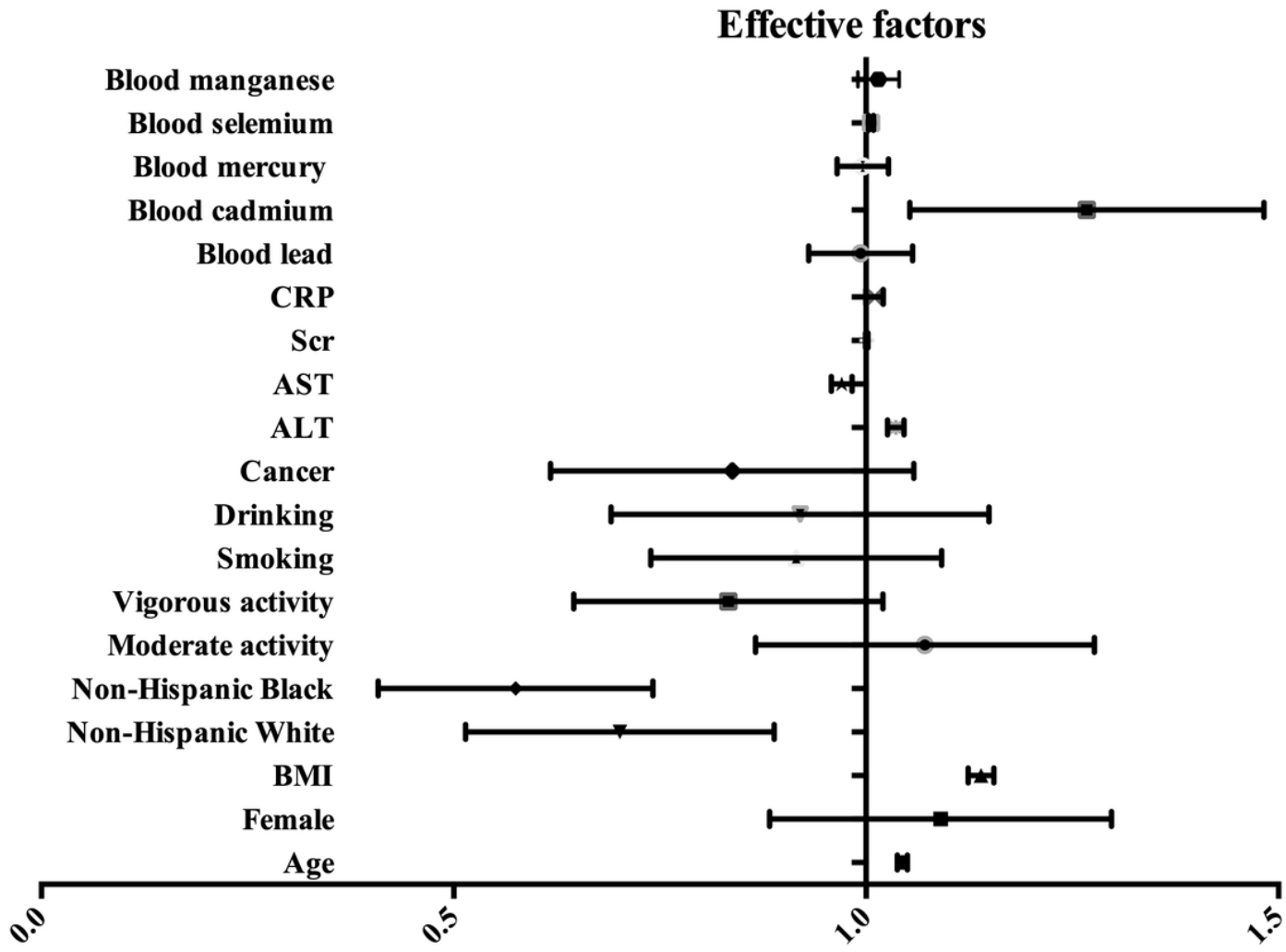

Figure 4

Forest plot of multivariate predictors for MetS.